# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Premeeting briefing

# Idelalisib for chronic lymphocytic leukaemia

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

## Key issues for consideration

### *Clinical effectiveness*

- Are the baseline characteristics of patients in Study 116 generalisable to UK patients with relapsed or refractory chronic lymphocytic leukaemia? The ERG stated that patients in Study 116 had a higher proportion of 17p deletions and TP53 mutations than would normally be observed in UK clinical practice.
- Are the results of Study 101-08 applicable to the 17p deletion or TP53 mutation population considering they are based on a sample of 9 patients?
- Can rituximab monotherapy be considered an appropriate comparator for a UK setting considering it is not recommended for use by NICE or professional guidance? The comparators listed in the NICE scope for the relapsed or refractory population were: FCR, bendamustine (with or without rituximab), chlorambucil (with or without rituximab), steroids plus rituximab and ofatumumab.

## *Cost Effectiveness*

**Base case analysis:**

- Is it reasonable to assume that 45% of patients whose disease did not respond to treatment would receive intravenous immunoglobulin (IVIG) therapy?
- The company assumed that the treatment benefits of idelalisib plus rituximab would continue for the rest of the patient's life. The ERG noted that this may be inappropriate and explored stopping the treatment benefit after 5 years. Which is the more appropriate approach to use?
- Is it appropriate to assume, when adjusting for crossover between the two arms of the trial, that idelalisib monotherapy has the same efficacy as idelalisib with rituximab. The ERG noted that if idelalisib monotherapy has a lower efficacy, then idelalisib with rituximab will be less cost-effective than the current results imply.
- The company assumed that ofatumumab had equivalent clinical efficacy to rituximab in the base case analysis. Is this a reasonable assumption?

**Additional comparators analysis:**

- What is the most appropriate method of estimating time-on-treatment for the comparisons with FCR, bendamustine with or without rituximab, chlorambucil with or without rituximab, rituximab with steroids and ofatumumab? The company assumed patients would complete the full dose of the treatments as stated in the marketing authorisations. The ERG commented that it is more appropriate to use the time-on-treatment data for rituximab monotherapy, reported in Study 116, to inform the time-on-treatment for the other comparators examined in the economic model.
- Was the method used by the company to calculate the cost effectiveness of the additional comparators appropriate? The company was unable to form an indirect comparison with the available data; instead they used data from randomised controlled trials and single-arm trials for the comparators listed in the scope.

## *Innovation*

- Can idelalisib plus rituximab be considered innovative?

### *End of life*

- Has idelalisib plus rituximab met the criteria listed in the supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses?

# 1 Remit and decision problem

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of idelalisib within its licensed indication for treating chronic lymphocytic leukaemia.

**Table 1 Decision problem**

| | Final scope issued by NICE | Decision problem addressed in the submission | Comments from the company | Comments from the ERG |
|---|---|---|---|---|
| Population. | • Adults with chronic lymphocytic leukaemia (CLL) who have received at least one therapy.<br>• Adults with untreated CLL associated with 17p deletion or TP53 mutation for which chemo-immunotherapy is not suitable. | As per the NICE scope. | None. | None. |
| Intervention. | Idelalisib plus rituximab | As per the NICE scope. | None. | None. |
| Comparators. | For adults with CLL 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). | For adults with CLL 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>For adults with untreated CLL associated with 17p deletion or TP53 mutation:<br>• Alemtuzumab<br>• Ofatumumab<br>• Best supportive care including steroids | For adults with CLL who have received at least one prior therapy:<br>• The company noted that rituximab was included because it is sometimes used in the relapsed and refractory population. In addition rituximab is the comparator in the pivotal trial.<br>For adults with untreated CLL associated with 17p deletion or TP53 mutation:<br>• The company noted that it excluded bendamustine and chlorambucil (considered to be cytotoxic chemotherapies) because they are not suitable for patients with high-risk forms of CLL. | For adults with CLL who have received at least one prior therapy:<br>• The ERG highlighted that rituximab is not a standard comparator in the relapse/refractory population. It noted the current best practice guidance which does not recommended its use. In addition the ERG noted that it was not listed as a comparator in the final NICE scope. |

| | | | | |
|---|---|---|---|---|
| | For adults with untreated CLL 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 to ongoing NICE technology appraisal) | | • The company noted that ofatumumab in combination with bendamustine or chlorambucil, and obinutuzumab in combination with chlorambucil have been excluded from the submission. The company noted that neither of the ongoing NICE technology appraisals have been published therefore the comparators are not part of standard of care. In addition the company note that these treatments are not suitable for patients with high-risk CLL. | |
| 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. | The ERG noted that all outcomes in the NICE scope were measured and reported in the company submission. |

# 2 The technology and the treatment pathway

2.1 Treatment options for people with chronic lymphocytic leukaemia vary depending on factors such as; disease stage, performance status, co-morbidities, assessment of fitness to tolerate chemotherapy and/or immunotherapy and TP53 status. In previously treated patients, the number and nature of prior treatments, their efficacy and toxicity and the availability of a transplant donor should all be taken into consideration.

2.2 In people with symptomatic disease who have not previously been treated, NICE technology appraisal guidance 174 recommends rituximab in combination with fludarabine and cyclophosphamide as an option for the first line treatment of chronic lymphocytic leukaemia. NICE technology appraisal guidance 216 recommends bendamustine as an option for the first-line treatment of chronic lymphocytic leukaemia for patients in whom fludarabine combination chemotherapy is not appropriate. Fludarabine monotherapy is not recommended for the first line use for people with chronic lymphocytic leukaemia (NICE technology appraisal guidance 119). NICE technology appraisal guidance (pending final guidance publication) recommends obinutuzumab in combination with chlorambucil as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable. NICE technology appraisal guidance (pending final guidance publication) recommends ofatumumab in combination with chlorambucil as an option for untreated chronic lymphocytic leukaemia only if the person is ineligible for fludarabine-based therapy and bendamustine is not suitable.

2.3 In people with relapsed or refractory chronic lymphocytic leukaemia NICE technology appraisal guidance 193 recommends rituximab in combination with fludarabine and cyclophosphamide (unless the person is refractory to fludarabine or has previously been treated with rituximab). NICE technology appraisal guidance 29 recommends oral fludarabine as an option for treating chronic lymphocytic leukaemia in people who are

refractory to first line chemotherapy. Ofatumumab is not recommended for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab (NICE technology appraisal guidance 202). The British Committee for Standards in Haematology (BCSH) also recommends either chlorambucil, with or without an anti-CD20 antibody or bendamustine in combination with rituximab for people whose disease does not respond to chlorambucil monotherapy initially (See Figure 1).

2.4 In people with a 17p deletion or TP53 mutation the BCSH recommend that first-line treatment should consist of alemtuzumab with or without high-dose pulsed steroids. Alemtuzumab does not have a marketing authorisation in the European Union (EU) but is available via a patient access programme agreed between the European Medicines Agency (EMA) and the company. In addition, ofatumumab is considered an option for patients who are refractory to alemtuzumab.

2.5 Idelalisib works by inhibiting signalling pathways that affect the growth, differentiation and proliferation of malignant cells in lymphoid tissues and bone marrow. It has a marketing authorisation for use ‘in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia 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’.

**Figure 1 Summary of British Committee Standards in Haematology guidance on management of chronic lymphocytic leukaemia[1] (page 43, table 12 of company submission)**

| Patient population | Summary of guidance |
|---|---|
| Treatment of untreated patients without TP53 abnormality who are fit enough to receive fludarabine | • Fludarabine, cyclophosphamide and rituximab |
| Treatment of untreated patients without TP53 abnormality who are not fit enough to receive fludarabine | • Chlorambucil or bendamustine, with/without anti-CD20 antibodies (rituximab and ofatumumab) |
| Relapsed chronic lymphocytic leukaemia without TP53 abnormality | • Patients relapsing ≥2 years after fludarabine-containing regimens who remain healthy enough to receive fludarabine, should receive fludarabine, cyclophosphamide and rituximab.<br>• Patients relapsing after chlorambucil who are healthy enough to receive fludarabine-based therapy should be considered for fludarabine, cyclophosphamide and rituximab.<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) | • 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.<br>• 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; NICE, National Institute for Health and Care Excellence. | |

[1] Adapted from the BCSH guidance on CLL: http://www.bcshguidelines.com/documents/Revised_CLL_guideline_july_13.pdf

## Table 2 Technology

| | Idelalisib in combination with rituximab | Rituximab in combination with fludarabine and cyclophosphamide (FCR) | Chlorambucil | Bendamustine | Ofatumumab | Alemtuzumab |
|---|---|---|---|---|---|---|
| **Marketing authorisation** | Idelalisib is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia who have:<br>• received at least one prior therapy or,<br>• first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. | Rituximab in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. | Chlorambucil is indicated in the treatment of chronic lymphocytic leukaemia. | First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. | Ofatumumab in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.<br><br>Ofatumumab is indicated for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. | Marketing authorisation withdrawn. Available to patients with chronic lymphocytic leukaemia through a patient access programme between the European medicines agency (EMA) and the company. |
| **Administration method** | Oral tablet. | Intravenous infusion. | Oral tablet. | Intravenous infusion. | Intravenous infusion. | Intravenous infusion. |
| **Dosage and cycles** | 150 mg, twice daily, until disease progression or unacceptable toxicity. | 375 mg/m$^2$ body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total.<br>The chemotherapy | 0.15 mg/kg/day until the total leucocyte count has fallen to 10,000 per µL.<br>Treatment may be resumed 4 weeks after the end of the first course and continued at a dosage of 0.1 | 100 mg/m$^2$ body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks. No maximum cycles reported. | 300 mg for the first infusion and 2,000 mg for all subsequent infusions.<br>The infusion schedule is 8 consecutive weekly infusions, followed 4-5 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions. | Gradual escalation to the maximum recommended single dose of 30 mg. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | should be given after rituximab infusion. | mg/kg/day. No maximum cycles reported. | | | |
| **List Price** | £3,114.75 for 60 tablets of either 100mg or 150mg at list price [BNF April 2015]<br><br>The proposed discount price reduces the list price of idelalisib by [redacted] for 60 tablets of either 100 mg or 150 mg. | 50-mL vial = £873.15 [BNF 2015] | 2mg 25-tab pack = £40.51[BNF April 2015] | 25-mg vial = £69.45 [BNF April 2015] | 5-mL vial = £182.00 [BNF April 2015].<br>Ofatumumab is currently subject to an ongoing NICE technology appraisal and as part of its submission has agreed a confidential patient access scheme to reduce the cost by [redacted] | Supplied through a patient access programme |
| **Company's estimated total cost of treatment** | The company's estimated total cost of idelalisib treatment is [redacted] (using proposed discount price).<br>Because idelalisib is taken until disease progression the company used the modelled time on treatment from Study 116 to estimate the total cost of treatment with idelalisib ([redacted]).<br><br>When the total modelled cost of rituximab is included (£12,521 for a maximum of 8 cycles) the total cost of treatment for idelalisib with rituximab is [redacted]. | The estimated total treatment cost of FCR is £12,453.<br><br>The company assumed 6 cycles, with the initial cycle costing £1727 and the subsequent cycles costing £2145. | The estimated total treatment cost of Chl is £1,361.<br><br>The company assumed a maximum of 12 cycles with 1 cycle costing £113. | The estimated total treatment cost of B is £8,499.<br><br>The company assumed a maximum of 12 cycles costing £1062 per cycle. | The estimated total treatment cost of ofatumumab is £40,586.<br><br>The company assumed a maximum of 12 cycles costing £546 for the initial dose and £3640 for the subsequent doses. These prices do not include the confidential patient access scheme. | Not applicable. |

# 3 Comments from consultees

3.1 A professional organisation noted that in current clinical practice people with relapsed or refractory chronic lymphocytic leukaemia are given a range of treatments which can include: chlorambucil, bendamustine or fludarabine with cyclophosphamide and rituximab. The organisation noted that bendamustine with rituximab or ofatumumab monotherapy could also be considered. It noted that for patients who have a 17p deletion, alemtuzumab with steroids can be considered.

3.2 A patient and carer organisation described how the toxicity of fludarabine-containing regimens often made them inappropriate therapies for the treatment of chronic lymphocytic leukaemia in older patients who may have comorbidities. The organisation noted that treatments such as chlorambucil, steroids or ofatumumab are easier to tolerate, but in many patients are of limited benefit, producing only short periods of remission. This means repeated courses of treatment are likely to be required, until eventually all suitable options are exhausted. Alemtuzumab can cause significant side effects, including an ongoing risk of infection. A patient and carer organisation noted that patients prefer to have treatment options available to them with the lowest side effect profile. In addition patients prefer treatment regimens with less burdensome administration methods, for example oral treatments. An organisation noted that because chronic lymphocytic leukaemia is currently incurable, the uncertainty of living with chronic lymphocytic leukaemia brings with it serious psychological and emotional issues combined with other physiological issues that impact negatively on quality of life.

3.3 A professional organisation reported that patients with a p53 mutation are unable to benefit from chemotherapy because the mutation leads to disease resistance. It noted that in clinical practice the incidence of p53 mutations increases with each treatment given. It estimates that in treatment naïve patients 5-10% of people will have a p53 mutation compared with 40-50% in heavily pre-treated patients. In addition multiple

courses of chemo-immunotherapies can cause long term toxicity meaning conventional chemotherapies are unsuitable.

3.4 A patient and carer organisation noted that idelalisib when taken in combination with rituximab is more effective and better tolerated than the current more intensive regimes. It noted this is important because the majority of patients with chronic lymphocytic leukaemia are not suitable for more intensive regimens. It highlighted that idelalisib requires less frequent visits to hospital for administration which can improve the patients quality of life. It also noted that idelalisib is associated with fewer side effects.

# 4 Clinical-effectiveness evidence

## *Systematic literature review*

4.1 The company's systematic literature review identified 4 randomised controlled trials (RCT) relevant to the decision problem for the relapsed and refractory chronic lymphocytic leukaemia population. The company noted that none of the trials identified in the literature review compared idelalisib plus rituximab directly with the appropriate comparators identified in the NICE scope. A trial by Furman (2014) (Study 116) was selected by the company to inform the clinical effectiveness of idelalisib in its submission. The trial compared idelalisib plus rituximab with rituximab plus placebo.

4.2 No RCTs were identified that investigated the effectiveness of idelalisib with rituximab in untreated chronic lymphocytic leukaemia patients with a 17p deletion or TP53 mutation. One phase II trial was identified (Study 101-08) which was a single-arm study of idelalisib and rituximab combination therapy in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma aged 65 years or older. The trial included a small subgroup of patients with a 17p deletion or TP53 mutation (n=9).

## *Overview of the clinical trials*

### Relapsed or refractory chronic lymphocytic leukaemia (Study 116)

4.3 Study 116 was a phase III, double blind, RCT which evaluated idelalisib in combination with rituximab compared with rituximab monotherapy in combination with placebo in people with chronic lymphocytic leukaemia. A total of 220 patients were randomised to receive either Idelalisib (150 mg oral tablets, twice daily) with rituximab (375 mg/m$^2$ at week 0, then 500 mg/m$^2$ at weeks 2, 4, 6, 8, 12, 16, 20) or rituximab (same dose) with placebo (matching tablet, twice daily, until progression). Patients were included if they were aged 18 years or older, had received at least 1 prior treatment line (either an anti-CD20 or 2 prior regimens with at least 1 cytotoxic chemotherapy) and had a reported Karnofsky progression score of 40 or more. Patients were excluded if their disease had progressed to more aggressive malignancies.

4.4 The primary outcome of Study 116 was progression free survival, defined as the interval from randomisation to first documentation of definitive disease progression or death from any cause (whichever is the earlier). Definitive disease progression was defined using the criteria from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL). The secondary outcomes included rates of overall (complete and partial) response, lymph-node response (defined as a decrease of 50% or more in lymphadenopathy), and overall survival. The primary and secondary endpoints were examined in the pre-specified subgroups. These included: the presence of a 17p deletion and/or TP53 mutation and presence of an immunoglobulin heavy-chain variable-region (IgVH) mutation (unmutated versus mutated [or indeterminate]). Health related quality of life was assessed using a 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.

4.5 Patients could crossover from rituximab monotherapy to idelalisib 150 mg twice daily in an extension study (Study 117) if they had disease progression confirmed by an independent review committee. For the intention to treat (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. Progression free survival was calculated using the Kaplan-Meier method. A Cox proportional hazards model with adjustment for stratification was used to calculate hazard ratios. The company considered 3 statistical methods to attempt to account for bias due to cross-over, and evaluate overall survival in line with NICE decision support unit (DSU) guidance. It chose to use the Rank Preserving Structural Failure Time (RPSFT) method because it assumed the treatment effect of idelalisib plus rituximab was equal for all patients regardless of when the treatment was received.

**Untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation (Study 101-08)**

4.6 Study 101-08 was a phase II, single-arm study of idelalisib and rituximab combination therapy in people previously untreated with chronic lymphocytic leukaemia. A total of 48 patients were enrolled in the study, across centres in the US, to receive idelalisib (150 mg oral tablets, twice daily) and rituximab (375 mg/m$^2$ weekly, continuously for 48 weeks). Patients were treated for 48 weeks in the primary study and patients who completed 48 weeks without a progression event could continue to receive idelalisib in an extension study. Only a small subset of patients (n=9) had a 17p deletion or TP53 mutation.

4.7 The primary outcome of the study was overall response rate which was defined as the proportion of patients who achieved a complete or partial response as defined according to IWCLL criteria. Secondary outcomes included adverse events, progression free survival and overall survival.

### ERG comments

4.8 The ERG noted that the search strategies were well constructed and updated to March 2015 on request following a clarification question. The ERG noted that the key trials for the clinical effectiveness and safety of idelalisib were included in the company submission. The ERG stated that the company searches for studies in untreated patients with 17p deletion or TP53 mutation included only the company's choice of comparators and not those listed in the final scope by NICE. It highlighted a phase-II study identified by the company (Pettitt et al 2012) which included 39 relapsed or refractory patients with a 17p deletion or TP53 mutation (17 of them previously untreated) comparing alemtuzumab with methylprednisolone for 16 weeks. The company excluded the study based on the marketing authorisation withdrawal of alemtuzumab, however the ERG noted that alemtuzumab is still available to patients via a patient access programme between the company and the EMA.

## *Clinical trial results*

### Study 116

4.9 A total of 220 patients were included in the trial which was conducted in 90 centres in the US and Europe (including the UK). The data cut off for the analysis was August 2013. The company stopped the blinded-phase of the trial after the first interim analysis (because the 2 sided p-value for the primary PFS analysis crossed the pre-specified alpha boundary of 0.001). A total of 110 patients were randomly assigned to each study group. All 110 patients in the idelalisib plus rituximab group and 107 in the rituximab plus placebo group received the assigned treatment. Of the 3 patients in the rituximab plus placebo group who did not receive study treatment, 2 patients withdrew from the study because of an adverse event and 1 patient had not received study treatment before the data cut off. The company noted that the mean age of patients in the trial was 71 and a total of 41.8% to 44.5% of patients had a 17p deletion and/or TP53

mutation in addition 82.7% to 84.5% were immunoglobulin variable region heavy chain non-mutated.

4.10 The results of the trial showed a statistically significant improvement in median progression free survival for idelalisib plus rituximab compared with rituximab plus placebo (19.4 months compared to 6.5 months). See Table 3.

**Table 3 Study 116 outcomes (Table 27, page 84 of company submission).**

| **Outcome** | **Study 116** | |
|---|---|---|
| | **Idelalisib + Rituximab (n=110)** | **Rituximab + Placebo (n=110)** |
| **Progression-Free Survival** | | |
| Median (months) | 19.4 (95% CI: 21.3, NR) | 6.5; (95% CI: 4.0, 7.3) |
| Adjusted HR (95% CI) | 0.15 (0.09, 0.24)<br>p=<0.001 [a] | |
| **Overall Survival [ITT analysis]** | | |
| Median (months) | NR | 20.8 (95% CI: 4.8, NR) |
| Adjusted HR (95% CI) | 0.34 (0.19, 0.60) p= 0.001[b] | |
| **Overall Survival [Crossover Adjusted RPSFT analysis]** | | |
| Median | NR | [redacted] |
| Adjusted HR (95% CI) | [redacted] | |

Key: CI, confidence interval; HR. Hazard Ratio; ITT, intention to treat; NR, Not reached, PFS, Progression free survival; RPSFT, rank preserving structural failure time.

[a] P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IgVH mutation

[b] P-value From Stratified Log-Rank Test adjusted for randomization stratification factors (17p deletion/TP53 mutation and IgVH mutation).

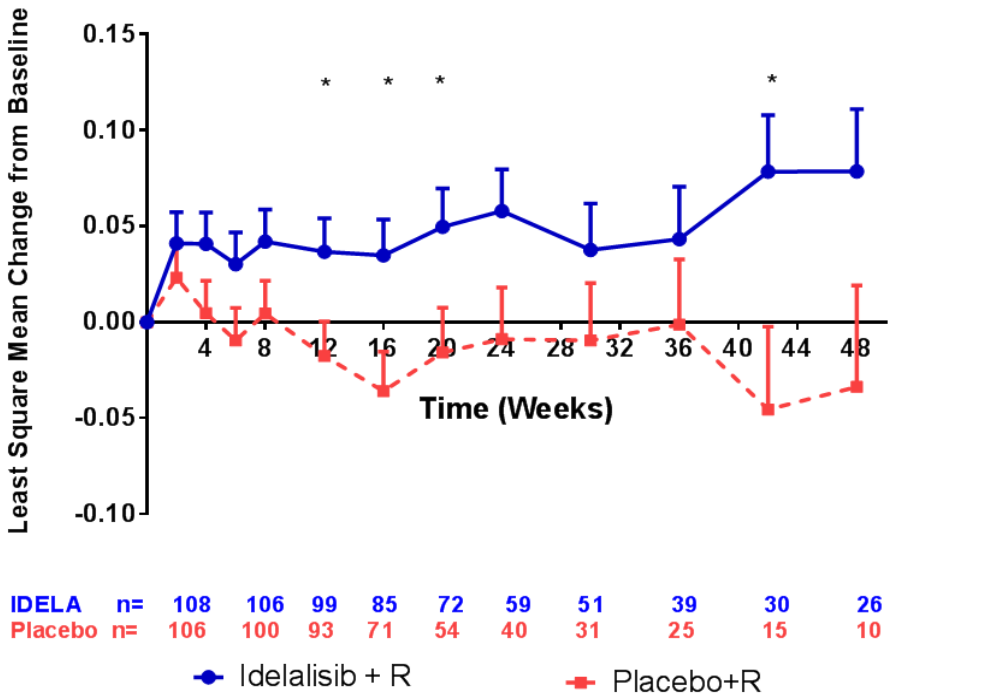
4.11 The company presented the results of the secondary outcomes analyses. The overall response rate was 83.6% for idelalisib plus rituximab compared with 15.5% for rituximab plus placebo. The odds ratio for overall response for idelalisib with rituximab compared to rituximab is 27.76 (95% CI: 13.4, 57.49). No patients in the trial experienced a

complete response; therefore, the entire overall response rate was made up of partial responders. The lymph node response rate was 96.2% in the idelalisib plus rituximab group compared to 6.7% in the rituximab plus placebo group. Further details of secondary outcomes results are given on pages 88-93 of the company submission.

4.12 The company presented the results for the pre-specified subgroups. In people without a 17p deletion and/or TP53 mutation the median progression free survival was 19.4 months in the idelalisib plus rituximab group compared to 8.1 months in the rituximab plus placebo group. For people with a 17p deletion and/or TP53 mutation progression free survival was not reached in the idelalisib plus rituximab group.

4.13 Health related quality of life data were collected using the EQ-5D measure (Figure 2) and the Functional Assessment of Cancer Therapy: Leukaemia (FACT-Leu) questionnaire. Patients receiving idelalisib showed improvement from baseline, with a statistically significant treatment effect for patients treated with the intervention in the EQ-5D analysis. The results of the FACT-Leu questionnaire showed patients in the idelalisib group had greater improvement in symptom compared to those in the rituximab group throughout each time point throughout of the trial.

**Figure 2 Mean change from baseline in the EQ-5D utility index (Study 116 ITT analysis set) (Figure 11, page 94 of company submission).**




*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

## Study 101-08

4.14 A total of 64 patients were included in the study which was conducted across sites in the US. A total of 62 patients completed the first 8 weeks of treatment and 43 patients completed 48 weeks. A total of 9 of the 64 patients included in Study 101-08 had a 17p deletion or TP53 mutation. The mean age of patients in the trial was 71 and over half (n=37) had IgVH non-mutated chronic lymphocytic leukaemia.

4.15 Median PFS was not reached for the overall population of patients with a 17p deletion or TP53 mutation. Progression free survival for the overall population at 36 months was 83%, compared with 100% for the 17p deletion or TP53 mutation patients. Overall survival for the whole study population at 36 months was 90% and 100% for the 17p deletion or TP53 mutation patients.

## *Results of the additional evidence*

4.16 The company also submitted additional evidence for the other comparator technologies listed in the NICE scope. The results of the company's systematic review did not identify any direct evidence comparing idelalisib with these comparators. A total of 3 RCTs and 9 non-RCT evidence were identified for the relapsed and refractory population. No additional evidence was identified in the untreated population. Results of the additional RCT evidence are presented in table 34, page 98 of the company submission. The results of the additional non-randomised and non-controlled evidence are presented in table 42, page 112 of the company submission.

### ERG comments

4.17 The ERG commented on the population of Study 116 and its applicability to UK patients (n=32 UK patients participating in the trial) with chronic lymphocytic leukaemia. It noted that the trial included a proportion of patients with a 17p deletion and/or TP53 mutation (43.2%). This type of disease does not respond to standard chemotherapy. The ERG noted that the baseline characteristics of patients in the trial represented a much higher-risk patient cohort than what is normally seen in UK clinical practice. The ERG also noted that the use of rituximab as a comparator was limited in its relevance to a UK population as it is not recommend by NICE or in BCSH guidance.

4.18 The ERG noted that the results of Study 116 should be interpreted with caution because the trial was stopped early for benefit. It notes that this type of stopping can lead to an overestimation of treatment effect.

## *Indirect and Mixed treatment comparison*

4.19 The company did not provide a mixed treatment comparison. The company noted that it was not possible to construct a connected treatment network from the current evidence base for the relapsed or refractory population because the only RCT data, other than Study 116,

that was identified was for cytotoxic chemotherapy regimens and no RCT data was identified for any anti-CD20 treatments. For the untreated 17p deletion or TP53 mutation population it noted that only one single-arm study was identified for idelalisib, and only one RCT was identified for the comparators (alemtuzumab compared to chlorambucil) therefore it was not possible to construct a network and perform an indirect/mixed treatment comparison.

**ERG comments**

4.20 The ERG agreed that it was not possible to indirectly link idelalisib plus rituximab with other comparators specified in NICE scope due to insufficient evidence, lack of relevant comparators, and heterogeneity between trial populations.

## *Adverse effects of treatment*

**Study 116**

4.21 The company noted a total of 15 patients had treatment-emergent adverse events that led to death (4 with idelalisib and rituximab, 11 with placebo and rituximab). It noted that causes of death were consistent with advanced chronic lymphocytic leukaemia and the underlying frailty, age, and poor prognosis of the study population.

4.22 The company reported that 32 patients (idelalisib with rituximab: 17.3%, 19 patients; placebo with rituximab: 12%, 13 patients) discontinued treatment due to an adverse event. Infections and infestations occurred in 11 of the 32 patients (idelalisib plus rituximab: 5 patients; rituximab plus placebo: 6 patients). Gastrointestinal disorders accounted for events in 6 of the patients with adverse events leading to discontinuation. Respiratory, thoracic, and mediastinal disorders accounted for events in 6 patients with adverse events leading to discontinuation (idelalisib with rituximab: 3 patients; placebo with rituximab: 3 patients).

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

**Study 101-08**

4.24 The company noted that all 64 patients in the trial received 1 dose or more of the study drug. The most common treatment related adverse events were diarrhoea/colitis (77%), rash (58%) and pyrexia (42%).

**ERG comments**

4.25 The ERG noted adverse effects and withdrawals were more frequent in the idelalisib plus rituximab group compared with the rituximab plus placebo group. For example the idelalisib plus rituximab group was associated with a greater incidence of severe adverse events (73.6%) compared to 53.7% in the rituximab plus placebo group. These included; neutropenia, pneumonia and diarrhoea. It noted that this led to an idelalisib dose reduction (from 150 mg/$^{d}$ to 100 mg/$^{d}$) in 18 patients. The ERG commented that overall, idelalisib was well tolerated and had a manageable safety profile when administered in combination with rituximab. It noted the occurrences of adverse events leading to death were more frequent in the rituximab plus placebo group. It noted that results of the tests for statistical were not provided by the company.

# 5 Cost-effectiveness evidence

## *Model structure*

5.1 The company submitted a de novo economic model for the relapsed or refractory chronic lymphocytic leukaemia population only. The base case analysis modelled the following:

- idelalisib plus rituximab with rituximab alone
- idelalisib plus rituximab with best supportive care
- idelalisib plus rituximab with ofatumumab.

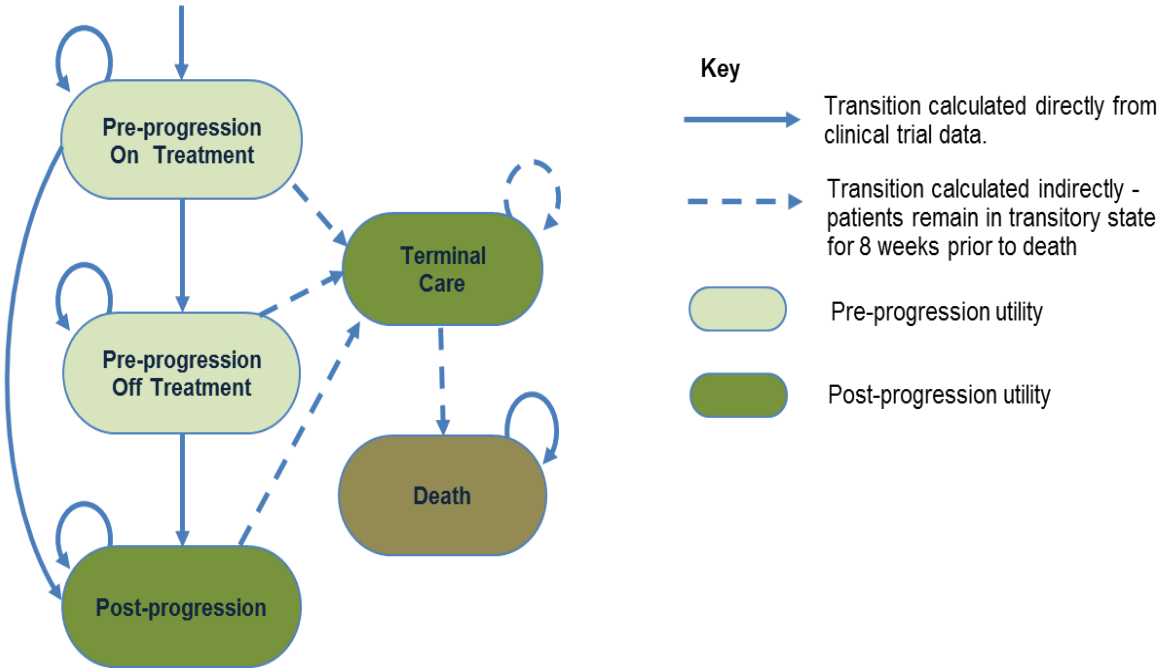
The company included an additional exploratory analysis of idelalisib plus rituximab with the other comparators listed in the NICE scope:

- Fludarabine, cyclophosphamide and rituximab
- Bendamustine
- Bendamustine plus rituximab
- Chlorambucil
- Chlorambucil plus rituximab
- Steroids plus rituximab

5.2 The company used a Markov model with time-dependent transition probabilities. It used weekly cycle lengths (with half-cycle corrections) with a time horizon of 25 years. The mean age of patients entering the model was 71. A discount rate of 3.5% was applied to costs and health benefits and the analysis was conducted from an NHS and personal social services perspective.

5.3 For the base case analysis, data from Study 116 was used. The model consisted of 5 health states, namely ‘pre-progression on treatment’, ‘pre-progression off treatment’, ‘post progression’, ‘terminal care’ and ‘death’, as shown in figure 3. The “on treatment” state was determined by the area under parametric time-on-treatment curves. The “pre-progression off treatment” and “post-progression” states were informed by the parametric survival curve analysis of progression-free and overall survival data.

**Figure 3 Economic model health states and structure (Figure 16, page 154 of company submission).**




### ERG comments

5.4 The ERG noted that the model structure was appropriate and captured the features of the disease.

## *Model details*

### Clinical parameters

5.5 The company modelled the patient population of Study 116 for the base case analysis. All patients in the model had received a median of 3 prior therapies and were not eligible to receive cytotoxic-containing therapies. In addition a greater proportion of patients in the trial had a 17p deletion or TP53 mutation.

5.6 To inform the clinical parameters for idelalisib plus rituximab compared with ofatumumab monotherapy the company assumed equal efficacy for rituximab and ofatumumab. The company explained that this assumption reflected the results of the ORCHARRD study which is a network meta-analysis conducted in patients with diffuse large B-cell lymphoma which found no difference in efficacy between ofatumumab compared with

rituximab. The company also assumed equal efficacy for rituximab and best supportive care because there was insufficient data available to model this comparator.

5.7 To inform the model transition probabilities the company extrapolated the overall survival data beyond the trial cut-off. The company used the cross over adjusted overall survival data from Study 116 (patients could crossover from the rituximab monotherapy group to receive idelalisib [see section 4.9]). The cross over adjusted hazard ratio for overall survival was [redacted].

5.8 The company examined a number of parametric survival curves (exponential, Weibull, log-logistic and log-normal) to extrapolate the overall survival data. Each parametric model it fitted was compared with the observed data. The company used the Akaike Information Criterion statistic (an indication of the statistical fit between the observed KM data and the parametric model estimates) to assess the most appropriate functional form. The results of the analyses showed that the exponential model provided the most appropriate fit, followed by the Weibull. The company explained that, on inspection of the model, 5% of patients were still alive after 20 years which it deemed inappropriate. The company therefore chose the Weibull model, as the next best fit, to extrapolate the overall survival data.

5.9 The company explained that progression free survival data did not need to be adjusted for cross over before extrapolation because disease progression in the trial was the main reason for patient switches into idelalisib treatment from the rituximab monotherapy group of Study 116. The Akaike Information Criterion statistic suggested the Weibull model was the most appropriate curve to use to extrapolate beyond the trial data.

5.10 The company used time-on-treatment data from Study 116 to estimate the drug resource use for treating patients with idelalisib in the ‘pre-

progression on treatment state'. In the trial idelalisib was indicated to be taken until disease progression or unacceptable toxicity therefore the company noted that time-on-treatment followed a similar course to progression free survival. To extrapolate the data it determined that a Cox proportional hazards model should be used to calculate a hazard ratio for time-on-treatment compared with progression free survival (Hazard Ratio [HR] 1.31). It then applied this HR to the progression free survival curve for idelalisib plus rituximab to derive a time-on-treatment curve. For consistency the company used the same HR to estimate a time-on-treatment curve for the rituximab monotherapy arm of Study 116.

5.11 The company used the overall response rates reported in Study 116 to inform resource use assumptions in the model. Overall response rates in the idelalisib arm of the trial was 84%, and in the rituximab arm 15%. For the base case comparison to best supportive care, patients were assumed to have no overall response. For the base case comparison to ofatumumab, the overall response rates observed for rituximab plus placebo was applied.

***Additional comparators***

5.12 The company identified additional evidence from the literature for the additional comparators listed in the NICE scope. It selected those studies which reported overall survival and progression free survival so it could extrapolate the data over the model time horizon (see Table 4). No studies were identified for the comparison with chlorambucil or chlorambucil plus rituximab therefore the company assumed equal efficacy to bendamustine and bendamustine plus rituximab. It used the Weibull distribution and assumed the same shape parameter for rituximab monotherapy overall survival and progression free survival data extrapolation. The company validated the curves by visual inspection against the Kaplan-Meier data reported in the studies. In addition the company adjusted for differences in baseline characteristics between the different studies.

**Table 4 Summary of additional trial data used in the company analysis**

| Treatment Regimen | Median overall survival (months) | Median progression free survival (months) | Number of patients | Study Design |
|---|---|---|---|---|
| Fludarabine, cyclophosphamide and rituximab | 47 | 21 | 284 | Open-label, phase II study (Badoux 2011). |
| Bendamustine | 44 | 20 | 49 | Open label RCT (Niederle 2013) |
| Bendamustine + Rituximab | 34 | 15 | 78 | Open-label, phase II study (Niederle 2013) |
| Steroids + Rituximab | 31 | 12 | 29 | Single arm open label study (Pileckelyte 2011) |
| Ofatumuab | 15 | 6 | 79 | Single arm open label study (Wierda 2010) |

### Utilities

5.13 The company used EQ-5D data, collected alongside Study 166 to inform the utilities in the base case analysis for people in the 'pre-progression on treatment' state. It used a generalised estimation equation regression to determine whether there was a difference in quality of life between the study groups. No EQ-5D trial data were collected for patients 'post-progression' or 'post treatment discontinuation', therefore the company conducted a systematic literature review to identify studies reporting utilities for different chronic lymphocytic leukaemia health states. The company identified a range of studies which presented utilities for patients with chronic lymphocytic leukaemia. It chose to use Dretzke et al for the 'post-progression' and 'pre-progression off treatment' states. The company noted the study elicited utilities directly from a chronic lymphocytic leukaemia population which were reported in separate health states for pre and post-progressive disease. The company noted that utilities in the terminal care state were assumed to be equal to those in the post-progression state.

### *Adverse events*

5.14 For the base case analysis adverse event frequencies were derived from Study 116. The adverse events considered in the model were grade III or

IV events which occurred in at least 3% of patients in either treatment groups of Study 116. The company used a range of sources to inform the decrements used in the model (Table 5).

**Table 5 Summary of utility values for the cost-effectiveness analysis (Table 76, page 185 of company submission)**

| State | Utility value | Confidence interval | Justification |
|---|---|---|---|
| Progression-free, comparator | 0.75 | (0.72,0.78) | Study 116 EQ-5D data |
| IR treatment utility effect | 0.07 | (0.03,0.11) | |
| PFS Off treatment | 0.80 | (0.63,0.93) | From NICE technology appraisal guidance 193 (Rituximab for the treatment of relapsed of refractory CLL). |
| PPS | 0.60 | (0.48,0.71) | |
| **Adverse Events** | **Utility Decrement** | **Confidence interval** | **Justification** |
| Anaemia | -0.09 | (-0.07,-0.11) | NICE technology appraisal guidance 216 (bendamustine for the first-line treatment of CLL) |
| Febrile Neutropenia | -0.20 | (-0.16,-0.23) | Assumed equal to infection disutility |
| Sepsis | -0.20 | (-0.16,-0.23) | Assumed equal to infection disutility |
| Neutropenia | -0.16 | (-0.13,-0.2) | Tolley et al |
| Pneumonia | -0.20 | (-0.16,-0.23) | Assumed equal to infection disutility |
| Thrombocytopenia | -0.11 | (-0.09,-0.13) | Tolley et al. |
| Diarrhoea + Colitis | -0.20 | (-0.16,-0.23) | Assumed to be the same as febrile neutropenia (based on clinical advice) |
| **Key:** IR, idelalisib with rituximab; PFS, progression free survival; PPS, post progression survival. | | | |

## Costs

5.15 The company used the time-on-treatment curves (see section 5.10) from Study 116 to estimate the length of time patients would receive idelalisib plus rituximab and rituximab monotherapy in the pre-progression 'on treatment' state. The company used the same dosing regimen from Study 116 for idelalisib plus rituximab and rituximab monotherapy. For the other comparators it used the dosing regimens indicated in the product licence and assumed all patients in the model would receive the maximum dose and complete a full course of treatment.

5.16 The company used the Monthly Index of Medical Specialties (MIMS), and administration costs from 2012-13 NHS references costs to inform the costs in the model. The costs of the required weekly dosing regimens, determined by a patient's body surface area, used the mean pre-treatment body surface area of patients in Study 116. For all regimens except idelalisib with rituximab patients were assumed not to be treated beyond the maximum number of treatment cycles recommended by guidance documents. Idelalisib is taken until disease progression or unacceptable toxicity. For comparators outside of the base case analysis, treatment costs were applied to the pre-progressive disease proportion of the model cohort up to the maximum treatment duration. The unit costs associated with adverse events were taken from the 2012-13 NHS Reference Costs. The total cycle costs from the model are presented in table 6.

**Table 6 Total cost per drug cycle (Table 77, page 188 of company submission)**

| Regimen | Cycle type | Drug | Active Cycle Drug Costs | |
|---|---|---|---|---|
| | | | Each Component | Total by cycle type |
| Idelalisib + Rituximab | Initial cycle | Idelalisib | [redacted] | [redacted] |
| | | Rituximab | £1,257 | |
| | Subsequent cycles | Idelalisib | [redacted] | [redacted] |
| | | Rituximab | £1,676 | |
| Rituximab | Initial cycle | Rituximab | £1,257 | £1,257 |
| | Subsequent cycles | Rituximab | £1,676 | £1,676 |
| Fludarabine, cyclophosphamide and Rituximab | Initial cycle | Fludarabine | £446 | £1,727 |
| | | Cyclophosphamide | £24 | |
| | | Rituximab | £1,257 | |
| | Subsequent cycles | Fludarabine | £446 | £2,145 |
| | | Cyclophosphamide | £24 | |
| | | Rituximab | £1,676 | |
| Bendamustine | All cycles | Bendamustine | £1,062 | £1,062 |
| Bendamustine + rituximab | Initial cycle | Bendamustine | £744 | £2,000 |
| | | Rituximab | £1,257 | |
| | Subsequent cycles | Bendamustine | £744 | £2,419 |
| | | Rituximab | £1,676 | |
| Chlorambucil | | Chlorambucil | £113 | £113 |
| Chlorambucil + rituximab | Initial cycle | Chlorambucil | £109 | £1,366 |
| | | Rituximab | £1,257 | |
| | Subsequent cycles | Chlorambucil | £109 | £1,785 |
| | | Rituximab | £1,676 | |
| Steroids + rituximab | Initial cycle | Methylprednisolone | £1,367 | £3,881 |
| | | Rituximab | £2,513 | |
| | Second cycle | Methylprednisolone | £1,367 | £4,719 |
| | | Rituximab | £3,351 | |
| | Subsequent cycles | Methylprednisolone | £1,367 | £3,043 |
| | | Rituximab | £1,676 | |
| Ofatumumab | Initial cycle | Ofatumumab | £546 | £546 |
| | Subsequent cycles | Ofatumumab | £3,640 | £3,640 |

**Table 7 Costs associated with treatment-emergent adverse events (Table 86, page 200 of company submission)**

| Adverse Event | 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: HRGs, health related groups. | | |

5.17 The company assumed, based on expert advice, that the use of Intravenous immunoglobulin therapy would be applied to 45% of non-responders and 0% of responders in the 'pre progression' health states. The company estimated that the cost of IVIG was £13,706. This combined the acquisition cost and administration cost of 5 weekly infusions.

### ERG comments

5.18 The ERG noted the assumption made by the company that treatment effects continue beyond the trial. The ERG acknowledged that the treatment benefits of idelalisib may continue beyond the time horizon of the trial but it would be unlikely to continue for the rest of a patient's life. It noted that any reduction in treatment benefit following a discontinuation could result in a smaller treatment benefit for idelalisib with rituximab compared to its comparators.

5.19 The ERG highlighted a possible issue with the methodology used by the company to adjust for crossover in the trial. The ERG noted the company's analysis relies on the assumption that idelalisib has equal efficacy with idelalisib plus rituximab. It noted that a lower efficacy for idelalisib monotherapy would result in a lower treatment benefit for idelalisib plus rituximab compared with rituximab and the magnitude of

this change will only be substantial if idelalisib monotherapy is considered inferior to idelalisib with rituximab.

5.20 The ERG commented on the use of the constant shape parameter for the survival curves for the additional treatments. It noted that the company could have fitted survival models directly using the digitised Kaplan-Meier plots they generated. The ERG noted that this would help the extrapolation for the FCR data, where the model (assuming a constant shape) was a poor fit for the data. In addition, the ERG questioned why the company had chosen to use hazard ratios from Badoux et al to adjust for baseline differences in their extrapolations instead of the other studies identified in the literature review.

5.21 The ERG highlighted that utilities for patients who had discontinued treatment (taken from Dretzke et al) were higher than for those patients being treated with rituximab. It noted that this difference was more than could be explained by the adverse event disutilities calculated from Study 116. This meant patients discontinuing from idelalisib treatment maintained a higher quality of life than those still being treated with rituximab (an assumption not justified in the company submission) Finally, It noted that for all other treatment options considered (ofatumumab, best supportive care, FCR etc.) the company assumed they had the same pre-progression utilities as rituximab, and therefore a lower on treatment utility than idelalisib. The ERG noted that no justification was given for setting the utilities to be equal to the lower rituximab utility rather than the higher idelalisib utility.

5.22 The ERG noted that in the company's base case, costs for idelalisib, rituximab and ofatumumab were accrued until treatment discontinuation, whilst for other comparators patients were assumed to complete the full maximum dosing indicated for that product. The ERG note a more realistic approach would be to use time-on-treatment data from Study 116 to estimate the proportion of the maximum number of doses actually

administered for rituximab monotherapy, in the same way as was done for idelalisib, and apply the costs to these estimated time-on-treatment data.

5.23 The ERG noted concerns with the assumptions on frequency of resource use parameters, with specific concerns about the amount of patients who did not respond to treatment being given IVIG therapy. The ERG note that this is important because the biggest difference in clinical outcomes between idelalisib plus rituximab and rituximab monotherapy was the ORR. This meant that the clinical assumptions made in the model resulted in considerably higher disease management costs for patients on rituximab than those on idelalisib plus rituximab.

## *Company's base-case results and sensitivity analysis*

5.24 The company presented the results of the base case analysis using the proposed discount price for idelalisib.

**Table 8 Base case results (Tables 89-91, page 214 of company submission)**

| **Idelalisib with rituximab compared with rituximab** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **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 |
| **Idelalisib with rituximab compared with best supportive care** | | | | | | | |
| | **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 |
| **Idelalisib with rituximab compared with 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; QALYs, quality adjusted life year | | | | | | | |

5.25 The company conducted a range of deterministic sensitivity analyses on the base case parameters. The results showed that the survival curve parameter estimates had the greatest influence on the results.

**Figure 4 Tornado diagram showing one way sensitivity analysis results, idelalisib plus rituximab compared to rituximab plus placebo (Figure 43, page 230, of company submission)**

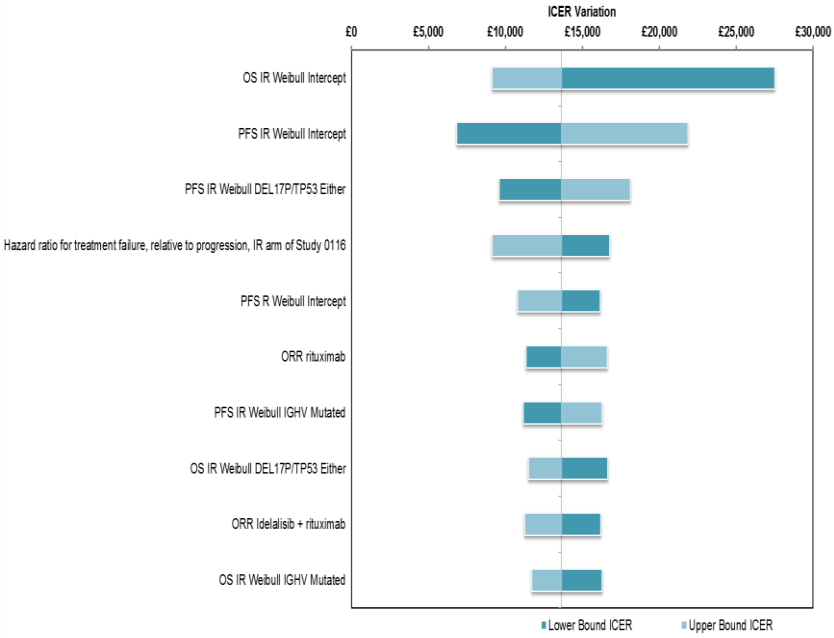



**Figure 5 Tornado diagram showing one way sensitivity analysis results, idelalisib plus rituximab compared to best supportive care (Figure 44, page 230, of company submission)**

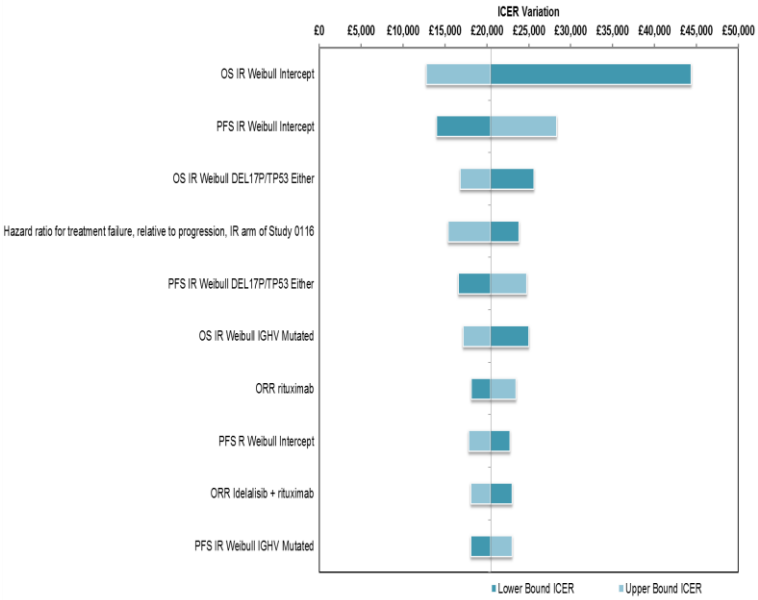
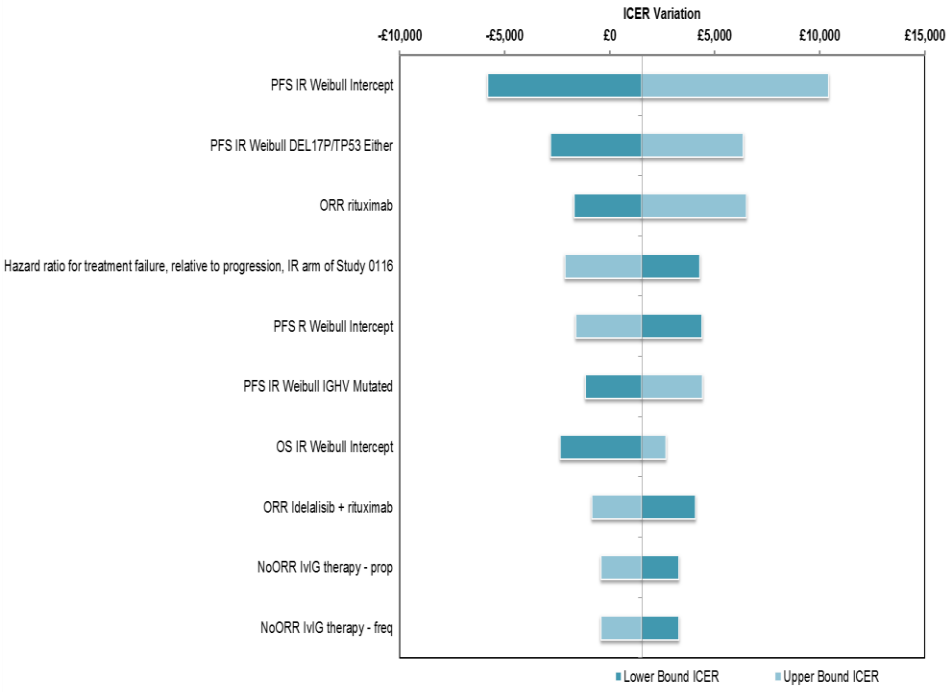


**Figure 6 Tornado diagram showing one way sensitivity analysis results, idelalisib plus rituximab compared to ofatumumab (Figure 45, page 232, of company submission)**




5.26 The company conducted a probabilistic sensitivity analysis for the base case parameters. The company presented scatter plots and cost effectiveness acceptability curves for the 3 base case comparisons. The results showed idelalisib with rituximab was cost-effective with a 90% probability compared with rituximab monotherapy, an 80% probability compared with best supportive care and a 100% probability compared with ofatumumab monotherapy at a willingness to pay threshold of £30,000 per QALY gained.

5.27 The company conducted a range of scenario analyses on the base case assumptions. These included examining a range of different time horizons, health state utility estimates, functional forms of the overall survival extrapolation curve, and various assumptions around costs. The results showed that decreases in the time horizon, the use of alternative utility estimates, the exclusions of time-on-treatment data from Study 116 and the removal of terminal care costs all increased the ICER for idelalisib

with rituximab compared with rituximab, whilst the use of the exponential model for overall survival reduced the ICER.

5.28 The company examined the effect of a discounted cost of ofatumumab in the base case analysis (see Table 9). The results showed that if a selection of discounts was applied, the ICER for idelalisib plus rituximab would remain below £20,000 per QALY gained compared with ofatumumab monotherapy up to a discount of 75%.

**Table 9 Sensitivity of ICER using an ofatumumab price discount (Table 117, page 239 of company submission)**

| Ofatumumab Price Discount | ICER versus ofatumumab |
|---|---|
| 0% | £1,527 |
| 25% | £5,973 |
| 50% | £10,419 |
| 75% | £14,866 |
| **Key:** ICER, incremental cost effectiveness ratio | |

## *Company scenarios*

### Additional comparators

5.29 The results of the comparison of idelalisib plus rituximab (using the proposed discount price for idelalisib) for the additional comparators in the NICE scope are presented in Table 7.

**Table 7 Exploratory comparison to treatments outside of Study 116, using external clinical data (Table 118, page 241 of company submission)**

| Comparator | Costs | Life Years | QALYs | Incremental (IR) | | | ICER (compared to IR) |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| FCR | [redacted] | 0.53 | 0.40 | £63,232 | 4.10 | 2.41 | £26,215 |
| B | [redacted] | 2.08 | 1.44 | £49,677 | 2.55 | 1.36 | £36,424 |
| BR | [redacted] | 1.68 | 1.17 | £35,910 | 2.95 | 1.64 | £21,910 |
| Chl | [redacted] | 1.72 | 1.14 | £55,471 | 2.91 | 1.67 | £33,224 |
| Chl+R | [redacted] | 1.38 | 0.92 | £66,267 | 3.25 | 1.89 | £35,082 |
| Steroids+R | [redacted] | 2.08 | 1.42 | £23,689 | 2.55 | 1.38 | £17,106 |
| Ofatumumab | [redacted] | 1.17 | 0.85 | £8,323 | 3.46 | 1.96 | £4,254 |
| Key: B, bendamustine; Chl, chlorambucil; FCR, fludarabine, cyclophosphamide and rituximab; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; R, rituximab | | | | | | | |

### Subgroup analyses

5.30 The company presented a subgroup analysis for patients in Study 116 with a 17p deletion or TP53 mutation. The results of the analysis showed an increase in the ICERs for the three base case comparators: £20,200 per QALY gained for the comparison with rituximab, £27,543 per QALY gained for the comparison with best supportive care and £7,066 per QALY gained for the comparison with ofatumumab. For further details see page 242 of the company submission.

### ERG comments

5.31 The ERG noted that because no attempt was made to account for differences in the study population to patients in the UK the results of the company analyses could be uncertain. In addition it noted that the plausibility of the results may be affected by the assumption that ofatumumab and best supportive care are assumed to have equal efficacy to rituximab monotherapy. Finally the ERG stated that even though the methodology used to conduct the analysis for the other comparators in the NICE scope were less reliable than those from a formal evidence synthesis, many of these comparators are used in the UK and therefore results from these analyses (with appropriately conservative assumptions) are important for understanding the cost-effectiveness of idelalisib compared with other available treatments.

## *ERG exploratory analyses*

5.32 The ERG conducted an exploratory analysis examining the following:

- Health state utilities for the pre-progression and post-progression states: Using the Dretzke et al. utilities and adverse events disutilities applied to the frequency of adverse events in Study 116.
- Time on treatment: Using the time-on-treatment data for rituximab monotherapy to inform estimated drug costs rather than assuming all patients complete the full course. For treatments outside Study 116

patients were assumed to take the same proportion of the maximum dosing duration as for rituximab monotherapy in Study 116.

- Fludarabine, cyclophosphamide and rituximab survival curve: Using the statistically best fitting survival curve for fludarabine, cyclophosphamide and rituximab, rather than using the constant shape parameter with the rituximab monotherapy curve.
- Duration of treatment benefit: The duration of treatment benefit for agents other than rituximab was assumed to be 5 years.

**Table 11 ERG exploratory analyses (Tables 50-53, page 109-110 of ERG report)**

| Scenario | Total cost | Total QALY | Inc. cost | Inc. QALY | ICER |
|---|---|---|---|---|---|
| Idelalisib plus rituximab (ERG base case) | [redacted] | 2.35 | | | |
| **Comparators compared idelalisib plus rituximab (ERG base case)** | | | | | |
| Rituximab | [redacted] | 0.91 | £24,335 | 1.44 | £16,947 |
| BSC | [redacted] | 0.91 | £37,418 | 1.44 | £26,058 |
| Ofatumumab (base case) | [redacted] | 0.91 | £1,132 | 1.44 | £788 |
| FCR | [redacted] | 0.24 | £71,177 | 2.11 | £33,795 |
| Bendamustine | [redacted] | 1.42 | £48,821 | 0.92 | £52,815 |
| Bendamustine + rituximab | [redacted] | 1.16 | £34,921 | 1.18 | £29,548 |
| Chlorambucil[a] | [redacted] | 1.13 | £53,779 | 1.21 | £44,315 |
| Chlorambucil[b] + rituximab | [redacted] | 0.92 | £64,893 | 1.43 | £45,445 |
| Steroids + rituximab | [redacted] | 1.40 | £22,751 | 0.95 | £24,065 |
| Ofatumumab [c] | [redacted] | 0.85 | £8,006 | 1.49 | £5,355 |

Abbreviations: BSC, best supportive care. Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio

[a] Assumption – no evidence available

[b] Assumption – no evidence available

[c] Ofatumumab – evidence of effectiveness from literature.

5.33 In addition to the changes made to the base case analysis the ERG undertook an additional analysis exploring the frequency of intravenous immunoglobulin therapy for responders and non-responders. In the company's model, no IVIG therapy was given for responders, whilst 45% of non-responders required 1.24 cycles per month. The impact on the ICER for two comparators (rituximab monotherapy and bendamustine

monotherapy) is shown in tables 12 and 13. The results show the ICER is sensitive to the changes in the frequency of intravenous immunoglobulin therapy.

**Table 12 Impact of frequency of IVIG therapy on ICER; Idelalisib plus rituximab compared with rituximab (Table 54, page 110, of ERG report)**

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

**Table 13 Impact of frequency of IVIG therapy on ICER; Idelalisib plus rituximab compared with bendamustine (Table 55, page 110 of ERG report)**

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

5.34 The second additional sensitivity analysis undertaken by the ERG concerned the adjustment factors used to account for baseline differences in study populations, when comparing idelalisib with treatments not in Study 116. The results showed that these factors have a minimal impact on the ICERs.

## *Innovation*

5.35 Justifications for considering idelalisib to be innovative:

- For relapsed or refractory chronic lymphocytic leukaemia: The company explained that idelalisib offers a step change in the management of chronic lymphocytic leukaemia. It's reasons include that it significantly and substantially improves the way that current need

is met. It notes that it meets a need which the NHS has identified as being important. It stated that idelalisib has a robust evidence base, providing research on the populations in which the product is effective, and has demonstrated an appropriate level of effectiveness.

- For untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation the company consider idelalisib to be innovative because there are currently no treatment options available for these patients and the results of the evidence submitted show a clear treatment benefit.

# 6 End-of-life considerations

6.1 The company presented evidence to support making a case for end of life criteria in its submission. The evidence is presented in table 14.

**Table 14 End-of-life considerations (Table 56, page 146 of company submission)**

| **Criterion** | **Data available** |
|---|---|
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | **For relapsed chronic lymphocytic leukaemia patients**:<br>RPSFT analysis: **Mean overall survival** in Study 116 (from restricted means analysis):<br>• Idelalisib plus rituximab: [redacted])<br>• Rituximab: [redacted]<br>**For untreated patients:**<br>• Results not available for the 17p deletion / TP53 population as no deaths seen during the trial |
| 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 chronic lymphocytic leukaemia patients**:<br>RPSFT analysis: **Mean overall survival** in Study 116 (from restricted means analysis):<br>• Idelalisib plus rituximab: [redacted])<br>• Rituximab: [redacted] |
| The treatment is licensed or otherwise indicated for small patient populations | **Chronic lymphocytic leukaemia indications**:<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>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>Based on data published by Cancer Research UK using the Haematological Malignancy Research Network (HMRN) the estimated yearly number of FL patients in England and Wales is 1,677. The number requiring treatment at third line and subsequent settings is 384. |

**ERG comments**

6.2 The ERG noted that the company chose to use the restricted means analysis from Study 116 to inform the first and second criteria for end of life considerations. The ERG stated that it would be more consistent to use the economic model to inform the life expectancy. The ERG noted that the model showed the mean undiscounted life years for rituximab plus placebo is 1.39 and 4.63 years for idelalisib plus rituximab. It also noted that the mean undiscounted life years for bendamustine (which could be considered a more relevant treatment for a UK population) was 2.08.

# 7 Equality issues

7.1 No equality issues were identified at consultation or during the scoping workshop.

# 8 Authors

**Victoria Kelly**
Technical Lead

**Sally Doss**
Technical Adviser

with input from the Lead Team (Judith Wardle, Stephen O'Brien and Paul Miller).

# Appendix A: Clinical efficacy section of the draft European public assessment report

8.1 A copy of the EPAR can be found at the following link: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003843/WC500175379.pdf