NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Single Technology Appraisal
ID 764 Idelalisib for treating chronic lymphocytic leukaemia
Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Gilead	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. There are inconsistencies with the way in which the Appraisal Committee (the Committee) has defined the patient population in this area, which undermine the provisional recommendations. We are disappointed that, following their initial consideration of the evidence, the Committee has been unable to recommend idelalisib in any patient group. We believe that the existing recommendations misrepresent the patient population for which there is evidence, and that there should be acknowledgement of this 'high risk' subgroup (as represented in the British Committee for Standards in Haematology [BCSH] guidelines) for whom there is robust evidence and who are not eligible for chemotherapy because they relapse early (within 24 months) or have 17p deletion or TP53 mutation. This patient group have a life expectancy of less than 24 months and are a small population in whom treatment with idelalisib plus rituximab results in an overall survival (OS) gain of more than 3 months compared with rituximab alone, thus falling within the NICE end-of-life criteria.	Comments noted. The Committee have considered the new evidence submitted by the company and the responses it received during the appraisal consultation from clinical and patient experts. The Committee have amended the recommendations accordingly. Please see section 1 of the FAD.

Consultee	Comment [sic]	Response
	Has all of the relevant evidence been taken into account? No. The relevant and key evidence has not been taken into account in the Committee's preferred cost-effectiveness analysis, which means the provisional recommendations are not a suitable basis for guidance to the NHS. The first key issue relates to the use of intravenous immunoglobulin replacement (IvIG) therapy. In light of the sensitivity of results to IvIG assumptions being highlighted as an area of key concern in the ACD, every effort has been made to further scrutinise and validate IvIG assumptions in the model. Analyses to date have been based on an IvIG cost estimated assuming a dose of 0.4g/kg IvIG therapy administered five times for one active treatment week, and includes administration costs for five infusions. Further research suggests that, while this is the immune-modulatory dose used for treatment of many conditions, such as myasthenia gravis, acquired haemophilia and autoimmune von Willebrand syndrome, when IvIG is administered to address a secondary antibody deficiency, as would be the case in relapsed and refractory CLL, a treatment week comprises 0.4g/kg IvIG therapy administered once.	Comments noted. The Committee considered the new evidence submitted by the company relating to intravenous immunoglobulin therapy and the ERG's critique. The FAD has been updated accordingly. Please see section 4.11 of the FAD for further details.

Consultee	Comment [sic]	Response
	If an active IvIG treatment week is assumed to comprise one administration of 0.4g/kg IvIG therapy instead of five, the total drug acquisition and administration cost falls by 80%. We regret that what we now believe was an incorrect assumption has informed cost-effectiveness results considered to date, and present corrected results, including the full suite of requested additional analyses, to assist the Committee in their appraisal. Correcting this assumption leads to an increase in ICERs, but ICERs which are far more robust to assumptions regarding the proportion of patients who will receive IvIG therapy in practice. The second key issue relates to the eschewing of EQ-5D utility data from Study 116 in the Committee's preferred base, which we propose fails to take into account key evidence. In Paragraph 4.14 of the ACD, the Committee are reported to have 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". We demonstrate in this response that the inconsistencies referred to are easily avoided by changing one assumption in the model, and argue that there is no defensible justification for ignoring the available EQ-5D data in the cost-effectiveness analyses.	The Committee considered the company's amendments to the use of trial EQ-5D data in the pre-progression states and the ERG's critique of the change. The FAD has been updated accordingly. Please see section 4.12.

Consultee	Comment [sic]	Response
	Section 1 presents additional cost-effectiveness analyses conducted to address uncertainties highlighted by the Committee. These include the requested investigations into uncertainty around (i) the length of relative treatment benefit for idelalisib with rituximab, (ii) the proportion of responders and non-responders receiving IvIG therapy and (iii) the subgroup of Study 116 patients with refractory disease. These analyses are presented for the model, revised as requested by the Committee, and repeated with additional changes to IvIG cost assumptions and utility data in order to provide the Committee with a cost-effectiveness case, which we propose takes into account all of the relevant evidence using the best available assumptions and data, to inform final appraisal decisions. The updated results show idelalisib with rituximab to be a cost-effective end-of-life treatment for patients who are unsuited to chemotherapy, due to early relapse (within 24 months) or the presence of 17p deletion or TP53 mutation, and importantly demonstrate this finding to be robust to plausible changes in IvIG and treatment benefit extrapolation assumptions.	The Committee considered the new evidence submitted by the company and considered its implications on the most plausible ICER for the relevant comparisons. The FAD has been updated accordingly. Please see sections 3.51-3.56 for a summary of the new evidence and sections 3.57-3.61 for the ERG's critique of the new evidence.

Consultee	Comment [sic]	Response
	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? No, however, we believe it is unethical to propose (ACD Section 4.24) that patients with previously untreated CLL with a 17p deletion or TP53 mutation, a known prognostic indicator of poor response, should be required to go through the process of receiving ineffective treatment in order to demonstrate this poor response before they are considered eligible for treatment with idelalisib. In light of the information provided, we ask that the Committee revises its preliminary recommendations and reconsiders recommending idelalisib with rituximab: • for untreated CLL patients whose disease is associated with a 17p deletion or TP53 mutation • for previously treated CLL patients who are unsuitable for chemotherapy due to one or more of the following clinical indicators: o a response to previous treatment of less than 24 months, in line with clinical practice and BCSH guidelines o their disease is associated with a 17p deletion or TP53 mutation	Comments noted. The Committee considered all the evidence submitted, including evidence from the clinical trials and patient and clinical expert testimonies. It also carefully considered the comments received from consultees and commentators in response to the appraisal consultation document. The Committee considerations and recommendations were updated accordingly. Please see section 1 of the FAD.

Consultee	Comment [sic]	Response
	Facutal inaccuracies in the ACD Document states: “Idelalisib (Zydelig, Gilead Sciences) is an inhibitor of enzymes…” Please reword to read “Idelalisib (Zydelig, Gilead Sciences) is a first-in-class inhibitor of enzymes…”	Comment noted. Section 2.1 of the FAD has now been updated.
	Document states “Treatment is continued until disease progression or unacceptable toxicity.” However, as per the summary of product characteristics, treatment can be resumed once the adverse event has been resolved. Therefore, please reword “Treatment is continued until disease progression or unacceptable toxicity. As per the SmPC, in most cases, treatment can be resumed at 100mg twice daily where the adverse event has been resolved.”	Comment noted. Section 2.3 of the FAD has now been updated.
	The document states “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.” However, it appears that the responses to the ERG questions have not been factored into the results of the systematic review, as there were another two RCTs that were identified as being relevant to the decision problem that were identified in the literature review update in response to the ERG questions. Please amend to read “The company’s systematic literature review identified 6 randomised controlled trials that were relevant to the decision problem because they included patients whose disease was relapsed and refractory.”	Comment noted. Section 3.1 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states "…whose disease was relapsed and refractory." Please reword to read "…whose disease was relapsed or refractory."	Comment noted. Section 3.1 of the FAD has now been updated.
	The document states "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)." This is incorrect; patients received idelalisib or placebo until progression or withdrawal due to tolerability issues.	Comment noted. Section 3.3 of the FAD has now been updated.
	At the end of point 3.3, the document states "Patients were excluded if their disease had progressed to more aggressive malignancies" This could be made a little more specific. As such, please reword to read "Patients were excluded if they had a known histological transformation from CLL to an aggressive lymphoma (i.e., Richter transformation)."	Comment noted. Section 3.3 of the FAD has now been updated.
	The document states "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." This is incorrectly worded and should be updated to read "Patients were included if they were aged 18 years or older, had previously had at least one treatment line (either an anti-CD20 or at least two previous cytotoxic regimens) and had a reported Karnofsky progression score of 40 or more."	Comment noted. Section 3.3 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states "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." As such, not all the subgroups were listed here and the sentence should be modified to reflect the fact that other subgroups were investigated. Please update to read "The primary and secondary end points were examined in a number of pre-specified subgroups, which included: patients with a 17p deletion, *TP53* mutation or both, and patients without a 17p deletion or *TP53* mutation; and patients with or without an IgVH mutation."	Comment noted. Section 3.3 of the FAD has now been updated.
	The document states "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." This is incorrect; the treatment in Study 117 was idelalisib monotherapy.	Comment noted. Section 3.5 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states “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.” Please reword to clarify and better reflect the study: “Of the 3 patients randomised to the rituximab plus placebo group, 2 withdrew from the study because of an adverse event before study treatment initiation, and 1 had not received the study treatment before the data cut-off.”	Comment noted. Section 3.6 of the FAD has now been updated.
	The document states “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).” There is an error in this sentence on one of the confidence intervals stated. Please change to read “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] 12.3, not reported) compared with 6.5 months (95% CI 4.0 to 7.3).”	Comment noted. Section 3.7 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states "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)." As such, a statistically significant difference is mentioned but no p-value is provided. Please add the p-value here and change the sentence to read "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; p=0.0001)."	Comment noted. Section 3.7 of the FAD has now been updated.
	The document states "The company also presented the results of the crossover-adjusted analysis but these were presented as academic in confidence." These data have now been presented at the 20th Congress of the European Hematology Association (EHA) in June 2015 and as such, are no longer considered as academic in confidence.[13] The source is attached.	Comment noted. Section 3.7 of the FAD has now been updated.
	The document states "Progression-free survival for the overall population at 36 months was 83%." To provide the comparative PFS for the 17p deletion/*TP53* mutation population, the sentence should be amended to "Progression-free survival for the overall population at 36 months was 83%, compared with 100% for the 17p deletion/*TP53* mutation patients."	Comment noted. Section 3.17 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states “The most common treatment-related adverse events were diarrhoea or colitis (77%), rash (58%) and pyrexia (42%).” This sentence does not reflect the adverse event data correctly because the adverse events mentioned are treatment-emergent, not treatment related. Therefore, this sentence should read instead “The most common treatment-emergent adverse events were diarrhoea or colitis (77%), rash (58%) and pyrexia (42%).”	Comment noted. Section 3.18 of the FAD has now been updated.
	The document states “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.” However, it appears that the responses to the ERG questions have not been factored into the results of the systematic review. As such, the number of studies identified in the systematic review is incorrect and the document should instead read “The company’s systematic review did not identify any evidence directly comparing idelalisib with these comparators, but identified 5 randomised controlled trials and 13 non-randomised controlled trials in the relapsed/refractory population.”	Comment noted. Section 3.19 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states "No additional evidence was identified in the untreated population." However, if this is referring to any RCT or non-RCT evidence for the untreated mutation population, this is incorrect. We identified one RCT (Hillmen et al, 2007), which compared alemtuzumab versus chlorambucil in a previously untreated population.[10] Within this study, results (median PFS, and overall response rate) were reported for the subgroup of patients with a 17p deletion (11 patients vs. 10 patients) so these can be used to some extent to compare with the results of the idelalisib 101-08 study, which showed high efficacy of idelalisib even though this was a sicker population than the Hillmen et al study.	Comment noted. Section 3.31 of the FAD has now been updated.
	The document states "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." This is incorrect. The company assumed a shape parameter equal to that estimated for treatment arm data from Study 116, in which patients received idelalisib plus rituximab, to allow estimation of survival curves for the exploratory comparisons to external trial data. Treatment arm data were chosen as, unlike comparator arm data, these had not been confounded by crossover.	Comment noted. Section 3.31 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states "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." This is incorrect. For comparisons to external study data (i.e. not the comparator arm of Study 116), treatment costs were applied to the proportion of patients remaining in the 'progression-free' health states in the model, up to maximum treatment durations. The proportion of modelled patients who progressed before maximum treatment durations were not assumed to complete the full course of treatment.	Comment noted. Section 3.3 of the FAD has now been updated.
	The document states "The company estimated that the cost of intravenous immunoglobulin therapy, incorporating the acquisition cost and administration of 5 weekly infusions, was £13,706." This wording is ambiguous. To clarify, £13,706 was the estimated one-week intravenous immunoglobulin therapy cost based on one active treatment week comprising 5 infusions. The frequency of active treatment weeks was assumed to be every 3.5 weeks, based on British Committee for Standards in Haematology guidelines.[1]	Comment noted. Section 3.35 of the FAD has now been updated.

Consultee	Comment [sic]	Response
	The document states “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.” This is incorrect. This discussion concerned comparators outside of the base case only, as base case comparisons used Study 116 ToT data to inform cost assumptions for rituximab, BSC and ofatumumab.	Comment noted. This information was included in the ACD, but has been removed following the Committee’s consideration of the new evidence. Please see section 3.34 of the FAD.

Consultee	Comment [sic]	Response
Chronic Lymphocytic Leukaemia Support Association	p3 para 1.1 This Committee decision is the opposite of the decision taken by the Scottish Medicines Consortium (SMC) on 9 March 2015 and based on the same evidence and we need to understand the key reasons for this. "Idelalisib is approved for use within NHS Scotland in combination with Rituximab for the treatment of adult patients with relapsed CLL who are unsuitable for chemotherapy and treatment naïve patients with 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy." Dr. Angus Broom, Consultant Haematologist, Western General Hospital, NHS Lothian said: "The SMC's decision on Idelalisib marks a significant advance for patients with CLL in Scotland, as it is a life-extending treatment with the potential to help alleviate both the emotional and physical impact for patients and families living with CLL. Idelalisib provides physicians with a new treatment option for previously untreated patients with markers of aggressive CLL disease or relapsed CLL." We would like to further highlight that a Scientific Advisory Group convened during the SMC review of this medicine by the European Medicines Agency (EMA) noted that the size of the treatment effect is unprecedented in this pre-treated and frail patient group and the activity in subgroups with 17p deletion or TP53 mutation is important in view of their poor responsiveness to conventional therapy.	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's economic analysis and the ERG's critique and further analyses. Following the submission of additional evidence from the company and consideration of comments it received from clinical and patient experts during the appraisal consultation, the recommendations were updated accordingly. Please see section 1 of the FAD.
	p3. para 1.2 The committee is not minded to approve this combination for refractory patients. This is the hardest decision to understand as the drug combination is clearly uniquely effective for this group and there is no current alternative for these patients. Patients who do not respond are unconcerned by apparently arbitrary definitions of refractory and relapsed, their sole concern is to receive an effective alternative.	

Consultee	Comment [sic]	Response
	p11. para 3.20 We reject the assertion by the ERG 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. Patients experience shorter and shorter remission times with each chemotherapy treatment so inevitably patients require many treatments within a short timeframe. In addition the TP53 deleted/mutated clone will increase over time and with each aggressive treatment.	The ERG's comments related to the difference between the patients in Study 116 (high-risk relapsed less than 24 months after last treatment) and those whose disease relapses more than 24 months after the last treatment. Section 3.20 of the FAD has been updated.
	p11. para 3.21 The ERG noted that the results should be interpreted with caution because the trial was stopped early leading to possible overestimation of treatment effect. What is the evidence for this assertion in trials using novel therapies?	The ERG used the following reference on page 18 of its report to support this statement: Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. BMJ. 2012;344:e3863.
	p25. para 4.5. The committee has noted that the trial was conducted in patients who were generally older with more co-morbidities (average age 71) and who had on average at least three prior therapies. We reject this premise because according to SEER data, between 2003 and 2007, the median age at diagnosis for CLL was 72 years. (Source: Neoplastic Diseases of the Blood, Borthakur & O'Brien.). As stated earlier, once patients relapse, subsequent treatments occur more frequently, so an average of 3 prior therapies is not untypical.	The Committee heard from the clinical specialists who noted the difference between the patients in Study 116 (high-risk relapsed less than 24 months after last treatment) and those whose disease relapses more than 24 months after the last treatment. Section 4.5 of the FAD has been updated accordingly.
	p26. para 4.6. The committee noted the lack of comparative evidence for the 17p/TP53 population but acknowledged the drugs' effectiveness in this population. As there is no comparative therapy for this group of patients there is no ethical trial that can be devised to provide further evidence to the committee - we hope that the Committee can reconsider its decision in this regard.	The FAD has now been updated. Please see section 4.6.

Consultee	Comment [sic]	Response
	In conclusion, we appeal to the Committee to consider this appraisal holistically, rather than solely through financial modelling which will be sensitive to pricing - a decision between NICE and Gilead, and independent of patient need. There are many hundreds of patients now and in the future whose lives can be immensely improved by the availability of less toxic and more effective treatments. The CLLSA is very concerned about the potential lack of equity in patient access to these drugs. Patients are anxiously awaiting early approval of this novel combination and we trust that the lifeline that it offers them will not be denied.	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's economic analysis and the ERG's critique and further analyses. Following the submission of additional evidence from the company and consideration of comments it received from clinical and patient experts during the appraisal consultation, the recommendations were updated accordingly. Please see section 1 of the FAD.
The Royal College of Physicians	Page 23 section 4.1 The clinical experts have not advised that FCR is re-offered. Instead, they outlined that in the current setting FCR has been an effective solution for FIT patients in the pre-BCR-inhibitors era (MD Anderson data) and can be re-considered as per current NICE guidelines. Clearly new solutions are requested because PFS will become shorter after first line with the same treatment. New treatment solutions are therefore necessary in this type of patients.	Comment noted. The FAD has been updated see sections 4.1-4.3.
	Page 23 section 4.1 The Committee have confused the distinction of relapsed and refractory patients. According to the IWCLL criteria refractory patients relapse within 6 months. However, the BSH guidelines recommend that patients who have relapsed within 24 months from first treatment should be considered high-risk and recommended not treating with the same option but treating 'ideally' within clinical trials. This guideline was written when data on BCR-associated inhibitors were not available (2012).	Comment noted. The FAD has been updated see sections 4.1-4.3.

Consultee	Comment [sic]	Response
	Page 26 section 4.6 The Committee reasons against the lack of comparative evidence in study 101-08. To our knowledge, randomised trials in 17p- CLL have not taken place either nationally or internationally. Furthermore, our experts do not expect a trial for such a rare but unmet clinical need in this cohort in the near future.	Comment noted. The FAD has now been updated. Please see section 4.6.
	Page 36 section 4.24 It is true that data from only 9 patients with CLL 17p- treated with idelalisib front-line is currently available from the literature (Hillmen). The limited number is not dissimilar from that of other trials or clinical studies presented over the years on this rare but aggressive form of CLL. However, even in this limited number idelalisib appears highly effective for a population of patients who: i) are very likely to be refractory to conventional (immuno)chemotherapy and ii) will very likely acquire complex genetic lesions. The occurrence of a complex caryotype will make the patients even more likely to be refractory to old and novel genetic strategies in second or subsequent lines (Jain P, Blood. 2015 Mar 26;125(13):2062-7). This biological observation provides scientific evidence for the use of drugs alternative to chemotherapy in first line. Idelalisib is one of these alternative drugs. Also, CLL with 17p- is a clinically unmet need and does require a strategy. Idelalisib plus rituximab is an effective strategy. .	The Committee considered all the available clinical and cost-effectiveness evidence submitted including the clinical and expert testimonies. The FAD and its recommendations have been updated accordingly. Please see section 1 for the updated recommendations and section 4.6 for the Committee's considerations of the evidence for the untreated group.

Consultee	Comment [sic]	Response
	In conclusion, we believe that the ACD includes serious misinterpretations with relation to: • Clinical demand • Rarity of disease subset • Definition of relapsed patients We would further highlight that in front line CLL there is a trial of 64 patients treated with idelalusib plus rituximab which shows excellent results. These include nine 17p deleted patients with the same outcome as those without 17p del. This indicates that these patients should be treated with idelalisib + rituximab in front line as their outcome is better than those treated in relapse - this is always the case with CLL. The current ACD means that clinicians have to give patients with 17p del - an ineffective, expensive and toxic therapy -before moving to an effective therapy. We would also stress that there is a significant overall survival benefit for idelalisib + rituximab in refractory CLL. The current ACD denies refractory patients this life prolonging therapy	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company's economic analysis and the ERG's critique and further analyses. Following the submission of additional evidence from the company and consideration of comments it received from clinical and patient experts during the appraisal consultation, the recommendations were updated accordingly. Please see section 1 of the FAD.

Consultee	Comment [sic]	Response
United Kingdom Chronic Lymphocytic Leukaemia Forum	**The management of multiply relapsed frail patients** This patient cohort is very challenging to treat. The patients in the idelalisib 116 trial were elderly (median age 71), multiply treated (median 3 prior lines of therapy), poor performance status, poor marrow function and genetically resistant to chemotherapy (over 40% had TP53 disruption). Prior to the presentation of the idelalisib 116 trial (the main evidence for TAG488) and the ibrutinib Resonate trial, there were no randomised trials in CLL beyond first relapse. Although inclusion criteria were different between the 116 and Resonate trials, they both recruited heavily pre-treated patients who were relapsed and refractory (i.e. progressed within 6 months) with little in the way of standard chemotherapy options available. With both trials, the novel therapy has proven vastly superior in terms of progression free and overall survival.	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials and the clinical expert testimonies. Following the submission of additional evidence from the company the recommendations for the high-risk relapsed groups were updated. Please see section 1 of the FAD for the updated recommendations and Section 4.1-4.3 for the Committee's discussions on the treatment pathway and appropriate comparators for each subgroup.

Consultee	Comment [sic]	Response
	It appears that a key aspect of the difficulty NICE have with approving the use of idela / rituximab is deciding whether rituximab monotherapy, in the phase 3 Gilead 116 trial, was an appropriate control arm for both relapsed and refractory patients. I accept that rituximab monotherapy has little use in UK CLL practice, but I would argue that prior to access to ibrutinib or idelalisib, standard management of 4th line CLL in frail patients was palliative care. The GID-TAG488 document discusses a number of apparent alternative therapies for relapsed CLL that were proposed by the NICE scoping meeting, such as FCR / Bendamustine-R / Chlorambucil-R / high dose steroid-R. However, I would argue strongly that none of these treatment options have either an evidence base, or would be appropriate for this group of frail, heavily pre-treated patients. A single phase 3 randomised trial with FCR as second line therapy for very lightly pre-treated patients has been published, but otherwise, all other trials in relapsed CLL with the drug combinations discussed were small phase 2 very heterogeneous, poor quality trials. All alternative therapies (with the exception of ibrutinib) lack any randomised quality trial data applicable to the type of patient studied in the Gilead 116 idelalisib trial. If idelalisib and / or ibrutinib are not available to UK CLL patients there will simply be no alternative treatment except palliation, for this type of patient.	

Consultee	Comment [sic]	Response
	Possible differential benefit for 'refractory' patients compared with 'relapsed' patients The 116 trial included both refractory and relapsed patients, and the data from the trial were clear. Use of idelalisib provided a marked progression free survival and indeed a true overall survival compared with the control arm. So despite the provision for cross-over to get the active drug rather than placebo if patients progressed, there was still excess mortality in patients who were not randomised to idelalisib at the start of the trial. I am unable to see how NICE can separate the refractory patients (i.e. progression within 6 months of last therapy) from the relapsed patients in their analysis based on the data from this trial. It is clear that 'delayed' start of idelalisib in the trial (i.e. in patients randomised to placebo rather than idelalisib) had a direct impact on overall survival. If NICE approve idelalisib for refractory patients but not relapsed patients there is a very good chance this will re-create the early excess mortality seen in the trial, by denying relapsed patients early treatment with idelalisib. This will be even more striking for the TP53 disrupted patients who will have a very high chance of early death if denied either ibrutinib or idelalisib at relapse. Inevitably, a restriction of idelalisib to 'refractory' patients will push clinicians to give 2 cycles of ineffective therapy to patients who progress beyond 6 months to then make them eligible for idelalisib as 'refractory' patients. For some patients this will simply not work and early death will be the result. I am sure NICE would agree that this would not represent best practice.	Please see sections 4.1-4.6 of the FAD which has been updated following additional evidence submitted by the company.

Consultee	Comment [sic]	Response
	First Line treatment of TP53 disrupted CLL This group of patients represents around 5-8% of all first line patients who need therapy for active CLL. We know from multiple trials that these patients have poor response rates, early relapse and higher early mortality when treated with chemotherapy compared with non-TP53 disrupted patients. With the removal of the license for alemtuzumab, the only licensed drugs to treat first line CLL with TP53 disruption are ibrutinib or idelalisib / rituximab. Although there is no prospective randomised data in first line for these drugs with these particularly poor-risk patients, the data from the relapsed trials and the small non-randomised datasets from the first line trials were so striking that this indication was approved by the EMEA. It is simply not ethical to run a trial of 'novel agent' vs chemotherapy in the first line setting for TP53 disrupted patients and these trials will not be done. It is imperative these drugs are approved for use in first line, or again clinicians will inevitably have to give 2 cycles of ineffective therapy to patients just to move them rapidly to appropriate therapy when they are resistant to treatment. Again, this is simply 'bad medicine' and goes completely against the ethos of personalised medicine with precision-targeted therapies.	Please see sections 4.1-4.6 of the FAD which has been updated following additional evidence submitted by the company.

Consultee	Comment [sic]	Response
	Conclusions It is essential that UK CLL patients have access to novel CLL therapies at the time of relapse of their CLL in line with the inclusion criteria for the respective clinic trials, or as first line therapy if they are TP53 disrupted. Access to ibrutinib and idelalisib through clinical trials and the Cancer Drugs Fund has resulted in a complete shift in how relapsed CLL can be managed. The routine clinical experience with these drugs continues to increase rapidly across the UK. On a personal level, I now have over 30 patients on 'novel therapies' in my CLL clinic and I have many examples of patients who without doubt would have died by now without these drugs, but are instead enjoying an excellent quality of life taking daily tablet medication, and for the most part, staying out of hospital. I appreciate that this will represent a significant new cost pressure for the NHS, but managing CLL without access to these novel drugs will create huge difficulties for our patients and will undoubtedly lead to higher mortality rates for UK CLL patients.	Comment noted. The recommendations have been updated. Please see section 1 of the FAD.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response

Nominating organisation	Comment [sic]	Response
Clinical expert	Page 3 1.1. It appears NICE plan to reject the use of idelalisib in patients with 17p deletions/mutations. The data for recommending the use of idelalisib in patients with 17p deletion/mutation was based on a relatively small number of patients. However, as the Appraisal Committee know idelalisib was very effective in this patient group and that there are no licensed NICE approved alternatives for this particular patient sub-group. Thus what would the Appraisal Committee recommend to clinicians when treating 17p deleted/mutated patients. Also in 1.2 (page 3) it appears the Appraisal Committee may recommend idelalisib to be used in refractory CLL patients. Firstly the reason why patients with 17p deletion/mutation do so poorly is exactly because they are refractory to standard chemo-immunotherapy. So assuming the Appraisal Committee do ultimately approve idelalisib for use in refractory CLL patients are they asking clinicians to use what we know will be ineffective chemo-immunotherapy until they fulfil the criteria to be classified as refractory (no response or relapse within 6 months of last therapy)? To me it seems unethical for clinicians to knowingly use ineffective therapy with a high chance of patient's side effects. Furthermore we know that the p53 deleted/mutated clone will grow when using ineffective treatment as the non p53 deleted/mutated clone will still be killed by the chemo-immunotherapy. So by denying the patient access to upfront idelalisib but then allowing it to be used once the patient is refractory is likely to lead to an overall worse outcome than if the patient had been allowed upfront idelalisib as the p53 deleted/mutated clone will have grown during the period of chemo-immunotherapy.	Comments noted. Following the submission of additional evidence by the company the recommendations were updated. Please see section 1 of the FAD for the updated recommendations.

Nominating organisation	Comment [sic]	Response
	Page 3 1.1. It appears the Appraisal Committee plan to reject the use of idelalisib in patients with relapsed CLL. As the Appraisal Committee are aware the standard recommendation for patients who relapse from CLL is to potentially treat with the same agent/regimen if their response to their previous therapy lasted longer than 24 months. This is stated in the British Committee for Standards in Haematology (BCSH) Guidelines and is standard practice across the world and is based on several studies including that of Tam et al – November 2014. This study clearly shows that the effectiveness of retreating patients with fludarabine/cyclophosphamide/rituximab (FCR) who have previously received FCR is very much predicted by the duration of response to their first course of FCR. As can be seen from the survival curves there is only a limited time duration of survival in those whose first response duration following FCR lasted < 2 years. Also according to previous NICE appraisals a patient who previously received FCR should only receive FC at relapse as NICE has stated that rituximab should not be used at relapse in patients who have previously received rituximab – this would make survival even worse than that seen in the Tam paper. So given the evidence shown in the what would the Appraisal Committee be recommending a clinician should use in patients who received frontline FCR but who relapses within 2 years? Also this patient may have the opportunity of a potentially CLL curing/ life-saving allogeneic transplant – so denying the patient the opportunity to receive idelalisib is effectively condemning them to almost certain death when the patient would have had a very real chance of surviving with a reasonable quality of life.	The recommendations for the high-risk relapsed group have been updated. Please see section 1 of the FAD.

Nominating organisation	Comment [sic]	Response
	Page 3 1.2. It appears that the Appraisal Committee is not minded to recommend idelalisib in patients with refractory CLL. I found this rather surprising as the data showing idelalisib is effective in refractory CLL patients is very good and again I'm really not sure what the Appraisal Committee would expect a clinician who is treating a patient who for example is refractory to FCR? There are no other licensed/NICE approved agents for this patient group. Is the Appraisal Committee saying that the clinician should use treatment which everyone knows will not be effective- is that ethical? Obviously the outcome for this patient will be to succumb to their CLL when idelalisib would have prolonged survival with a good quality of life in the overwhelming majority of patients. Also if the refractory CLL patient had a potentially CLL curing/ life-saving allogeneic transplant option is it really acceptable simply to allow these patients to succumb to their disease by denying this patient group access to idelalisib?	The recommendations for the refractory group have been updated. Please see section 1 of the FAD.
	Page 11 3.2. The ERG noted that there was a high number of 17p deleted patients in the 116 study compared to what one would expect in "UK clinical practice". I questioned this comment at the Appraisal meeting as the 116 study included patients who had at least 1 prior therapy (3 on average) and had to have relapsed within 2 years of last therapy. Several studies have shown that in end stage CLL the often quoted figure is 40% of such patients will have p53 deletion/mutation. Also many of the patients in the 116 study were in fact UK patients. So how can the ERG say that the study was not representative of the UK patient population when it is this same UK population who took part in the 116 study?	The ERG's comments related to the difference between the patients in Study 116 (relapsed less than 24 months after last treatment) and those whose disease relapses more than 24 months after the last treatment. The FAD has been updated to clarify this. Please see section 3.20.

Nominating organisation	Comment [sic]	Response
	Page 23 4.1. As outlined above the standard approach to refractory CLL patients is either supportive care, rituximab monotherapy or clinical trials of a novel new agent. The text says “The clinical expert advised that re-treatment is offered to people for whom fludarabine-based regimen were suitable, and whose disease has not relapsed at least 6 months after, but within 24 months of treatment”. I think the Advisory Committee have mis-understood what the experts were saying as this statement is only correct for patients who for whatever reason had not received a purine based regimen as upfront therapy but at relapse are deemed suitable for a purine based regimen- in reality this is very few patients. For patients whose disease relapses after 24 months one of the treatment options is to offer the same treatment again. However that is not the case for those patients who relapse within 6-24 months - as stated in the BCSH Guidelines – see Tam above. To those who had previously received FCR who by definition of the fact they were previously fit enough to receive FCR other treatments will be attempted included clinical trials or off licensed drugs eg alemtuzumab, lenalidomide or ofatumumab with for those with a suitable donor these therapies acting as a bridge to allograft.	Please see section 4.1-4.3 of the FAD which has now been updated to reflect these changes.

Nominating organisation	Comment [sic]	Response
	For those patients who were not fit for upfront FCR or a similar bendamustine regimen then if they relapse between 6-24 months the treatment options are very limited. The only reason why for this patient group “the same treatment if offered” is simply the lack of any other licensed effective agent- they will not be eligible for the alemtuzumab compassionate use programme as they do not have 17p deletion/mutation and they will not be eligible for ofatumumab because they are not double refractory to fludarabine/alemtuzumab. The 116 study had a median population age of 71 so idelalisib will be of great value to this patient group and without doubt prolong life. Thus I would respectfully request the review their interpretation of section 4.1.	

Nominating organisation	Comment [sic]	Response
	Pages 23/24 – 4.2. The Advisory Committee rightly refer to the BCSH guidelines which state refractory disease is defines as inadequate response or relapse within 6 months. This definition is really not of much clinical value for as stated above the same BCSH Guideline also say that patients who relapse within 24 months should not be offered the same therapy they have just received. So the term refractory is semi-meaningless in this context and there has been some discussion about whether refractoriness should be re-defined within the BCSH Guidelines as being relapse within 24 months. However, the term refractory and its definition as relapse within 6 months is still applied to national and international clinical trials and hence it was felt inappropriate to have a unique UK definition of refractoriness. One other consideration is it will be easy to make a relapsed patient become eligible for idelalisib as a refractory patient simply by giving the patient a therapy which they – the clinician and patient - know will be ineffective. So if we take a patient who relapsed from say FCR between 6 and 24 months and give him chlorambucil monotherapy and one could be really cynical and give 2mg orally on alternate days – then clearly this will not do anything and the disease will progress. The clinician can now say the patient is refractory to chemotherapy and hence eligible for Idelalisib after 2 months of chlorambucil therapy! I understand this sort of practice is already taking place in England to access drugs – idelalisib and similar agents - from the CDF.	Please see section 4.2 of the FAD which has now been updated.

Nominating organisation	Comment [sic]	Response
	Page 30 4.13 and Page 36 4.23. I stated at the Advisory Committee meeting that overall 10-20% of all CLL patients are hypogammaglobulinaemic. However when considering heavily pre-treated patients – such as those in the 116 study - and those who had received prior rituximab the number of patients requiring IVIG would in my opinion be ~25%.	Please see sections 3.52 and 4.11 of the FAD which has now been updated.
	Page 33 4.17. I do find it surprising that given the lack of a licensed therapy for 17p deleted/mutated patients that the Advisory Committee have ruled out the use of idelalisib in this patient group. I appreciate that the 17p deleted/mutated subgroup may have been small but I would respectfully request that the Advisory Committee reconsider this as there will never be a phase 3 study to address this patient group which is a real area of unmet clinical need.	Please see sections 4.1-4.6 of the FAD which has now been updated.
	Page 34 4.20/4.21/4.23 I would take issue with the interpretation of the end of life criteria. As one can see from the Tam survival curve in patients who initially received FCR who then get retreated with FCR at relapse. Clearly for those who relapsed within 1 year and possibly 2 years of receiving their initial FCR the end of life criteria apply. I would therefore respectfully ask the Advisory Committee to re-consider its interpretation of the end of life criteria and access to idelalisib. To me the end of life criteria apply to many patients who relapse within 2 years of initially receiving FCR.	Please see sections 4.15-4.16 of the FAD which has now been updated.

Nominating organisation	Comment [sic]	Response
	Page 37 As outlined above I would respectfully request/urge the Advisory Committee to reconsider its present recommendation in 17p deleted/mutated patients but also in relapsed patients who have received a purine based regimen as initial therapy such as FCR but who relapse within 24 months. Firstly there are really no suitable licensed alternative therapies and the end of life criteria should be applied.	The recommendations have been updated. Please see section 1 of the FAD.
	Page 38 I welcome the acknowledgement for the Advisory Committee that more treatments are required for 17p deleted/mutated patients and hence would respectfully request they consider asking Gilead to provide more evidence for this patient group.	The recommendations have been updated. Please see section 1 of the FAD.
	Page 38/39 I concur with the Advisory Committee that to split refractory from relapsed CLL patients but have concerns that it has cherry picked the definition of refractory from the BCSH Guidelines which is really out of date and chosen to ignore the clinical evidence and other statement in the BCSH Guidelines which does not recommend re-treating patients with the same regimen who have relapsed within 24 months of initial therapy.	The recommendations have been updated. Please see section 1 of the FAD.

Nominating organisation	Comment [sic]	Response
	Page 41. The average age of diagnosis of CLL in the UK is 72 years. Clearly therefore the average age of first treatment in the UK must be higher than 72 years. I do not therefore concur with the Advisory Committee's view that the patient group in the 116 study is not representative of the UK CLL population and as stated above the UK provided many patient for this study. Likewise I disagree that the 42% p53 deleted/mutated patients is not typical of heavily pre-treated patients as the figure widely quoted is 40% of "end stage" patients and I'm sorry to say that without the likes of idelalisib these patients can be classified as "end stage".	Please see section 4.5 of the FAD which has now been updated.
	Page 47 Please refer to my comments above re-relapsed patients and the applicability of the small population end of life criteria.	Comment noted.
Clinical expert	Page 23 section 4.1 The clinical experts have NOT advised that FCR is re-offered, I have said that in the current setting FCR has been an effective solution for FIT patients in the pre-BCR-inhibitors era (MD Anderson data) and can be re-considered as per current NICE guidelines. Clearly new solutions are requested because PFS will become shorter after first line with the same treatment. New treatment solutions are demanded in this type of patients.	Comment noted. The FAD has been updated see sections 4.1-4.3.

Nominating organisation	Comment [sic]	Response
	Page 23 section 4.1 The committee are confusing the distinction of relapsed and refractory patients. According to the IWCLL criteria REFRACTRY patients relapse within 6 months. However the BSH guidelines recommend that patients who have relapsed within 24 months from first treatment should be considered high-risk and recommended not treating with the same option but treating 'ideally' within clinical trials. This guideline was written when data on BCR-associated inhibitors were not available (2012).	The FAD has been updated see sections 4.1-4.3.
	Page 36 section 4.24 It is true that data from only 9 patients with CLL 17p- treated with Idelalisib front-line is currently available from the literature (Hillmen). The limited number is not dissimilar from that of other trials or clinical studies presented over the years on this rare but aggressive form of CLL. However, even in this limited number Idelalisib appears highly effective for a population of patients who i) are very likely to be refractory to conventional (immuno)chemotherapy and ii) will very likely acquire complex genetic lesions. The occurrence of a complex caryotype will make the patients even more likely to be refractory to old and novel genetic strategies in second or subsequent lines (Jain P, Blood. 2015 Mar 26;125(13):2062-7). This biological observation provides scientific evidence for the use of drugs alternative to chemotherapy in first line. Idelalisib is one of these alternative drugs. Also, CLL with 17p- is a clinically unmet need and does requires a strategy. Idelalisib plus rituximab is obviously an effective strategy.	The FAD has been updated see sections 4.6.

Nominating organisation	Comment [sic]	Response
	Page 26 section 4.6 The committee argues against the lack of comparative evidence in study 101-08. To my knowledge, there have not ever been randomised trials nationally or internationally in 17p- CLL. How could we ever expect such a trial for a rare but unmet clinical need for this cohort in the near future?	Comment noted. The FAD has been updated see sections 4.6

Comments received from commentators

Commentator	Comment [sic]	Response
Novartis	**Has all of the relevant evidence been taken into account?** • Whilst on the whole we believe the relevant evidence has been taken into account, it is important to note that ofatumumab is no longer funded by the Cancer Drugs Fund and its use is extremely limited in the double refractory setting (i.e., the position reflecting its relevance as a comparator in this appraisal). Therefore it is questionable as to whether it should be included as a comparator in the evaluation.	Comment noted. The FAD has been updated. Please see section 4.3.

Commentator	Comment [sic]	Response
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Ofatumumab is available for all indications at a discount agreed in a patient access scheme associated with TA344 (Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia). Therefore if the Committee believe that ofatumumab is still relevant as a comparator, the interpretation of the cost effectiveness evidence should reflect the fact that the ICER for idelalisib in this comparison is likely to be significantly higher using currently available pricing.	The FAD has been updated. Please see section 4.3 for the list of relevant comparators for this appraisal.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? • Yes	Comment noted.

No comments received from members of the public.