ERG comments on the Gilead Response to: Appraisal Consultation Document - Idelalisib for treating chronic lymphocytic leukaemia [ID764]

Questions	*Examples of the company response*	*ERG comments*
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	"The patient group in Study 116 represents this high risk patient group i.e. those who relapse within 24 months (early relapsers), a proportion (over 40%) of whom have 17p deletion or TP53 mutation…"	The Company's comments about Study 116 are correct. The company refer to the study
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	"While we feel the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence base, we note some factual inaccuracies and have provided details of these in Section 2)."	Please refer to our comments on the factual error check.
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 ERG do not have any comments to add.
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."	The ERG do not have any comments to add.

ERG response the factual inaccuracies identified by Gilead in the ACD
The following factual inaccuracies were identified in the ACD:

Paragraph number in ACD	*Comment*	*ERG response*
2.1	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…"	We agree.
2.3	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."	We agree.
3.1	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."	The company are correct. The ACD reports "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". In section 4.2.1 the ERG reported the following: ***"Refractory or relapsed CLL population (SR #1):*** This review included six RCTs: study 116 (Furman et al., 2014),[1] Robak et al. (2010),[5] Niederle et al. (2013)[6] Leblond et al. (2012)[9] Byrd et al. (2014),[10] and Awan et al. (2014).[11]"
3.1	The document states "…whose disease was relapsed and refractory." Please reword to read "…whose disease was relapsed or refractory."	Agree
3.3	The document states "A total of 220	Agree

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	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.	
3.3	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).”	Agree
3.3	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.”	Agree
3.4	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	Agree

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	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."	
3.5	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.	The study should be "study 116" as stated in the ERG report. We agree with the remaining rewording.
3.6	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."	Agree
3.7	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	Agree

Paragraph number in ACD	*Comment*	*ERG response*
	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)."	
3.7	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)."	Agree
3.7	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.	The ERG do not have any comments to add.
3.17	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."	Agree
3.18	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	Agree

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	common treatment-emergent adverse events were diarrhoea or colitis (77%), rash (58%) and pyrexia (42%).”	
3.19	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.”	In section 1.2 the ERG stated the following: ***“Refractory or relapsed CLL population (SR #1):*** This review included six RCTs: study 116 (Furman et al., 2014),[1] Robak et al. (2010),[5] Niederle et al. (2013)[6] Leblond et al. (2012)[9] Byrd et al. (2014),[10] and Awan et al. (2014).[11] The review also included 13 non-RCTs as having relevant comparators: Furman et al. (2013),[12] Coiffier et al. (2008),[13] Wierda et al. (2010),[14] Tam et al. (2006),[15] Badoux et al. (2011),[16] Smolej et al. (2012),[17] Lopez et al. (2013),[18] Fischer et al. (2011),[19] Pileckyte et al. (2011),[20] Donnellan et al. (2014),[21] Sanhes et al. (2014a),[22] Zagoskina et al. (2014),[23] and Smolej et al. (2014b).[24]”
3.19	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.	The Hillmen study was discussed in the original ERG report (e.g. section 4.2.2)
3.31	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 clarification is correct. The constant shape parameter was used when comparing to data outside of Study 116.

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	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.	
3.34	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.	This clarficiation is correct. It should read that for other comparators (outside Study 116) "all patients remaining in the progression-free state would complete the full course of treatment"
3.35	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]	References to the old cost assumptions surrounding IvIG therapy no longer appear relevant, in light of the new costs presented in the revised models.
4.12	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	This clarification is correct. The comment should be restricted to treatments outside of those informed by Study 116 data.

Paragraph number in ACD	*Comment*	*ERG response*
	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.	

ERG comments on the additional cost-effectiveness analyses undertaken

The company provides three new sets of analyses, based on various combinations of altered assumptions. Assumptions that vary between the different scenarios (and the base case model presented in the original submission) are as follows:

- The use of Study 116 EQ-5D utility data versus Dretzke et al data to inform utilities in the pre-progressive state.
- A five year duration of treatment benefit with idelalisib versus the lifetime treatment benefit previously assumed.
- A new, lower estimate of the cost of IvIG therapy, resulting from the correction of an inaccurate assumption in the original submission (originally an assumption of five administrations per week was assumed; this has now been reduced to one). The new estimate of £2,741 represents a decrease of 80% from the value in the initial submission. This new assumption does seem a more appropriate one, as per the cited DH clinical guidelines.

Revised base case

The first new analysis presented, labelled by the company as the "revised base case", does not include the new corrected assumption on the cost of IvIG therapy, and therefore is not relevant for decision making purposes. However, it does allow us to validate the new results submitted by the manufacturer against those produced by the ERG when making the same modifications to the model. The results obtained, while not identical (£16,977 per QALY against £16,947 per QALY for IR versus R) are similar enough as to raise no concerens about the validity of the new results submitted.

Proposed base case

The models listed as the "corrected base case" and the "proposed base case" both incorporate the new cost of IvIG and the reduction in the duration of treatment benefit. The "corrected base case" model uses the ERG's suggested approach of using data from Dretzke et al. for all utility values, whilst the proposed base case makes use of Study 116 EQ-5D data. The ERG's objection to how such data were used in the original submission was the inconsistent utilites generated, where pre-progressive patients discontinuing from idelalisib were assumed to permanently maintain a higher HRQoL than those treated with rituximab (until disease progression). This has been addressed in the new submission by assigning the utility from the rituximab arm of Study 116 to those patients discontinuing from idelalisib treatment. With this modification made to address the previous concern, the ERG is now happy with the manufacturer's suggestion that the "proposed base case" be used as the primary analysis. It is, however, important to note that this model still includes the assumption of 45% of non-responding patients requiring IvIG therapy, and 0% of responders.

Results – Proposed base case

The new base case assumption lead to an ICER for IR versus R of £26,403 per QALY. ICERs for IR versus other possible treatment options were as follows:

- £35,275 per QALY versus best supportive care
- £10,668 per QALY versus ofatumumab monotherapy
- £25,106 per QALY versus FCR
- £28,284 per QALY versus steroids plus rituximab
- £32,607 per QALY versus bendamustine with rituximab
- £34,922 per QALY versus chlorambucil with rituximab
- £44,302 per QALY versus chlorambucil monotherapy
- £49,523 per QALY versus bendamustine monotherapy

Two important univariate sensitivity analyses are also presented, looking at the impact of changing the proportion of patient (responders/non-responders) requiring IvIG, and varying the duration of idelalisib treatment benefit. These are summarised in the tables below:

Table 1: Sensitivity of the proposed base case ICER, IR versus R, to the proportion of patients assumed to receive IvIG therapy

		% Overall responders receiving IvIG therapy				
		0%	*5%*	10%	15%	20%
% Non-responders receiving IvIG therapy	20%	£27,773	£29,547	£31,321	£33,095	£34,869
	25%	£27,499	£29,273	£31,047	£32,821	£34,595
	30%	£27,225	£28,999	£30,773	£32,547	£34,321
	35%	£26,951	£28,725	£30,499	£32,273	£34,047
	40%	£26,677	£28,451	£30,225	£31,999	£33,773
	45%	£26,403*	£28,177	£29,951	£31,725	£33,499
* Proposed Base Case ICERs						

Table 2: The sensitivity of Proposed Base Case ICERs to the restriction applied to relative treatment benefit estimated for IR OS

	Corrected ICER, idelalisib with rituximab versus		
Limit applied to relative treatment benefit for idelalisib	**Rituximab**	**BSC**	**Ofatumumab**
3 years	£33,850	£45,674	£12,880
4 years	£29,135	£39,091	£11,480
5 years	£26,403*	£35,275*	£10,668*
No relative limit applied	£21,317	£28,174	£9,156
* Proposed Base Case ICERs			

Whilst these new analyses address several important areas of uncertainty from the original submission, there are still considerable uncertainties present in the new data. The areas of uncertainty which are likely to make the most substantial different to the cost-effectiveness of idelalisib are listed below.

Parameter/model feature	**Current assumption**	**Likely impact of varying assumption**
Patient population	Study 116 population is modelled, which is assumed to be sufficiently similar to the UK CLL treatment population that results can be extrapolated to this group	If the treatment benefit of idelalisib is less in the populations in the scope than Study 116, then idelalisib would become less cost-effective than it currently appears
Adjustment for crossover in rituximab monotherapy arm of Study 116.	Idelalisib monotherapy has the same efficacy as idelalisib with rituximab.	If idelalisib monotherapy is less effective than idelalisib with rituximab, idelalisib will become less cost-effective than it currently appears
Clinical outcomes for ofatumumab monotherapy	Ofatumumab monotherapy has equal efficacy and safety to rituximab monotherapy	Unclear. Depend on whether ofatumumab is considered more or less effective than rituximab
Adjustment for differences in baseline populations (comparisons outside Study 116)	The proportional hazards models from Badoux et al. can adequately adjust for baseline population differences	Unclear. There is likely to be considerable error in the adjustment factors calculated, but it is unclear in which direction that error would lie

Finally, the results from the new model are highly sensitive to the cost-effectiveness threshold chosen. Results from the probabilistic sensitivity analysis indicate that, whilst IR is cost-effective versus R in 97% of simulations at £50,000 per QALY, it is only cost-effective in 62% and 12% of simulations at £30,000 and £20,000 per QALY, respectively.

The equivalent results for IR versus BSC are 88% at £50,000 per QALY, 22% at £30,000 per QALY and 0% at £20,000 per QALY.

Additional comments from the ERG clinical advisor:

- "I do believe this drug is effective from my anecdotal use of this compound. I do strongly agree there is unmet clinical need when in relapsed refractory and p53 deleted patients there is nothing else to give and clinician is faced with impossible situation. Re-treatment of the relapsed patients with chemotherapy indeed worsens their disease by increasing genetic complexity (although we do not yet know what effect signalling inhibitors like Idelalisib or Ibrutinib will have)."
- "The drug company has presented the trial where the testing of the new agent was done against Rituximab monotherapy and placebo, the treatment which is not effective in CLL. Is the data available from the crossover trial 117 which was extension trial of 116? This would provide the key information."
- "Idelalisib is expensive, together with Ibrutinib it will cause significant financial pressures on NHS therefore the data should be robust to justify the spending."
- "The response written by Dr C Fegan is very good and comprehensive and I agree with all the points but paragraph 7, regarding use of IvIg (based only on his personal experience). Indeed paragraph 4.1 on page 23 in ACD caused a lot of controversy and I must admit it is confusing when I read it now. Dr Fegans comment on this issue is very good."
- "If a new trial is not realistic, I strongly believe that Gilead should set up a retrospective, compulsory database to gather information on responses, side-effect profile and use of IvIg (this should be a condition of approval by NICE). This would be particularly important in p53 deleted patients when the evidence is based on 9(!) patients in the trial, at least it would provide retrospective data."
- "Regarding IvIg, as nobody has any data, Gilead could interrogate the sites participating in 116 trial to acquire the proper evidence rather than using assumptions and the model?"
- "As the patients in the 116 study were a very challenging group (relapsed and refractory to previous treatment) and yet Idelalisib has worked, could Gilead find historical trial/s for relapsed refractory patients and do a form of "analysis" for this specific group of patients."
- "Overall survival in the 116 publication was only 12 months, difference was only 8% but already significant p=0.02 (HR for death, 0.28; 95% CI, 0.09 to 0.86), they probably have 24 months follow up, could they provide that data to strengthen NICE decision?"