NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Idelalisib for treating chronic lymphocytic leukaemia

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using idelalisib in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using idelalisib in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 9th July 2015

Second Appraisal Committee meeting: 22nd July 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Idelalisib, in combination with rituximab, is not recommended:

- for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or
- for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed.

1.2 The Committee is minded not to recommend idelalisib, in combination with rituximab, for chronic lymphocytic leukaemia in adults whose disease is refractory and retreatment with previous regimens is not considered appropriate.

1.3 The Committee recommends that NICE requests further analyses from the company, which should be made available for the second Appraisal Committee meeting, and should include:

- a revised cost-effectiveness analysis for the comparison of idelalisib plus rituximab with rituximab alone, best supportive care and ofatumumab incorporating the changes made to the company model (see sections 3.48-3.50):
  - Reducing the length of treatment benefit for idelalisib plus rituximab to 5 years
  - Using utility values from Dretzke et al. (2010) for both the pre-progression and post-progression model states
- A sensitivity analysis exploring the length of treatment benefit of idelalisib plus rituximab from treatment discontinuation up to 5 years

- A sensitivity analysis exploring the effects of reducing the proportion of non-responders having intravenous immunoglobulin from 45% to 20% or less and increasing the number of responders having intravenous immunoglobulin from 0% to 20%
- A sensitivity analysis exploring the effect of using clinical effectiveness data from the subgroup of people in Study 116 whose disease is refractory.

1.4 People whose treatment with idelalisib was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Idelalisib (Zydelig, Gilead Sciences) is an inhibitor of enzymes that regulate important cellular functions including proliferation, cell death and migration. It has a marketing authorisation in the UK for use 'in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least 1 prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy'.

2.2 The summary of product characteristics lists the following adverse reactions to idelalisib, alone or with rituximab, as affecting more than 10% of patients: infections, neutropenia, diarrhoea, transaminase increase, rash, pyrexia and increased triglycerides. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dose and schedule in the summary of product characteristics is 150 mg taken orally, twice daily. Treatment is

continued until disease progression or unacceptable toxicity. Idelalisib is priced at £3114.75 for 60 150-mg tablets (British national formulary 2015). The mean cost of a 1-year treatment course for idelalisib is £37,922. The company has arranged a nationally available price reduction that provides a simple discount to the list price of idelalisib. The level of the discount is commercial in confidence.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Gilead Sciences and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness evidence

Systematic review

3.1 The company's systematic literature review identified 4 randomised controlled trials that were relevant to the decision problem because they included patients whose disease was relapsed and refractory. 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.

3.2 No randomised controlled trials were identified that investigated the effectiveness of idelalisib with rituximab in untreated chronic lymphocytic leukaemia in patients with a 17p deletion or TP53 mutation.

Previously treated chronic lymphocytic leukaemia (Study 116)

3.3 The company presented the results of Study 116, which was a phase III, double-blind, randomised controlled trial done across 90 centres in the US and Europe (including the UK). The study evaluated idelalisib plus rituximab compared with rituximab plus

placebo in people with chronic lymphocytic leukaemia. A total of 220 patients were randomised to have either idelalisib (150 mg oral tablets, twice daily) plus rituximab (375 mg/m^2 at week 0, then 500 mg/m^2 at weeks 2, 4, 6, 8, 12, 16 and 20) or rituximab (same dose) plus placebo (matching tablet, twice daily, until progression). Patients were included if they were aged 18 years or older, had previously had at least 1 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

3.4 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 was sooner). Definitive disease progression was defined using the criteria from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL). Secondary outcomes included rates of overall response (complete and partial), lymph-node response (defined as a decrease of 50% or more in lymphadenopathy) and overall survival. The primary and secondary end points were examined in pre-specified subgroups, which were: patients with a 17p deletion, TP53 mutation or both, and patients without a 17p deletion or TP53 mutation. 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.

3.5 Patients could cross over from the rituximab plus placebo group to having idelalisib plus rituximab in an extension study (Study 117) if their disease progression were confirmed by an independent review committee. The intention-to-treat analysis was done

according to the treatment to which patients were randomised, and this included patients who had crossed over to the idelalisib plus rituximab group of 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.

Results of Study 116

3.6 The company stopped the blinded phase of the trial after the first interim analysis, because the 2-sided p-value for the primary progression-free survival analysis crossed the prespecified alpha boundary of 0.001. All 110 patients in the idelalisib plus rituximab group and 107 of 110 in the rituximab plus placebo group had the assigned treatment. Of the 3 patients in the rituximab plus placebo group who did not have the study treatment, 2 withdrew from the study because of an adverse event and 1 had not had the study treatment before the data cut-off. The mean age of patients in the trial was 71 years. Between 41.8% and 44.5% of patients had a 17p deletion or TP53 mutation (or both), and 82.7% to 84.5% had an immunoglobulin variable region heavy chain non-mutation.

3.7 The results showed a statistically significant improvement in median progression-free survival for idelalisib plus rituximab compared with rituximab plus placebo of 19.4 months (95% confidence interval [CI] 21.3, not reported) compared with 6.5 months (95% CI 4.0 to 7.3). The reported hazard ratio (HR) was 0.15 (95% CI 0.09 to 0.24, p=<0.001). The intention-to-treat analysis for median overall survival showed a statistically significant difference for idelalisib plus rituximab compared with rituximab plus placebo (HR 0.34, 95% CI 0.19 to 0.60). The company also presented the results of the crossover-adjusted analysis but these were presented as academic in confidence.

3.8 In terms of secondary outcomes, 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 with rituximab was 27.76 (95% CI 13.4 to 57.49). No patients in the trial had a complete response, meaning that the overall response rate was entirely made up of partial responders. The lymph node response rate was 96.2% in the idelalisib plus rituximab group compared with 6.7% in the rituximab plus placebo group.

3.9 The company also presented the results for the prespecified subgroups. In patients without a 17p deletion or TP53 mutation, median progression-free survival was 19.4 months in the idelalisib plus rituximab group compared with 8.1 months in the rituximab plus placebo group. For people with a 17p deletion or TP53 mutation, progression-free survival was not reached in the idelalisib plus rituximab group. In the rituximab plus placebo group, median progression-free survival was 4.0 months.

3.10 Patients having idelalisib plus rituximab showed improvements in health-related quality of life, with the EQ-5D analysis showing a statistically significant treatment effect. The results of the FACT-Leu questionnaire also showed that patients in the idelalisib plus rituximab group had greater symptom improvement than patients in the rituximab group at each time point throughout the trial.

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

3.12 The company reported that 32 patients – 19 (17.3%) of those having idelalisib plus rituximab and 13 (12.0%) of those having rituximab plus placebo – discontinued treatment because of an adverse event. Infections and infestations occurred in 11 of the 32 patients who discontinued (5 having idelalisib plus rituximab and 6 having rituximab plus placebo) and gastrointestinal disorders occurred in 6. Respiratory, thoracic, and mediastinal disorders accounted for a further 6 patients discontinuing because of adverse events (3 having idelalisib plus rituximab and 3 having rituximab plus placebo).

3.13 The company noted that the most commonly reported adverse events in the idelalisib plus rituximab group 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 reactions (30.6%, 33).

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

3.14 Study 101-08 was a phase II, single-arm study of idelalisib plus rituximab in patients with untreated chronic lymphocytic leukaemia. A total of 64 patients were enrolled in centres across the US to have idelalisib (150 mg oral tablets, twice daily) and rituximab (375 mg/m^2 weekly, continuously for 48 weeks). Only a small subset of patients (n=9) had a 17p deletion or TP53 mutation.

3.15 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.

Results of Study 101-08

3.16 Of the 64 patients who were enrolled, 43 completed 48 weeks of treatment. The mean age of patients in the trial was 71 years. Only 9 of the 64 patients had a 17p deletion or TP53 mutation, and 37 had immunoglobulin heavy-chain variable-region non-mutated chronic lymphocytic leukaemia.

3.17 At 36 months no patients with a 17p deletion or TP53 mutation had a progression event. Progression-free survival for the overall population at 36 months was 83%. Overall survival at 36 months was 100% for the 17p deletion or TP53 mutation patients and 90% for the whole study population.

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

Evidence for other comparators listed in the NICE scope

3.19 In addition to the comparison of idelalisib plus rituximab compared with rituximab alone, best supportive care and ofatumumab, the company also submitted evidence for the other comparator technologies listed in the NICE scope, namely fludarabine cyclophosphamide plus rituximab, bendamustine with or without rituximab, chlorambucil with or without rituximab, and steroids plus rituximab. The company's systematic review did not identify any evidence directly comparing idelalisib with these comparators, but identified 3 randomised controlled trials and 9 non-randomised controlled trials in the relapsed and refractory population. No additional evidence was identified in the untreated population.

ERG comments

3.20 The ERG commented on the population of Study 116 and its applicability to people with chronic lymphocytic leukaemia in the UK (of the 220 patients enrolled, 32 were UK patients). It noted that the trial included some patients (43.2%) with a 17p deletion or TP53 mutation; 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, because it is neither recommended by NICE nor by the British Committee on Standards in Haematology guidance.

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

Cost-effectiveness evidence

Economic model structure

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

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

- fludarabine, cyclophosphamide and rituximab
- bendamustine
- bendamustine plus rituximab
- chlorambucil
- chlorambucil plus rituximab
- steroids plus rituximab.

3.24 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 years. A discount rate of 3.5% was applied to costs and health benefits and the analysis was done from an NHS and personal social services perspective.

3.25 The base-case analysis used data from Study 116. The model consisted of 5 health states, namely pre-progression on treatment, pre-progression off treatment, post progression, terminal care and death. 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.

Clinical parameters and assumptions

3.26 To inform the clinical parameters for idelalisib plus rituximab compared with ofatumumab, the company assumed equal efficacy for rituximab and ofatumumab. The company explained that this assumption reflected the results of the ORCHARRD study, a network meta-analysis in patients with diffuse large B-cell lymphoma which found no difference in efficacy between ofatumumab and rituximab. The company also assumed equal efficacy for rituximab and best supportive care because there were insufficient data available to model this comparator.

3.27 To inform the model transition probabilities, the company extrapolated the overall survival data beyond the trial cut-off. The company used the crossover-adjusted overall survival data from Study 116 (patients could crossover from the rituximab plus placebo group to instead have idelalisib plus rituximab). The company used the Akaike Information Criterion statistic (an indication of the statistical fit between the observed Kaplan–Meier 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.

3.28 The company explained that progression-free survival data did not need to be adjusted for crossover before extrapolation, because disease progression in the trial was the main reason for patients crossing over to the idelalisib plus rituximab group. The Akaike Information Criterion statistic suggested that the Weibull model was the most appropriate curve to use to extrapolate beyond the trial data.

3.29 The company used time-on-treatment data from Study 116 to estimate the drug resource use for idelalisib in the pre-progression on treatment state. In the trial, idelalisib was indicated to be taken until disease progression or unacceptable toxicity, so 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. This produced a hazard ratio of 1.31. It then applied this to the progression-free survival curve for idelalisib plus

rituximab to derive a time-on-treatment curve. For consistency, the company used the same hazard ratio to estimate a time-on-treatment curve for the rituximab plus placebo group of Study 116.

3.30 The company used the overall response rates reported in Study 116 to inform resource use assumptions in the model. The overall response rates were 84% in the idelalisib plus rituximab group and 15% in the rituximab plus placebo group. For the comparison with best supportive care, patients were assumed to have no overall response. For the comparison with ofatumumab, the overall response rate for rituximab plus placebo was applied.

Other comparators listed in the NICE scope

3.31 The company identified additional evidence from the literature for the other comparators listed in the NICE scope (table 1). It selected those studies which reported overall survival and progression-free survival so it could extrapolate the data over the model time horizon. No studies were identified for the comparison with chlorambucil or chlorambucil plus rituximab, so the company used data from a published phase III trial (Knauf et al) in patients with untreated chronic lymphocytic leukaemia and applied the reported hazard ratios to the bendamustine and bendamustine plus rituximab survival curves. The company used the Weibull distribution for extrapolation of overall survival and progression-free survival data and assumed the same constant shape parameter for rituximab when used alone. The company validated the curves by visual inspection against the Kaplan–Meier data reported in the studies. It also adjusted for differences in baseline characteristics between the different studies.

Table 1 Results of the studies used to inform the company's additional comparator 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 randomised controlled trial (Niederle 2013)
Bendamustine plus rituximab	34	15	78	Open-label, phase II study (Niederle 2013)
Steroids plus rituximab	31	12	29	Single-arm open-label study (Pileckelyte 2011)
Ofatumumab	15	6	79	Single-arm open-label study (Wierda 2010)

Utility values and adverse events

3.32 The company used EQ-5D data collected alongside Study 116 to inform the utility values for patients 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. The company also assumed that utility values in the terminal care state were equal to those in the post-progression state. However, no EQ-5D trial data were collected for patients in the post-progression or post-treatment discontinuation states, so the company conducted a systematic literature review to identify studies reporting utility values for different chronic lymphocytic leukaemia health states. The company identified a range of studies, and chose to use Dretzke et al. (2010) for the post-progression and pre-progression off treatment states.

3.33 The company derived adverse event frequencies directly from Study 116. Those considered in the model were grade 3 or 4

events which occurred in at least 3% of patients in either treatment groups of Study 116.

Resource use and costs

3.34 The company used the time-on-treatment curves from Study 116 to estimate the length of time patients would have idelalisib plus rituximab and rituximab alone in the pre-progression on treatment state. The company used the same dosing regimen from Study 116 for idelalisib plus rituximab and rituximab alone. For the other comparators it used the dosing regimens indicated in the product licence and assumed that all patients in the model would have the maximum dose and complete a full course of treatment.

3.35 Based on expert advice, the company assumed that intravenous immunoglobulin therapy would be used in 45% of non-responders and 0% of responders in the pre-progression health states. The company estimated that the cost of intravenous immunoglobulin therapy, incorporating the acquisition cost and administration of 5 weekly infusions, was £13,706.

Company's base-case results and sensitivity analyses

3.36 When using the nationally available price reduction, treatment with idelalisib plus rituximab was associated with higher costs and greater quality-adjusted life year (QALY) gains compared with rituximab alone. Using the nationally available price reduction, the deterministic incremental cost-effectiveness ratio (ICER) for idelalisib plus rituximab compared with rituximab alone was £13,634 per QALY gained (incremental costs £26,128; incremental QALYs 1.92). Compared with best supportive care, the ICER for idelalisib plus rituximab was £20,461 per QALY gained (incremental costs £39,211; incremental QALYs 1.92). Compared with ofatumumab, the ICER was £1527 per QALY gained (incremental costs £2926; incremental QALYs 1.92).

3.37 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.

3.38 The company conducted a probabilistic sensitivity analysis for the base-case parameters, presenting scatter plots and cost-effectiveness acceptability curves for the 3 base-case comparisons. The results showed that idelalisib plus rituximab was cost effective with a 90% probability compared with rituximab alone, an 80% probability compared with best supportive care, and a 100% probability compared with ofatumumab (at a maximum acceptable ICER of £30,000 per QALY gained). The mean probabilistic ICER for the comparison of idelalisib plus rituximab with rituximab alone was £13,680 per QALY gained. For idelalisib plus rituximab compared with ofatumumab, the mean probabilistic ICER was £1692 per QALY gained; for the comparison with best supportive care, it was £20,021 per QALY gained. The mean probabilistic ICER for the comparison of idelalisib plus rituximab with rituximab alone was £13,680 per QALY gained. For the comparison with ofatumumab the mean probabilistic ICER was £1692 per QALY gained and for the comparison with best supportive care, £20,021 per QALY gained.

Company's exploratory scenarios

3.39 When using the nationally available price reduction for idelalisib, treatment with idelalisib plus rituximab was associated with both higher costs and greater QALY gains compared with:

- fludarabine, cyclophosphamide and rituximab: £26,215 per QALY gained (incremental costs £63,232; incremental QALYs 2.41).

- bendamustine: £36,424 per QALY gained (incremental costs £49,677; incremental QALYs 1.36).
- bendamustine plus rituximab: £21,910 per QALY gained (incremental costs £35,910; incremental QALYs 1.64).
- chlorambucil: £33,224 per QALY gained (incremental costs £55,471; incremental QALYs 1.67).
- chlorambucil plus rituximab: £35,082 per QALY gained (incremental costs £66,267; incremental QALYs 1.89).
- steroids plus rituximab: £17,106 per QALY gained (incremental costs £23,689; incremental QALYs 1.38).
- ofatumumab (clinical effectiveness from literature): £4,254 per QALY gained (incremental costs £8232; incremental QALYs 1.96).

3.40 The company presented a subgroup analysis for patients in Study 116 with a 17p deletion or TP53 mutation. The results showed an increase in the ICERs for all 3 base-case comparators: £20,200 per QALY gained for the comparison with rituximab alone, £27,543 per QALY gained for the comparison with best supportive care and £7066 per QALY gained for the comparison with ofatumumab.

ERG comments

3.41 The ERG noted the company's assumption 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 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 with the other regimens.

3.42 The ERG highlighted a possible issue with the company's methodology to adjust for crossover in the trial, noting that the

company's analysis relies on the assumption that idelalisib alone has equal efficacy to idelalisib plus rituximab. It stated that a lower efficacy for idelalisib alone would result in a lower treatment benefit for idelalisib plus rituximab compared with rituximab and the magnitude of this change would only be substantial if idelalisib alone is considered inferior to idelalisib plus rituximab.

3.43 The ERG commented on the company's use of the constant shape parameter for the survival curves for the other treatments. It noted that the company could have fitted survival models directly using the digitised Kaplan–Meier plots that were generated. The ERG noted that this would improve the extrapolation for the fludarabine, cyclophosphamide and rituximab 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 its extrapolations instead of the other studies identified in the literature review.

3.44 The ERG noted that in the company's base case, costs for idelalisib, rituximab and ofatumumab were accrued until treatment discontinuation, but for other comparators patients were assumed to complete the full maximum dosing indicated for that product. The ERG stated that 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.

3.45 The ERG noted that because no attempt was made to account for differences between the study populations and UK patients, the results of the company's analyses may be uncertain. In addition, it noted that the plausibility of the results may be affected by assuming that ofatumumab and best supportive care have equal

efficacy to rituximab alone. Finally, the ERG stated that even though the methodology used to conduct the analyses for the other comparators in the NICE scope was less reliable than that used in the formal evidence synthesis, many of the comparators are used in the UK and therefore results from these analyses (with appropriately conservative assumptions) are important to understanding the cost-effectiveness of idelalisib compared with other available treatments.

3.46 The ERG raised concerns with the assumptions relating to the frequency of resource use parameters, specifically about the number of patients whose disease did not respond to treatment being given intravenous immunoglobulin therapy. The ERG noted that this is important because the biggest difference in clinical outcomes between idelalisib plus rituximab and rituximab alone was the overall response rate. This meant that the clinical assumptions made in the model resulted in considerably higher disease management costs for patients having rituximab alone than those having idelalisib plus rituximab.

3.47 The ERG highlighted that utility values for patients who had discontinued treatment (taken from Dretzke et al.) were higher than those for patients having rituximab. It noted that this difference was more than could be explained by the adverse event disutilities calculated from Study 116, and meant that patients discontinuing idelalisib maintained a higher quality of life than those still having rituximab (an assumption not justified in the company submission)

ERG exploratory analyses

3.48 The ERG conducted an exploratory analysis changing the following parameters:

- Using the Dretzke et al. utility values to inform both the pre-progression and post-progression model states, instead of those collected alongside Study 116 for the pre-progression state.
- Using time-on-treatment data for rituximab monotherapy to inform estimated drug costs rather than assuming that all patients completed the full course. For treatments outside Study 116, patients were assumed to take the same proportion of the maximum dosing duration as for rituximab alone in Study 116.
- Using the statistically best fitting survival curve for fludarabine, cyclophosphamide and rituximab, rather than using the constant shape parameter with the curve for rituximab alone, as used in the company model.
- Changing the length of treatment benefit for agents other than rituximab to 5 years.

3.49 Applying the nationally available price reduction for idelalisib, treatment with idelalisib plus rituximab was associated with higher costs and greater QALY gains compared with:

- rituximab: £16,947 per QALY gained (incremental costs £24,335; incremental QALYs 1.44).
- best supportive care: £26,058 per QALY gained (incremental costs £37,418; incremental QALYs 1.44).
- ofatumumab (base case): £788 per QALY gained (incremental costs £1132; incremental QALYs 1.44).
- fludarabine, cyclophosphamide and rituximab: £33,795 per QALY gained (incremental costs £71,177; incremental QALYs 2.11).
- bendamustine: £52,815 per QALY gained (incremental costs £48,821; incremental QALYs 0.92).
- bendamustine plus rituximab: £29,548 per QALY gained (incremental costs £34,921; incremental QALYs 1.18).

- chlorambucil: £44,315 per QALY gained (incremental costs £53,779; incremental QALYs 1.21).
- chlorambucil plus rituximab: £45,445 per QALY gained (incremental costs £64,893; incremental QALYs 1.43).
- steroids plus rituximab: £24,065 per QALY gained (incremental costs £22,751; incremental QALYs 0.95).
- ofatumumab (clinical effectiveness from literature): £5355 per QALY gained (incremental costs £8006; incremental QALYs 1.49).

3.50 The ERG did an additional analysis exploring the frequency of intravenous immunoglobulin therapy for patients whose disease responds to treatment compared with patients whose disease does not respond. In the company's model, 45% of patients whose disease does not respond had 1.24 cycles of intravenous immunoglobulin therapy. Patients whose disease does respond had none at all. The ERG explored increasing the number of cycles to responders and decreasing the number of cycles for non-responders. The results showed that the ICER was sensitive to the changes; when responders had 0.5 cycles of intravenous immunoglobulin and non-responders had 1.0 cycle, the ICER for idelalisib with rituximab compared with rituximab alone increased from £16,947 per QALY gained to £52,369 per QALY gained.

3.51 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of idelalisib, having considered evidence on the nature of chronic lymphocytic leukaemia and the value placed on the benefits of idelalisib by people with the

condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee discussed the current clinical management of chronic lymphocytic leukaemia. The Committee heard from the clinical experts that treatment options for disease which has been previously treated depends on the person's suitability for certain treatments, the treatments they have already had and the time since the last disease relapse. The clinical experts advised that re-treatment is offered to people for whom fludarabine-based regimens (such as fludarabine, cyclophosphamide and rituximab) were suitable, and whose disease had not relapsed at least 6 months after, but within 24 months of treatment. For people for whom fludarabine-based therapy is unsuitable and who already had therapy with alkylating agents (such as bendamustine or chlorambucil, with or without rituximab), and whose disease had not relapsed at least 6 months after but within 24 months of treatment, a further course of the same treatment is offered. The clinical experts noted that in people with previously treated disease that had relapsed within 6 months, treatment options were rituximab or best supportive care. Alternatively these people may be considered for inclusion in a clinical trial of a novel therapy. The Committee discussed the clinical management of untreated chronic lymphocytic leukaemia in people with a 17p deletion or TP53 mutation. It heard from the clinical experts that people with this type of disease have very limited treatment options, which can include high-dose pulsed steroids with alemtuzumab. The Committee concluded that more treatment options are needed.

4.2 The Committee considered the population in the marketing authorisation which included people with chronic lymphocytic

leukaemia whose disease has been previously treated. The Committee discussed whether there were different subgroups in the population of people with previously treated chronic lymphocytic leukaemia that should be considered separately. It noted that the British Committee for Standards in Haematology defines relapse as disease progression at least 6 months after achieving a complete response or partial response, and refractory disease as treatment failure or disease progression within 6 months of treatment. The Committee was aware that there are fewer treatment options for people whose disease is refractory than for people whose disease has relapsed (see section 4.1), meaning different comparators for the 2 populations and, in turn, making separate analyses more appropriate. The Committee concluded that in people whose disease has been previously treated, it was reasonable to consider 2 distinct subgroups: relapsed and refractory. The Committee further concluded that, for the purposes of this appraisal, 'people whose disease has relapsed' refers to people whose disease has progressed at least 6 months after achieving a complete or partial response and 'people whose disease is refractory' refers to people whose disease has progressed within 6 months of treatment and retreatment with fludarabine-based regimens or an alkylating agent is not considered appropriate.

4.3 The Committee considered the relevance of the comparators listed in the NICE scope. It was aware that rituximab alone was not included as a comparator in the NICE scope because it is not established practice in the NHS. It also noted the subgroups identified in section 4.2, and agreed that rituximab was not a relevant comparator in people whose disease has relapsed. The Committee accepted that rituximab could be considered a relevant comparator in people for whom further treatment with fludarabine-based regimens or an alkylating agent was unsuitable (that is,

people whose disease is refractory). The Committee concluded that fludarabine-based regimens or an alkylating agent were relevant comparators for the population with previously treated relapsed disease, and that rituximab, ofatumumab and best supportive care were appropriate comparators for people with refractory disease.

4.4 The Committee heard from the clinical and patient experts about the nature of the condition and the benefits of idelalisib. The patient experts described how the toxicity of fludarabine-containing regimens often makes them inappropriate for older patients who may have comorbidities. It heard that treatments such as chlorambucil, steroids or ofatumumab are easier to tolerate, but in some patients produce only short periods of remission. The clinical experts also noted that alemtuzumab can cause serious side effects, including an ongoing risk of infection. The Committee heard from the clinical experts that idelalisib is associated with fewer side effects compared with other treatments for chronic lymphocytic leukaemia. The patient experts emphasised that patients prefer oral treatments like idelalisib. The Committee also heard that because patients are on life-long treatment, the uncertainty of living with chronic lymphocytic leukaemia brings psychological and emotional issues as well as physical ill-health.

4.5 The Committee considered the evidence submitted by the company for idelalisib plus rituximab compared with rituximab in people with relapsed or refractory chronic lymphocytic leukaemia which has been previously treated. The Committee noted the results of Study 116, which showed that idelalisib plus rituximab had a statistically significant improvement in progression-free survival and overall survival compared with rituximab (see section 3.7). The Committee considered the generalisability of the results to patients in the UK with chronic lymphocytic leukaemia. It noted that the trial was conducted in patients who were generally older with more co-

morbidities (mean age of 71 years) and who had on average had at least 3 prior therapies. In addition, 43.2% of patients in the trial had a 17p deletion or TP53 mutation. The Committee concluded that idelalisib plus rituximab provided a notable statistically significant improvement in progression-free survival and overall survival compared with rituximab.

4.6 The Committee considered the evidence submitted by the company on the clinical effectiveness of idelalisib plus rituximab in people whose disease was untreated and who had a 17p deletion or TP53 mutation. It noted that the evidence for this population was limited because it was based on a single-arm trial (Study 101-08) of 64 patients, only 9 of which had a 17p deletion or TP53 mutation. The Committee noted the results of the trial, which showed that at 36 months none of the patients having idelalisib plus rituximab had disease progression. It heard from the company that idelalisib's marketing authorisation had been granted partly on evidence from Study 116 (because a large proportion of patients [43.2%] had a 17p deletion or TP53 mutation), in addition to the evidence from Study 101-08. The Committee concluded that although Study 116 did provide corroborative evidence, even if added to the single-arm Study 101-08, the lack of comparative evidence and few patients meant that the results could not be used to inform its decision-making for this subgroup of patients.

4.7 The Committee considered the company's rationale for not submitting an indirect or mixed treatment comparison of idelalisib plus rituximab compared with the other comparators listed in the NICE scope. It heard from the ERG, which agreed with the company that a network could not be formed within the current evidence base. The Committee heard from the company that in the absence of an indirect comparison, in order to proceed with the economic modelling for the other comparators listed in the NICE

scope (fludarabine cyclophosphamide and rituximab, bendamustine with or without rituximab, chlorambucil with or without rituximab, steroids plus rituximab) it had provided an additional analysis following a systematic literature review (see section 3.31). The Committee was aware that the face validity of this approach had not been demonstrated and noted that the overall survival data for bendamustine plus rituximab were less than for bendamustine alone, which seemed counterintuitive. However, the ERG noted that in the absence of a network meta-analysis this was a suitable approach to take. The Committee accepted that a network meta-analysis was not possible for the indirect comparison of idelalisib plus rituximab compared with the other comparators in the NICE scope, and that the company's alternative approach should be considered in the economic analysis.

Cost effectiveness

4.8 The Committee considered the model presented by the company, the associated assumptions and the critique presented by the ERG. It noted that the company had submitted an economic model which addressed the population with previously treated chronic lymphocytic leukaemia and not the population with untreated disease and a 17p deletion or TP53 mutation. The Committee considered the structure of the company's model and concluded that it appropriately captured the main aspects of previously treated chronic lymphocytic leukaemia, and was therefore appropriate for decision-making within the limitations of the comparators and parameters used (see sections 4.9–4.14). The Committee noted, however, that the company did not model the population with untreated disease and a 17p deletion or TP53 mutation. It heard from the ERG that the company had modelled the 17p deletion or TP53 mutation subgroup from Study 116, but because the patients in this trial had previously treated disease the results were not

applicable to patients with untreated disease. The Committee therefore concluded it could not make any inferences about the cost effectiveness of idelalisib plus rituximab in people with untreated chronic lymphocytic leukaemia and a 17p deletion or TP53 mutation group.

4.9 The Committee considered the comparators included in the company's model for people with previously treated chronic lymphocytic leukaemia. It noted that the company had not considered comparators other than rituximab, best supportive care and ofatumumab in its base-case analysis, and recalled the clinical specialists' advice that other treatments (such as fludarabine, cyclophosphamide and rituximab, and chlorambucil and bendamustine) would be given if a patient had relapsed chronic lymphocytic leukaemia. It was aware that there was no direct evidence for these other comparators and an indirect comparison was not possible. It noted that the company had assumed that best supportive care and ofatumumab had equal efficacy to rituximab, and heard from the clinical experts that this was a fair assumption. The Committee was reminded of the subpopulations for patients with previously treated disease (as discussed in section 4.2), and concluded that rituximab was an appropriate comparator only in patients whose disease is refractory to fludarabine-based regimens or alkylating agents.

4.10 The Committee considered the clinical effectiveness parameters used in the model. It heard from the ERG that the company's model contained an assumption that time on treatment was restricted, but that the benefits of treatment with idelalisib plus rituximab continued after both the time horizon of the trial and treatment discontinuation. The Committee heard from the ERG that these assumptions were not plausible and may have overestimated the treatment effect of idelalisib plus rituximab. The Committee noted

that the company had not measured the effect of this assumption (although the ERG tested this in its exploratory analysis; see sections 3.48–3.50). The Committee heard from the clinical experts that patients would continue to have treatment for chronic lymphocytic leukaemia until disease progression or until the treatment stopped working. Indeed, after stopping treatments, rebound deterioration can occur. The Committee concluded that the treatment benefit of idelalisib plus rituximab is unlikely to continue beyond treatment discontinuation, and therefore considered the ERG's changes to the company's model to be more plausible.

4.11 The Committee considered the clinical effectiveness parameters in the company's model for the other comparators listed in the NICE scope. It noted that because an indirect comparison was not possible (see section 4.7), the company had fitted survival data reported in the literature to the same shape parameter as the rituximab survival curves (see section 3.31). The ERG noted that this approach was appropriate in the absence of a more robust comparison. However, it noted that there was a poor fit between the modelled data and those reported in the study for fludarabine, cyclophosphamide and rituximab. The Committee heard from the ERG that it had repeated the analysis using the statistically best-fitting survival curve. The Committee noted the ERG's amendments and concluded that in the absence of an indirect comparison of idelalisib plus rituximab with the other comparators in the NICE scope, the methodology used by the company, with the ERG's adjustments, was appropriate.

4.12 The Committee considered the cost and resource use parameters used by the company in the economic evaluation. It heard from the ERG that the company had assumed all patients in the progression-free survival state would complete the full

recommended course for all treatments other than idelalisib and rituximab. This approach overestimated the drug treatment costs because it is unlikely that all patients would complete the full recommended course of treatment. The clinical experts noted that it would be inappropriate to assume all patients would complete the full treatment course. The Committee discussed the ERG amendments to the company's model, which used the time-on-treatment data from the rituximab arm of Study 116 to estimate the time on treatment for the other comparators. In the ERG amendments, patients in the progression-free survival state completed the same proportion of the treatment course as those having rituximab in Study 116. The Committee concluded that it was inappropriate to assume that patients would have the maximum dose of the other comparator treatments, and that the ERG's amendments were more plausible.

4.13 The Committee further considered the resource use assumptions in the company's model. It heard from the ERG that the company had assumed 45% of patients whose disease did not respond to treatment would have intravenous immunoglobulin therapy. The Committee noted that the cost of intravenous immunoglobulin therapy was £13,706 for treatment and administration. It heard from the clinical experts that although there is no guidance on the use of intravenous immunoglobulin therapy, in clinical practice it would be unusual for such a high proportion of patients to have it; a more realistic approximation is 20% or less. The clinical experts also noted that intravenous immunoglobulin therapy is sometimes administered to patients whose disease responds to treatment. The Committee heard from the ERG that in its exploratory analyses, it reduced the amount of intravenous immunoglobulin therapy received by patients whose disease did not respond and this resulted in large increases in the incremental cost-effectiveness

ratio (ICER) for idelalisib plus rituximab compared with rituximab (see section 3.50). The Committee noted that the ERG had only explored a small range of reductions in intravenous immunoglobulin therapy in patients whose disease did not respond to treatment and that it had not explored increasing the proportion of intravenous immunoglobulin therapy in patients whose disease responded. The Committee concluded that to inform its decision-making, it needed additional analyses exploring different proportions of patients with non-responding and responding disease having intravenous immunoglobulin therapy.

4.14 The Committee considered the utility parameters used by the company in its economic model. It heard from the ERG that because the company had used a mixture of sources for its utility values (see section 3.32) there were a number of inconsistencies in the results (see section 3.47). The ERG stated that it had explored using the Dretzke et al. (2010) values for both the pre-progression and post-progression states in its amendments to the company's base case, but that these changes did not significantly impact the ICERs for idelalisib plus rituximab compared with its comparators. The Committee concluded that although EQ-5D data collected alongside the trial should be used whenever possible, in this instance the lack of trial EQ-5D data for the post-progression state and the inconsistencies in the data meant that it was appropriate to use the Dretzke et al. values in the company model.

4.15 The Committee considered the most plausible ICER for idelalisib plus rituximab compared with rituximab in people with previously treated refractory chronic lymphocytic leukaemia. The Committee noted that in the company's base-case analysis, after using the nationally available price reduction, the deterministic ICER was £13,634 per quality-adjusted life year (QALY) gained. Following the ERG's amendments, the ICER was £16,947 per QALY gained (see

section 3.36 and section 3.49). However, the Committee was aware that reducing the proportion of people whose disease did not respond having intravenous immunoglobulin therapy increased the ICER substantially (see section 3.50). The Committee agreed that with the available information, it was not possible to determine the most plausible ICER for the comparison of idelalisib plus rituximab with rituximab in people with previously treated refractory chronic lymphocytic leukaemia. The Committee concluded that further analyses should be provided by the company exploring the effects of reducing intravenous immunoglobulin therapy use in people whose disease does not respond to 20% or less, and increasing intravenous immunoglobulin therapy use in those whose disease does respond to 20%.

4.16 The Committee considered the most plausible ICER for people with previously treated relapsed chronic lymphocytic leukaemia. The Committee agreed that rituximab was not an appropriate comparator for this population and it therefore considered the results of the company's exploratory analyses of idelalisib with rituximab compared with the other comparators listed in the NICE scope (see section 3.39). When the ERG's amendments were applied (see sections 3.48–3.50), the ICERs reported for all 7 of the comparisons were over £30,000 per QALY gained (see section 3.49). The Committee noted that when the adjustments to the proportions of people having intravenous immunoglobulin therapy are made, the ICERs are likely to increase further. The Committee agreed that the most plausible ICERs for idelalisib plus rituximab compared with the other comparators listed in the NICE scope in people with previously treated relapsed chronic lymphocytic leukaemia were above the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained). The Committee concluded that idelalisib plus

rituximab is not recommended in people with previously treated relapsed chronic lymphocytic leukaemia.

4.17 The Committee considered the use of idelalisib plus rituximab in people with untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation. It noted that the clinical evidence provided by the company was limited and that the company had not presented a cost-effectiveness analysis for this population. The Committee concluded that idelalisib plus rituximab could not be recommended in people with untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation.

4.18 The Committee discussed how innovative idelalisib plus rituximab is in its potential to make a significant and substantial impact on health-related benefits. It understood that idelalisib is a novel agent and that there was a high level of unmet need in this disease area, and it agreed that idelalisib offered a step change in the treatment of chronic lymphocytic leukaemia. However, the Committee considered that all health-related benefits had been adequately captured by the QALYs in the model in so far as the model was adequate for decision-making.

4.19 The Committee considered 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. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- 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.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.20 The Committee discussed the end-of-life criteria in turn. It noted the clinical expert's view that the life expectancy of people with relapsed chronic lymphocytic leukaemia is on average 4–6 years. For people with refractory chronic lymphocytic leukaemia, the Committee noted the clinical experts' view that life expectancy is expected to be less than 24 months. It also noted the results of Study 116 which showed life expectancy in the rituximab arm was less than 24 months. The Committee concluded that the short life expectancy criterion was not met for the subgroup of people with relapsed chronic lymphocytic leukaemia, but met for people with refractory chronic lymphocytic leukaemia.

4.21 The Committee discussed the life extension criterion. It noted that for people with relapsed chronic lymphocytic leukaemia, the information on life extension provided by the company was not relevant because rituximab was not an appropriate comparator in this group. For people with refractory chronic lymphocytic leukaemia, the mean overall survival reported by the company showed a life expectancy greater than 3 months with idelalisib plus rituximab compared with rituximab alone (data supplied academic in confidence and so cannot be reported here). The Committee concluded that the life extension criterion was not met for people

with relapsed chronic lymphocytic leukaemia but was met for people with refractory chronic lymphocytic leukaemia.

4.22 The Committee discussed the evidence for the small population size. It noted evidence provided by the company which showed that fewer than 7000 people are likely to have idelalisib plus rituximab. The Committee also heard from the clinical experts that the number of people with previously treated chronic lymphocytic leukaemia is likely to be around 1400. The Committee concluded that both the relapsed and refractory chronic lymphocytic leukaemia groups fulfil the small population end-of-life criterion.

4.23 The Committee concluded overall that for people with previously treated relapsed chronic lymphocytic leukaemia, idelalisib plus rituximab was not cost effective (see section 4.16) and did not meet the end-of life criteria. For people with previously treated refractory chronic lymphocytic leukaemia, the Committee noted that idelalisib plus rituximab could be considered under the supplementary advice to the Committee on end-of-life treatments. The Committee concluded that it could not assess whether idelalisib plus rituximab is a cost-effective treatment option, because it did not have sufficient information to assess the most plausible ICER. The Committee was minded not to recommend idelalisib plus rituximab in people with previously treated refractory chronic lymphocytic leukaemia. The Committee recommends that NICE requests further analyses from the company, which should be made available for the second Appraisal Committee meeting, and should include:

- a revised cost-effectiveness analysis for the comparison of idelalisib plus rituximab with rituximab alone, best supportive care and ofatumumab incorporating the changes made to the company model (see sections 3.48-3.50):

  - Reducing the length of treatment benefit for idelalisib plus rituximab to 5 years
  - Using utility values from Dretzke et al. (2010) for both the pre-progression and post-progression model states
- A sensitivity analysis exploring the length of treatment benefit of idelalisib plus rituximab from treatment discontinuation up to 5 years
- A sensitivity analysis exploring the effects of reducing the proportion of non-responders having intravenous immunoglobulin from 45% to 20% or less and increasing the number of responders having intravenous immunoglobulin from 0% to 20%
- A sensitivity analysis exploring the effect of using clinical effectiveness data from the subgroup of people in Study 116 whose disease is refractory.

4.24 The Committee agreed that it had received insufficient information for people with previously untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation to inform its decision-making. It noted that further information had been requested for people with refractory chronic lymphocytic leukaemia and any final recommendations for this population could be applied to people with untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation when their disease becomes refractory.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Idelalisib, in combination with rituximab, is not recommended: • for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or • for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed. The Committee concluded that in people whose disease has been previously treated, it was reasonable to consider 2 distinct subgroups: relapsed and refractory. The Committee further concluded that, for the purposes of this appraisal, 'people whose disease has relapsed' refers to people whose disease has progressed at least 6 months after achieving a complete or partial response and 'people whose disease is refractory' refers to people whose disease has progressed within 6 months of treatment and retreatment with fludarabine-based regimens or an alkylating agent is not considered appropriate The Committee is minded not to recommend idelalisib, in combination with rituximab, for chronic lymphocytic leukaemia in adults whose disease is refractory and retreatment with previous regimens is not considered appropriate. The Committee recommends that NICE requests further analyses from the company, which should be made available for the second Appraisal Committee meeting, and should include: • a revised cost-effectiveness analysis for the comparison of idelalisib plus rituximab with rituximab alone, best supportive care and ofatumumab	1.1 4.2 1.2 1.3

	incorporating the changes made to the company model (see sections 3.48-3.50): − Reducing the length of treatment benefit for idelalisib plus rituximab to 5 years − Using utility values from Dretzke et al. (2010) for both the pre-progression and post-progression model states • A sensitivity analysis exploring the length of treatment benefit of idelalisib plus rituximab from treatment discontinuation up to 5 years • A sensitivity analysis exploring the effects of reducing the proportion of non-responders having intravenous immunoglobulin from 45% to 20% or less and increasing the number of responders having intravenous immunoglobulin from 0% to 20% • A sensitivity analysis exploring the effect of using clinical effectiveness data from the subgroup of people in Study 116 whose disease is refractory.	
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee discussed the clinical management of untreated chronic lymphocytic leukaemia in people with a 17p deletion or TP53 mutation. It heard from the clinical experts that people with this type of disease have very limited treatment options, which can include high-dose pulsed steroids with alemtuzumab. The Committee concluded that more treatment options are needed. The Committee concluded that in people whose disease has been previously treated, it	4.1 4.2

	was reasonable to consider 2 distinct subgroups: relapsed and refractory. The Committee further concluded that, for the purposes of this guidance, 'people whose disease has relapsed' refers to people whose disease has progressed at least 6 months after achieving a complete or partial response and 'people whose disease is refractory' refers to people whose disease has progressed within 6 months of treatment and retreatment with fludarabine-based regimens or an alkylating agent is not considered appropriate.	
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Idelalisib (Zydelig, Gilead Sciences) is an inhibitor of enzymes that regulate important cellular functions including proliferation, cell death and migration. The Committee discussed how innovative idelalisib plus rituximab is in its potential to make a significant and substantial impact on health-related benefits. It understood that idelalisib is a novel agent and that there was a high level of unmet need in this disease area, and it agreed that idelalisib offered a step change in the treatment of chronic lymphocytic leukaemia. However, the Committee considered that all health-related benefits had been adequately captured by the QALYs in the model in so far as the model	2.1, 4.18

	was adequate for decision-making.	
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that fludarabine-based regimens or an alkylating agent were relevant comparators for the population with previously treated relapsed disease, and that rituximab, ofatumumab and best supportive care were appropriate comparators for the population with refractory disease.	4.3
Adverse reactions	The summary of product characteristics lists the following adverse reactions to idelalisib, alone or with rituximab, as affecting more than 10% of patients: infections, neutropenia, diarrhoea, transaminase increase, rash, pyrexia and increased triglycerides. For full details of adverse reactions and contraindications, see the summary of product characteristics.	2.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered the evidence submitted by the company for idelalisib plus rituximab compared with rituximab in people with relapsed or refractory chronic lymphocytic leukaemia which has been previously treated. The Committee considered the evidence submitted by the company on the clinical effectiveness of idelalisib plus rituximab in people whose disease was untreated and who had a 17p deletion or TP53 mutation. It noted	4.5 4.6

	that the evidence for this population was limited because it was based on a single-arm trial (Study 101-08) of 64 patients, only 9 of which had a 17p deletion or TP53 mutation.	
Relevance to general clinical practice in the NHS	The Committee considered the generalisability of the results to patients in the UK with chronic lymphocytic leukaemia. It noted that the trial was conducted in patients who were generally older with more co-morbidities (mean age of 71 years) and who had on average had at least 3 prior therapies. In addition, 43.2% of patients in the trial had a 17p deletion or TP53 mutation.	4.5
Uncertainties generated by the evidence	The Committee concluded that although Study 116 did provide corroborative evidence, even if added to the single-arm Study 101-08, the lack of comparative evidence and few patients meant that the results could not be used to inform its decision-making for this subgroup of patients.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted the results of Study 116, which showed that idelalisib plus rituximab had a statistically significant improvement in progression-free survival and overall survival compared with rituximab.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the model presented by the company, the associated assumptions and the critique presented by the ERG. It noted that the company had submitted an economic analysis which addressed the population with previously treated chronic lymphocytic leukaemia only. The Committee considered the comparators included in the company's model. It noted that the company had not considered comparators other than rituximab, best supportive care and ofatumumab in its base-case analysis, and recalled the clinical specialists' advice that other treatments (such as fludarabine, cyclophosphamide and rituximab, and chlorambucil and bendamustine) would be given if a patient had relapsed chronic lymphocytic leukaemia. It was aware that there was no direct evidence for these other comparators and an indirect comparison was not possible.	4.8 4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee heard from the ERG that the company's model contained an assumption that time on treatment was restricted, but that the benefits of treatment with idelalisib plus rituximab continued after both the time horizon of the trial and treatment discontinuation. The Committee heard from the ERG that these assumptions were not plausible and may have overestimated the treatment effect.	4.10
	The Committee noted that there was a poor fit between the modelled overall survival and progression free survival data and those reported in the study for fludarabine, cyclophosphamide and rituximab. The Committee heard from the ERG that it had repeated the analysis using the statistically best-fitting survival curve.	4.11
	It heard from the ERG that the company had assumed all patients in the progression-free survival state would complete the full recommended course for all treatments other than idelalisib and rituximab. This approach overestimated the drug treatment costs because it is unlikely that all patients would complete the full recommended course of treatment.	4.12

	The Committee further considered the resource use assumptions in the company's model. It heard from the ERG that the company had assumed 45% of patients whose disease did not respond to treatment would have intravenous immunoglobulin therapy. The Committee noted that the cost of intravenous immunoglobulin therapy was £13,706 for treatment and administration.	4.13
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The ERG stated that it had explored using the Dretzke et al. (2010) values for both the pre-progression and post-progression states in its amendments to the company's base case, but that these changes did not significantly impact the incremental cost-effectiveness ratios (ICERs) for idelalisib plus rituximab compared with its comparators. The Committee concluded that although EQ-5D data collected alongside the trial should be used whenever possible, in this instance the lack of trial EQ-5D data for the post-progression state and the inconsistencies in the data meant that it was appropriate to use the Dretzke et al. values in the company model.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	

What are the key drivers of cost effectiveness?	The Committee noted that when the adjustments to the proportions of people having intravenous immunoglobulin therapy are made, the ICERs are likely to increase further.	4.16

Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered the most plausible ICER for idelalisib plus rituximab compared with rituximab in people with previously treated refractory chronic lymphocytic leukaemia. After applying the nationally available price reduction, the deterministic ICER was £13,634 per quality-adjusted life year (QALY) gained. Following the ERG's amendments, the ICER was £16,947 per QALY gained. However, the Committee was aware that reducing the proportion of people whose disease did not respond having intravenous immunoglobulin therapy increased the ICER substantially. The Committee agreed that with the available information, it was not possible to determine the most plausible ICER for the comparison of idelalisib plus rituximab with rituximab in people with previously treated refractory chronic lymphocytic leukaemia.	4.15
	The Committee considered the most plausible ICER for people with previously treated relapsed chronic lymphocytic leukaemia. The Committee agreed that rituximab was not an appropriate comparator for this population and it therefore considered the results of the company's exploratory analyses of idelalisib with rituximab compared with the other comparators listed in the NICE scope (see section 3.39). When the ERG's amendments were applied (see sections 3.48–3.50), the ICERs reported for all the comparisons were over £30,000 per QALY gained (see section 3.49).	4.16

Additional factors taken into account		
Nationally available price reduction	The company has arranged a nationally available price reduction which provides a simple discount to the list price of idelalisib. The level of the discount is commercial in confidence.	2.3
End-of-life considerations	The Committee concluded that the short life expectancy criterion was not met for the subgroup of people with relapsed chronic lymphocytic leukaemia, but met for people with refractory chronic lymphocytic leukaemia. The Committee concluded that the life extension criterion was not met for people with relapsed chronic lymphocytic leukaemia but was met for people with refractory chronic lymphocytic leukaemia The Committee concluded that both the relapsed and refractory chronic lymphocytic leukaemia groups fulfil the small population end-of-life criterion.	4.20 4.21 4.22
Equalities considerations and social value judgements	No equalities issues were identified.	

5 Implementation

5.1 The company has arranged a nationally available price reduction which provides a simple discount to the list price of idelalisib. The level of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the nationally available price reduction should be directed to [NICE to add details at time of publication]

5.2 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. http://www.nice.org.uk/guidance/TA202 NICE technology appraisal guidance 202 (2010).
- Rituximab for the treatment of relapsed chronic lymphocytic leukaemia. http://www.nice.org.uk/guidance/TA193. NICE technology appraisal guidance 193 (2010).
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. http://www.nice.org.uk/guidance/TA216. NICE technology appraisal guidance 216 (2011).
- Rituximab for first-line treatment of chronic lymphocytic leukaemia. http://www.nice.org.uk/guidance/TA174. NICE technology appraisal guidance 174 (2009).
- Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. http://www.nice.org.uk/guidance/TA119. NICE technology appraisal guidance 119 (2007).

Under development

- GP Referral for suspected cancer. NICE clinical guideline, publication expected June 2015.
- Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. NICE technology appraisal guidance, publication expected June 2015.
- Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. NICE technology appraisal guidance, publication expected June 2015

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date.

The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Andrew Stevens
Chair, Appraisal Committee
June 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel
Institute of Brain and Behaviour Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Dept of Primary Care and Population Health, University College London

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Iain Miller
Founder & CEO, Health Strategies Group

Dr Paul Miller
Director, Payer Evidence, Astrazeneca UK Ltd

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Claire Rothery
Research Fellow in Health Economics, University of York

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager

Victoria Kelly
Technical Lead(s)

Dr Sally Doss
Technical Adviser

Lori Farrar
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Kandala, N-B., Pink, J., Tsertsvadze, A., Sutcliffe, P., Court, R., Walewska, R., Clarke, A. Idelalisib Single Technology Appraisal - Idelalisib for relapsed chronic lymphocytic leukaemia [ID764]: A Single Technology Appraisal. Warwick Evidence, 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Gilead Sciences

II. Professional/expert and patient/carer groups:

- Chronic Lymphocytic Leukaemia Support Association
- Leukaemia CARE
- Lymphoma Association
- Association of Cancer Physicians
- Cancer Research UK
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- GlaxoSmithKline (chlorambucil, ofatumumab)
- Roche Products (rituximab, obinutuzumab)
- National Cancer Research Institute
- Warwick evidence
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Idelalisib for previously treated chronic lymphocytic leukaemia by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Christopher Fegan, Director of Research and Development, nominated by Gilead – clinical expert
- Dr Francesco Forconi, Consultant and Associate Professor, nominated by Royal College of Physicians – clinical expert
- Nick York, Nominated by CLL Support Association – patient expert
- Trisha Gardom, CLL Patient Advocate, nominated by CLL Support Association – patient expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Gilead