Gilead Response to:

National Institute for Health and Care Excellence

Appraisal Consultation Document - Idelalisib for treating chronic lymphocytic leukaemia [ID764]

July 2015

Dear Meindert,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for idelalisib for treating chronic lymphocytic leukaemia (CLL) [ID764]. We have provided our responses below under the specific ACD consultations questions, with further information in Section 1 related to the requested additional analyses and Section 2 outlining factual inaccuracies in the ACD.

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.

Further evidence to support this statement is provided below.

We also draw the Committee's attention to a number of key issues, which were the subject of much conversation at the 22nd July 2014 Scoping Workshop but not considered in the 21st May 2015 Appraisal Committee Meeting.

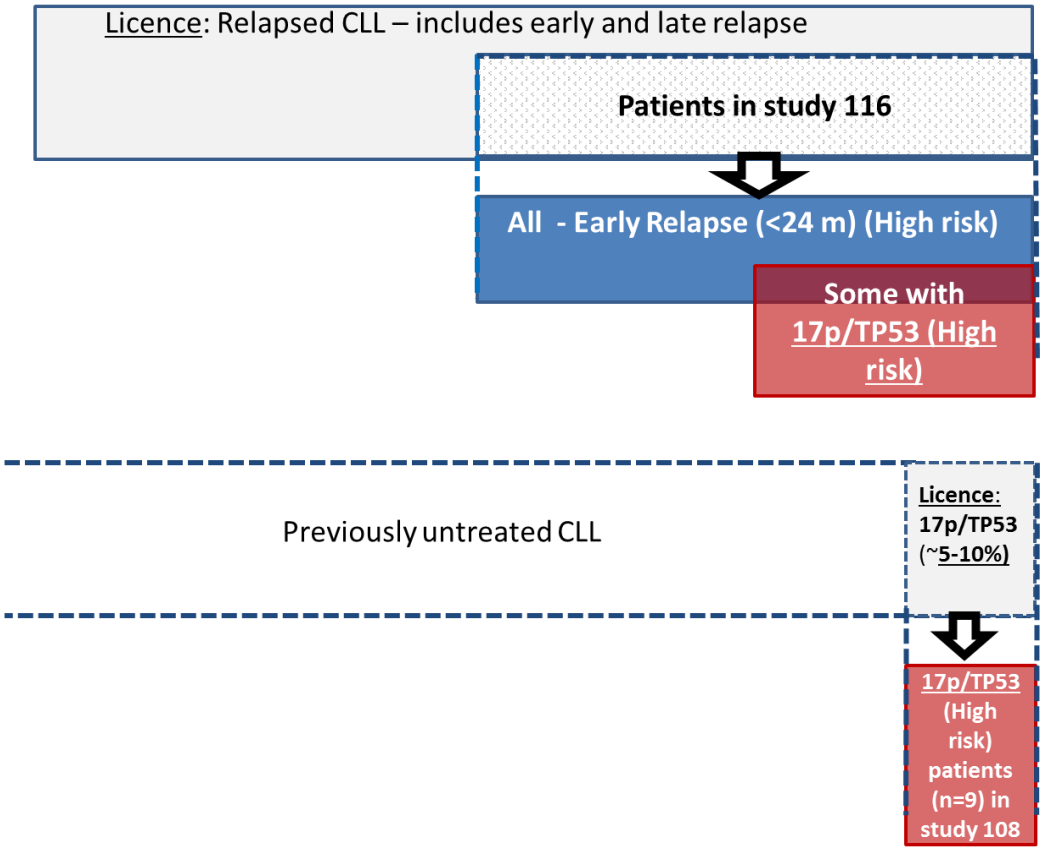
Defining the Patient Population – High Risk Group

The Committee has concluded (ACD Section 4.2) that people whose disease has been previously treated can be separated into two distinct subgroups; those with relapsed disease and those with refractory disease; and that recommendations can be made on the basis of this distinction.

We welcome the Committee's attempts to define an evidenced patient population by clear clinical indicators, but we challenge the Committee's separation of previously treated patients into 'relapsed' and 'refractory' subgroups as inappropriate and not aligned with the evidence base. We recognise that the population of patients with previously treated CLL in which idelalisib with rituximab is licensed is heterogeneous, and that the evidence for clinical and cost effectiveness is in a subgroup of this population who have a life expectancy of less than 24 months and are not suitable for chemotherapy.

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. This is the patient population described in the BCSH guidelines as high risk.[1] According to the European Guidelines (ESMO), patients with a 17p deletion or *TP53* mutation are considered as having very high risk CLL.[2] A summary diagram is provided (Figure 1), which details the patient populations included in idelalisib trials (relapsed and first line) and which, according to the guidelines, are described as high risk in the following ways: 1) Early relapsed and 2) 17p deletion/*TP53* mutation.

Figure 1: Summary of idelalisib clinical trial patients



1. High Risk - Early relapse

Clinicians generally do not use chemotherapy in patients who relapse from first-line chemotherapy treatment within 24 months, irrespective of genetic prognostic factors. These are the type of patients within Study 116.

In line with guidance across Europe,[2-7] the latest BCSH guidance[1] highlights the duration of response that should influence the choice of second-line therapy (i.e. whether or not patients are considered eligible for chemotherapy), with reference to evidence from the German CLL8 trial.[8] These data indicated that patients who experience less than 2 years progression-free survival (PFS) from first-line treatment can expect a median OS of 20.3 months or less from second-line treatment.[8] Consistent with this, relapse from previous treatment within 24 months was an inclusion criterion for Study 116; median OS for patients randomised to placebo was 20.8 months (11.6 months once adjusted for cross-over).

Extensive follow-up data from the MD Anderson 300-patient single-arm study shows CLL patients who are in remission following first-line treatment for up to 2 years to have a median life expectancy of 13 months or less when second line treatment is initiated.[9] Furthermore, the BCSH guidelines summarise the outcomes of patients with high risk disease and across all studies the median OS was less than 19.1 months.[1]

The small group of CLL patients who relapse within 24 months of first-line treatment have a life expectancy within NICE's end-of-life criteria; in addition to follow-up findings from the CLL8 and Anderson MD 300 trials described above, results from patients randomised to placebo in Study 116 attest to this. Results from patients randomised to receive idelalisib in Study 116 demonstrate the substantial increase in length and quality of life, which idelalisib with rituximab promises for this well-defined, high-risk, end-of-life patient group.

We ask that the Committee gives further consideration to these factors and reconsiders idelalisib plus rituximab for previously treated CLL patients who relapse within 24 months (e.g. early relapsers, ineligible for chemotherapy, who are part of high risk group).

2. High Risk - 17p deletion/*TP53* mutation

Previously treated CLL in adults with a 17p deletion or TP53 *mutation*

As stated above, clinicians do not use chemotherapy in patients who relapse from first-line treatment within 24 months, irrespective of genetic prognostic factors. Similarly, clinicians will not use chemotherapy in patients with CLL associated with a 17p deletion or *TP53* mutation, irrespective of treatment history.

These genetic prognostic factors may emerge following treatment, and a patient group exists who are previously treated with CLL associated with a 17p deletion or *TP53* mutation. These patients will exhibit particularly poor response to available cytotoxic treatments, and idelalisib with rituximab offers an effective, life-improving and -extending treatment option, as evidenced by results in the pre-specified subgroup of patients with a 17p deletion or *TP53* mutation in Study 116 presented in our submission.

Though such patients will exhibit poor response to available treatments, we are keen to stress that patients with CLL associated with a 17p deletion or *TP53* mutation need not and should not be further defined by treatment history.

We ask, in light of this, that the Committee recommends idelalisib with rituximab for all CLL patients with disease associated with a 17p deletion or *TP53* mutation, both previously treated and untreated as discussed below.

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

As stated above, we are disappointed that the Committee were unable to recommend idelalisib for use in this patient group.

In both the 22nd July 2014 Scoping Workshop for this appraisal and at the 21st May 2015 Appraisal Committee Meeting, clinical experts detailed those patient characteristics that would predict early relapse; paramount among these was the presence of 17p deletion or *TP53* mutation.

Patients with CLL associated with a 17p deletion or *TP53* mutation are clearly defined, are known to exhibit poor response to cytotoxic treatments and will not be treated with chemotherapy. The Committee heard of the highly limited, ineffective treatment options and short life expectancy that these patients currently experience, and the clear evidence for idelalisib with rituximab as an effective, tolerable and life-extending treatment alternative.

Paragraph 4.1 of the ACD records the Committee's conclusion that "*more treatment options are needed"* for untreated patients with a 17p deletion or *TP53* mutation. Indeed, there are no licensed therapies for this group of patients. Results from Study 101-08 and Study 116 are the best available evidence for an effective and cost-effective treatment, and predict idelalisib with rituximab to be a highly effective end-of-life treatment for this small patient population, who are currently bereft of effective treatment options.

In particular, we note Paragraph 4.24 of the ACD:

"*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."

As described in the Final Scope, only 5-10% of patients diagnosed with CLL have disease associated with a 17p deletion or *TP53* mutation: an estimated 135 to 270 people per year in England. At the time of submission, identified trial evidence of PFS for untreated patients with these genetic markers comprised data from only 30 patients, who were pre-specified subgroups in Study 101-08 (9 patients receiving idelalisib with rituximab, median PFS not reached) and Hillmen et al[10] (11 patients receiving alemtuzumab, median PFS 10.7 months; 10 patients receiving chlorambucil, median PFS 2.2 months). There are no known ongoing randomised controlled trials (RCTs) in this patient group and given the small patient numbers, there is little prospect of more robust clinical evidence becoming available.

It must also be noted that current BCSH guidelines and clinical practice are based on data from trials with very few patient numbers (Table 1).[1]

Table 1: Trials included in BCSH guidelines for patients with untreated CLL with a 17p deletion or *TP53* mutation[1]

Study	Regimen	Patients (n)	CR (%)	OR (%)	Median PFS (months)	OS (%)
Hellek et al (2010)	FC	29	4	45	0 (2 yrs)	41 at 2 yrs
	FCR	22	19	71	11	NA
Hillmen et al (2007)	A	11		64	11	NA
Pettitt et al (2012)	A + HDMP	17	65	100	18.3	38.9 (median)
Stilgenbauer et al (2011)	A + Dex	30	20	97	16.9	NA

Key: A, alemtuzumab; A + Dex, alemtuzumab + dexamethasone; A + HDMP, alemtuzumab + high dose methylprednisolone; CR, complete response; FC, fludarabine + cyclophosphamide; FCR, fludarabine + cyclophosphamide + rituximab; OR, overall response; OS, overall survival; PFS, progression-free survival; NA, not available; yrs, years

As stated above, there is little immediate prospect of more robust clinical evidence for the treatment of patients with untreated CLL associated with a 17p deletion or *TP53* mutation than that presented for idelalisib with rituximab in our submission, yet the provisional guidance would withhold effective

treatment from these patients on the basis of "*insufficient evidence*". We believe it would be indefensible, and maybe unethical, to consider guidance that may require these clearly defined and identifiable patients to endure and fail on ineffective treatment in order to prove their worthiness of a more effective alternative.

This point was raised by Dr Robert Marcus on behalf of Leukemia and Lymphoma Research at the Scoping Meeting for this appraisal on 22nd July 2014, and is reflected in the EMA's decision to license idelalisib with rituximab within this population based upon the available evidence.

We ask that the Committee reconsiders its provisional recommendation that idelalisib with rituximab should not be used for patients with untreated CLL associated with a 17p deletion or *TP53* mutation.

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).

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.[11]

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.

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.

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:
    - a response to previous treatment of less than 24 months, in line with clinical practice and BCSH guidelines
    - their disease is associated with a 17p deletion or *TP53* mutation

We look forward to the ensuing discussions at the next Committee meeting on 22nd July 2015.

Yours sincerely,

Sergio Sciuto
Market Access Manager, Oncology

1 Additional cost-effectiveness analyses conducted to address uncertainties highlighted by the Appraisal Committee

The additional analyses presented here address the important issues of uncertainty around immunoglobulin therapy assumptions and post-progression treatment benefit highlighted in the ACD.

As well as reporting the sensitivity analyses requested by the Committee using the base case assumptions specified, the full set of requested sensitivity analyses are repeated for alternative base case assumptions, which use what we believe to be corrected assumptions about immunoglobulin therapy use, as it has emerged that an IvIG assumption implicit in analyses to date is incorrect.

Analyses from three sets of base case assumptions are presented in this section.

- The first, the **Revised Base Case**, employs the Committee's two requested changes to the Company's base case analysis, using utility estimates from Dretzke et al. throughout and restricting OS beyond 5 years for the intervention arm of the model.
- The second, the **Corrected Base Case**, is similar to the Revised Base Case except contains corrected baseline immunoglobulin cost assumptions.
- The third, the **Proposed Base Case**, is similar to the Corrected Base Case, except Study 116 EQ-5D data are used to inform pre-progression health-related quality of life (HRQL) assumptions, in line with NICE guidance and correcting for an inconsistency in HRQL assumptions in the February 2015 submission, highlighted by the Committee. We believe these results from the Proposed Base Case analysis are the most appropriate for decision making, and provide justification for this belief.

Proposed Base Case ICERs are £26,403 versus rituximab, £35,275 versus best supportive care (BSC) and £10,668 versus ofatumumab.

Corrected immunoglobulin therapy assumptions lead to an increase in ICER estimates in comparison to rituximab, BSC and ofatumumab, yet idelalisib plus rituximab remains a clearly cost-effective end-of-life therapy for patients similar to those in Study 116. Crucially, this section demonstrates that this finding is robust to changes in immunoglobulin use assumptions, as well as extensive restrictions in treatment benefit extrapolations for idelalisib plus rituximab.

1.1 Additional analyses requested by the Appraisal Committee: the Revised Base Case

Following the Committee's recommendation for NICE to request further analyses from the company, we present deterministic and probabilistic results from a revised cost-effectiveness analysis. As requested, this revised analysis compares idelalisib plus rituximab with rituximab alone, BSC and ofatumumab, and incorporates the following changes to the base case analysis submitted by the company in February 2015:

- The relative OS benefit for idelalisib with rituximab predicted by extrapolation of Study 116 OS data, is restricted to 5 years
- Utility values from Dretzke et al are used instead of Study 116 EQ-5D data for all pre-progression health states.

Throughout this document, we refer to these this analysis as the **revised base case analysis**.

We present deterministic and probabilistic results, and as requested, explore uncertainty around IvIG therapy use and the length of relative OS benefit attributable to idelalisib plus rituximab, and show deterministic results for the subgroup of Study 116 patients whose disease was refractory.

1.1.1 Revised base case results

Deterministic Revised Base Case results are shown in Table 2, Table 3 and Table 4. The two requested changes to the base case analysis submitted by Gilead in February 2015 lead to a fall in the incremental QALY gain expected for idelalisib plus rituximab versus each base case comparator, while the restriction imposed on relative survival benefit decreases the total and incremental costs associated with idelalisib plus rituximab. The estimated ICERs versus rituximab (£16,977 [per QALY gained]) and in the conservative comparison to BSC (£26,084) are higher than the February 2015 base case, while in the comparison to ofatumumab, in which the estimated difference in total costs across model arms is small relative to comparisons to rituximab and BSC, the estimated ICER (£825) is lower than in the February 2015 base

case. Each ICER estimate remains well below a willingness to pay threshold of £50,000 per QALY gained for an end-of-life therapy.

The ICERs in Table 2 to Table 4 are marginally higher than the ERG base case ICERs presented in the ACD (£16,947 versus rituximab; £26,058 versus BSC; and £788 versus ofatumumab). The reason for this is not known, but is likely to lie in slight differences in the application of the relative survival benefit limitation in the model. Given the very marginal differences across results, and given the Revised Base Case ICERs presented here are slightly higher than the respective ERG ICERs, the differences are not considered important for optimal decision making.

Table 2: Revised base case deterministic results, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	1.39	0.91				
Idelalisib with rituximab	[redacted]	3.66	2.35	£24,388	2.27	1.44	£16,977
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 3: Revised base case deterministic results, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	1.39	0.91				
Idelalisib with rituximab	[redacted]	3.66	2.35	£37,471	2.27	1.44	£26,084
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 4: Revised base case deterministic results, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	1.39	0.91				
Idelalisib with rituximab	[redacted]	3.66	2.35	£1,185	2.27	1.44	£825
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

1.1.2 Probabilistic sensitivity analysis

Detailed probabilistic sensitivity analysis (PSA) results for the Revised Base Case, including PSA scatterplots and cost-effectiveness acceptability analyses, are reported in the Appendix, Section 4.1.1. Mean PSA ICERs are fair approximations to the deterministic ICERs presented in Section 1.1.1, while the estimated probabilities that idelalisib plus rituximab is cost effective for patients similar to those in Study 116, at a willingness to pay threshold of £50,000 per QALY gained, are 99% versus rituximab, 95% versus BSC and 100% versus ofatumumab.

1.1.3 Sensitivity analysis exploring the proportion of patients assumed to receive intravenous immunoglobulin therapy

Uncertainty around model assumptions regarding the proportions of responders and non-responders receiving IvIG therapy has been highlighted as a key issue for decision making by the Committee. Table 5, Table 6, and Table 7 show the sensitivity of Revised Base Case ICER results to variations in the proportions of responders and non-responders who are assumed to receive IvIG therapy, within requested bounds. The Committee heard very low estimates of IvIG use from Dr Forconi in the Appraisal Committee Meeting. For completeness, Table 8 shows Revised Base Case model results assuming no IvIG use.

Table 5, Table 6, and Table 7 demonstrate that the Revised Base Case is sensitive to IvIG assumptions, in particular to the proportion of responders who receive IvIG therapy. The assumptions associated with the highest estimated ICERs (£60,428 versus rituximab, £69,535 versus BSC, £44,277 versus ofatumumab) are that 20% of all patients receive IvIG while their disease is progression-free. It is considered highly unlikely that IvIG use will be equal and this high across patients whose disease responds to treatment and patients who have no response. Furthermore, in the majority of scenarios explored the Revised Base Case ICER remains well below the £50,000 threshold.

More importantly, assumptions underpinning the unit cost associated with IvIG therapy in the Revised Base Case are thought to be incorrect. The correct assumptions, that a treatment week for IvIG comprises one dose, not five doses, of 0.4g/kg IvIG therapy, imply a unit cost of 20% of that considered to date. With this change the model results are far more robust to IvIG use assumptions than those presented in this section and considered to date. The quantitative implications for results are illustrated in detail in Sections 1.2 and 1.3.

When IvIG use is removed from the analysis, the Revised Base Case ICERs are £29,633, £38,740 and £13,481 versus rituximab, BSC, and ofatumumab, respectively, as shown in Table 8.

Table 5: Sensitivity of the Revised 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%	£24,008	£33,113	£42,218	£51,323	£60,428
	25%	£22,602	£31,707	£40,812	£49,917	£59,022
	30%	£21,195	£30,300	£39,405	£48,511	£57,616
	35%	£19,789	£28,894	£37,999	£47,104	£56,209
	40%	£18,383	£27,488	£36,593	£45,698	£54,803
	45%	£16,977*	£26,082	£35,187	£44,292	£53,397

Key: ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin; R, rituximab
Notes: * Revised Base Case ICER, IR versus R

Table 6: Sensitivity of the Revised Base Case ICER, IR versus BSC, 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%	£33,115	£42,220	£51,325	£60,430	£69,535
	25%	£31,709	£40,814	£49,919	£59,024	£68,129
	30%	£30,303	£39,408	£48,513	£57,618	£66,723
	35%	£28,896	£38,001	£47,106	£56,211	£65,317
	40%	£27,490	£36,595	£45,700	£54,805	£63,910
	45%	£26,084*	£35,189	£44,294	£53,399	£62,504

Key: BSC, best suppotive care; ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin; R, rituximab
Notes: * Revised Base Case ICER, IR versus BSC

Table 7: Sensitivity of the Revised Base Case ICER, IR versus ofatumumab, 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%	£7,856	£16,961	£26,066	£35,172	£44,277
	25%	£6,450	£15,555	£24,660	£33,765	£42,870
	30%	£5,044	£14,149	£23,254	£32,359	£41,464
	35%	£3,638	£12,743	£21,848	£30,953	£40,058
	40%	£2,231	£11,336	£20,441	£29,546	£38,652
	45%	£825*	£9,930	£19,035	£28,140	£37,245

Key: ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin
Notes: * Revised Base Case ICER, IR versus ofatumumab

Table 8: Revised Base Case ICERs, assuming zero IvIG use

ICER assuming zero IvIG therapy use, idelalisib with rituximab versus		
Rituximab	**BSC**	**Ofatumumab**
£29,633	£38,740	£13,481

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IvIG, intravenous immunoglobulin

1.1.4 Sensitivity analysis exploring the length of treatment benefit assumed for idelalisib with rituximab

The Committee also requested information on the sensitivity of results to treatment-related survival benefit extrapolation assumptions. The ERG's recommendation that the relative treatment effect implied by independent extrapolation of OS curves be limited to 5 years, at which point only a small proportion of patients remain progression-free in the model, is considered a fair, conservative assumption in the absence of robust data on outcomes for patients who have progressed following treatment with idelalisib plus rituximab.

Table 9 shows the sensitivity of Revised Base Case ICERs to imposing further restrictions in the relative overall benefit of the idelalisib plus rituximab versus rituximab, to as few as 3 years post-randomisation. At this point, extrapolation is less than 16 months and nearly 12% of patients randomised to receive idelalisib with rituximab are predicted to be progression-free. It is worth recalling that this prediction used a Weibull model extrapolation, the most conservative of the range of statistical extrapolations explored in the submission. Table 9 shows ICERs to be reasonably robust to such an assumption, with the Revised Base Case ICER remaining below £34,000 per QALY gained in the conservative comparison to BSC.

Table 9 also shows Revised Base Case ICERs with no restrictions imposed upon the intervention survival curve, for consideration of the theoretical evidence provided by Gilead in response to ERG questions.

Table 9: The sensitivity of Revised Base Case ICERs to the restriction applied to relative treatment benefit estimated for IR OS

	ICER, idelalisib with rituximab versus		
Limit applied to relative treatment benefit for idelalisib	**Rituximab**	**BSC**	**Ofatumumab**
3 years	£21,441	£33,686	Dominant
4 years	£18,606	£28,858	£424
5 years	£16,977*	£26,084*	£825*
No relative limit applied	£13,972	£20,968	£1,564

Notes: * Revised Base Case ICERs
IvIG, intravenous immunoglobulin; ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; OS, overall survival

1.1.5 Sensitivity analysis using clinical data from the subgroup of patients from Study 116 whose disease was refractory

In response to the Committee's request for a sensitivity analysis exploring the effect of using clinical effectiveness data from the subgroup of patients in Study 116 whose disease is refractory, we provide results from these analyses, but note our reservations, in the accompanying letter, about dichotomising previously treated CLL patients according to whether or not their disease is refractory. Refractoriness was not specified in the Study 116 inclusion criteria; the only criterion related to previous response was relapse within 24 months and 149 patients (68%) had previous relapse between 6 and 24 months.

Following methods described in Section 5.3 of our February 2015 submission document, we fit various parametric curves to Kaplan Meier (KM) data for OS and PFS, for the subgroup of patients with refractory disease (71 patients, 32 of whom were randomised to receive idelalisib, 39 of whom were randomised to receive placebo), and determined best fit using AIC statistics and visual inspection of clinical plausibility.

Figure 2 and Figure 3 show the respective parametric curve fits to idelalisib with rituximab and rituximab KM OS data for the refractory subgroup. Table 10 shows AIC statistics for these curve fits, which suggest the Weibull model is the best fit to the data. The Weibull curve is selected for this subgroup analysis as it is the most conservative in extrapolation of survival for patients who received idelalisib plus rituximab, Weibull model assumptions are used in base case analyses. It should be noted that, the KM data are based on very few patients at the foot of the curve and so should be interpreted with caution, Figure 3 suggests the survival associated with rituximab plus placebo may be overestimated, and consequently the relative survival benefit of idelalisib plus rituximab for refractory patients may be underestimated by these subgroup analyses.

Figure 2: KM OS IR and parametric curve fits, refractory subgroup

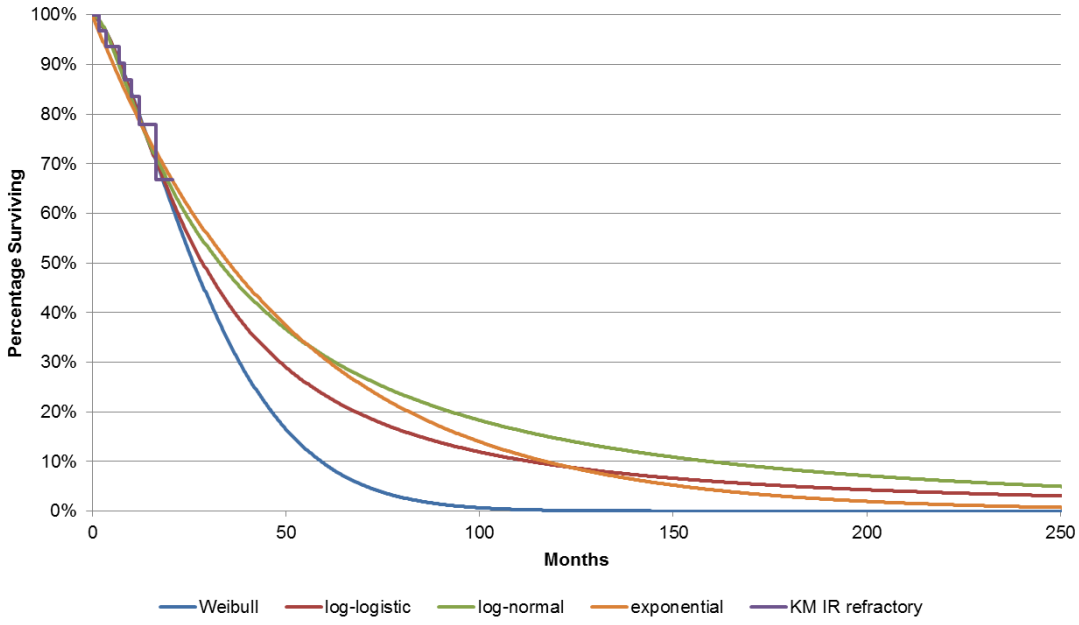


Figure 3: KM OS R and parametric curve fits, refractory subgroup

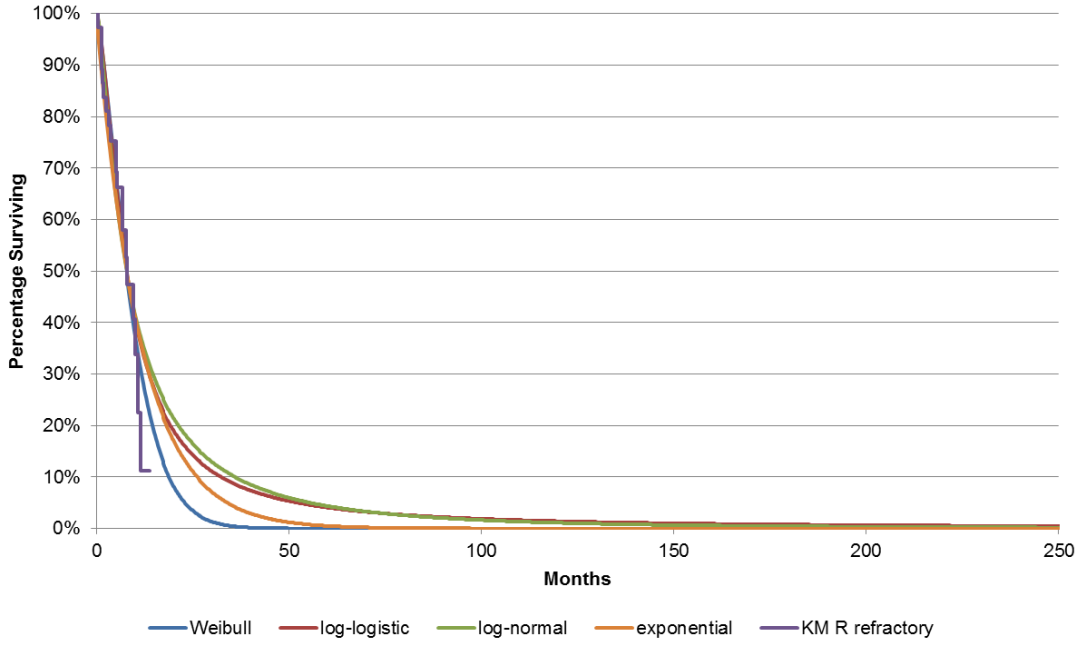


Table 10: AIC statistics, parametric curve fits to OS KM curves, refractory subgroup

Model	AIC – IR arm	AIC – R arm
Weibull	81.643	145.672
Log-logistic	81.638	147.879
Log-normal	81.678	149.250
Exponential	80.854	145.992
Key: AIC, Akaike Information Criterion; IR, idelalisib with rituximab; R, rituximab		

Figure 4 shows the Weibull parametric curve fits to KM OS data for both treatment arms of Study 116. These curves determine OS in subgroup analyses for refractory patients.

Figure 4: KM OS IR and R, refractory subgroup, and selected (Weibull) curve fits

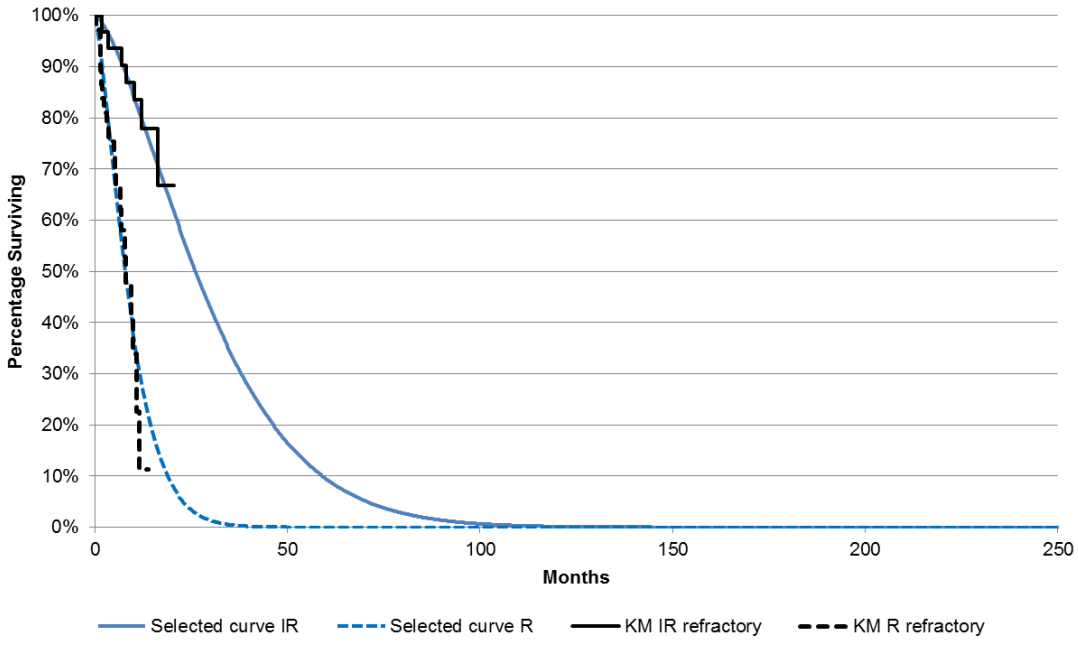


Figure 5 and Figure 6 show the respective parametric curve fits to KM PFS data for the refractory subgroup. Table 11 shows AIC statistics for these curve fits, which again suggest the Weibull model is the best fit to patient data. The Weibull curve is also the most conservative in its extrapolation assumptions and consistent with base case analyses, and for these reasons is selected to model PFS in analyses for the subgroup of refractory Study 116 patients.

Figure 5: KM PFS IR and parametric curve fits, refractory subgroup

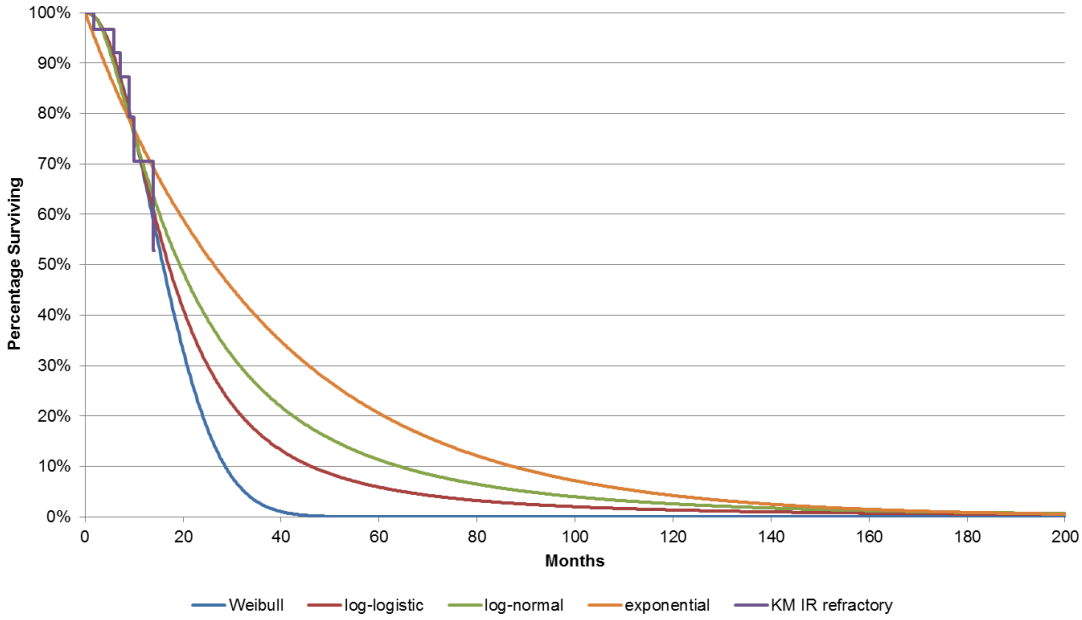


Figure 6: KM PFS R and parametric curve fits, refractory subgroup

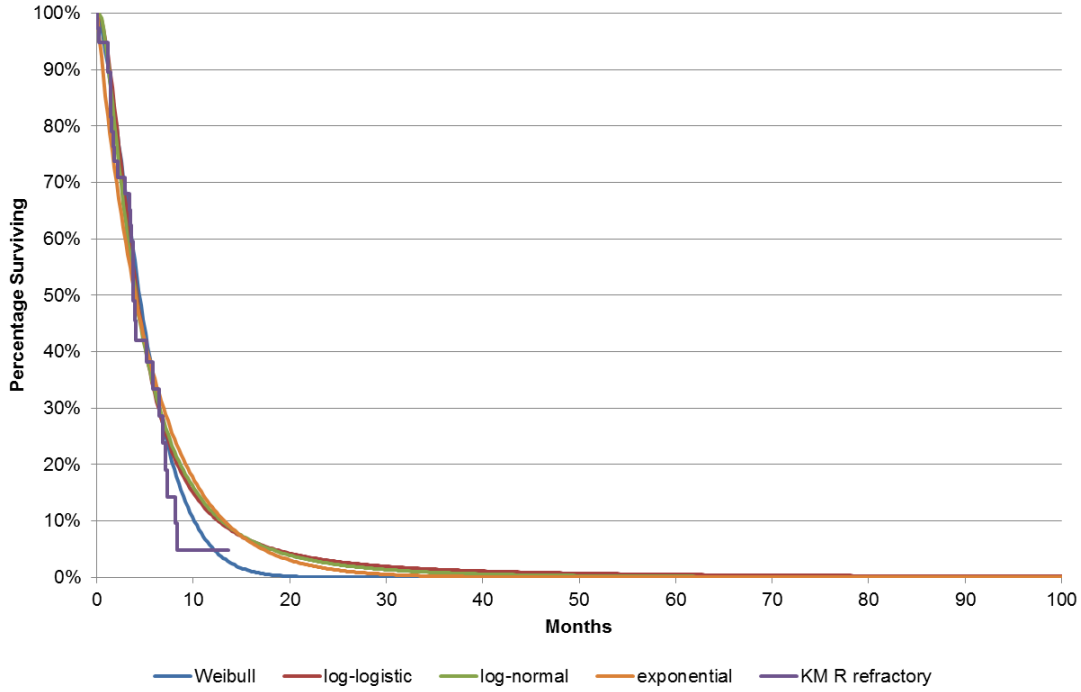


Table 11: AIC statistics, parametric curve fits to PFS KM curves, refractory subgroup

Model	AIC – IR arm	AIC – R arm
Weibull	65.090	152.510
Log-logistic	65.407	153.547
Log-normal	66.065	154.886
Exponential	66.887	155.927
Key: AIC, Akaike Information Criterion; IR, idelalisib with rituximab; R, rituximab		

Figure 7 shows the Weibull parametric curve fits to KM PFS data for both treatment arms of Study 116. These curves determine PFS in subgroup analyses for refractory patients.

Figure 7: KM PFS IR and R, refractory subgroup, and selected (Weibull) curve fits

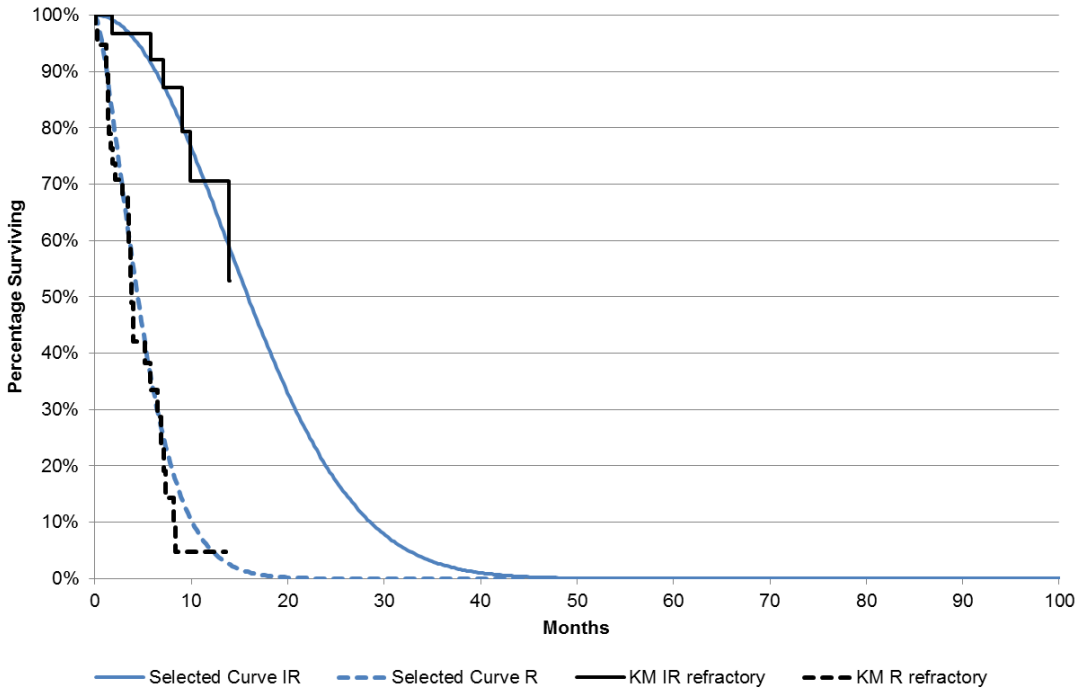


Table 12, Table 13 and Table 14 show sensitivity analysis results for the Revised Base Case using Weibull extrapolations of clinical effectiveness data from the subgroup of Study 116 patients whose disease is defined as refractory. Predicted survival is reduced for both model arms when only the subgroup of patients with refractory disease are considered. In comparison to Revised Base Case results in Section 1.1.1, the incremental QALYs

associated with idelalisib plus rituximab are reduced and ICERs marginally increase across comparisons, though remain well below an end-of-life threshold of £50,000 per QALY gained.

Table 12: Subgroup analysis for patients with refractory disease, Revised Base Case, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	0.80	0.56				
Idelalisib with rituximab	[redacted]	2.46	1.66	£24,609	1.66	1.11	£22,230
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 13: Subgroup analysis for patients with refractory disease, Revised Base Case, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	0.80	0.56				
Idelalisib with rituximab	[redacted]	2.46	1.66	£36,451	1.66	1.11	£32,927
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 14: Subgroup analysis for patients with refractory disease, Revised Base Case, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	0.80	0.56				
Idelalisib with rituximab	[redacted]	2.46	1.66	£3,323	1.66	1.11	£3,002
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

1.2 Further additional analyses: the Corrected Base Case

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, including and beyond the Committee's requests for further analyses.

Analyses to date have been based on a cost of £13,706 for IvIG therapy. As set out in Section 5.5 of the company submission, this cost was 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.[11]

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%, from £13,706 to £2,741. This change influences both the ICER and its sensitivity to assumptions about the proportion of patients who receive IvIG therapy. We regret that what we now believe was an incorrect assumption has informed cost-effectiveness results considered to date, and present results, including the full suite of requested additional analyses, for a corrected base case. This corrected base case differs from the Revised Base Case only in that the unit cost for IvIG therapy is assumed to be £2,741.

Throughout this document, we refer to this analysis as the **corrected base case analysis**.

1.2.1 Corrected base case results

Table 15, Table 16 and Table 17 show Corrected Base Case deterministic results. Relative to Revised Base Case results, total costs are reduced across

treatment arms due to the lower estimated financial burden of disease management. Incremental costs associated with idelalisib plus rituximab are increased, as IvIG use is assumed for non-responders only, and fewer patients in the control arm of Study 116 exhibited an overall response to treatment. The effect upon estimated ICERs is substantial, an increase in the estimated ICER of around £10,000 in each comparison.

For decision making, these changes draw estimated ICERs closer to the end-of-life willingness to pay threshold, but they remain far below the £50,000 level. Only in the conservative comparison to BSC, in which patients receiving no active treatment are assumed to experience the progression-free and OS effects of rituximab without the associated costs, is the Corrected Base Case ICER higher than £30,000 per QALY gained.

Table 15: Corrected base case deterministic results, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	1.39	0.91				
Idelalisib with rituximab	[redacted]	3.66	2.35	£38,933	2.27	1.44	£27,102
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 16: Corrected base case deterministic results, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	1.39	0.91				
Idelalisib with rituximab	[redacted]	3.66	2.35	£52,016	2.27	1.44	£36,209
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 17: Corrected base case deterministic results, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	1.39	0.91				
Idelalisib with rituximab	[redacted]	3.66	2.35	£15,731	2.27	1.44	£10,950
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

1.2.2 Probabilistic sensitivity analysis

Detailed PSA results for the Corrected Base Case are reported in the Appendix, Section 4.2.1.

Despite the increased ICERs resulting from the correction to the Revised Base Case, results indicate that the probability that idelalisib plus rituximab is cost-effective versus at a willingness to pay threshold of £50,000 remains 94% versus rituximab, 84% versus BSC and 100% versus ofatumumab.

1.2.3 Sensitivity analysis exploring the proportion of patients assumed to receive intravenous immunoglobulin therapy

Table 18 to Table 21 demonstrate the sensitivity of Corrected Base Case ICERs to IvIG use assumptions, replicating the analysis presented in Section 1.1.3 for the Revised Base Case.

With corrected assumptions for IvIG costs, the ICERs are far less sensitive to the proportions of responders and non-responders assumed to receive IvIG therapy. Consistent with the previous submission the base case assumes 0% of responders and 45% of non-responders receive IvIG therapy; in the most extreme deviation from base case assumptions, in which 20% of all patients are assumed to receive IvIG therapy, ICERs are less than £9,000 higher than base case results.

Importantly, following the correction to IvIG cost assumptions, none of the scenarios explored produce ICERs close to or above £50,000. With corrected assumptions, uncertainty around IvIG use is of far less importance from a decision-making perspective.

Table 18: Sensitivity of the Corrected 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%	£28,508	£30,329	£32,150	£33,971	£35,792
	25%	£28,227	£30,048	£31,869	£33,690	£35,511
	30%	£27,945	£29,766	£31,587	£33,408	£35,229
	35%	£27,664	£29,485	£31,306	£33,127	£34,948
	40%	£27,383	£29,204	£31,025	£32,846	£34,667
	45%	£27,102*	£28,923	£30,744	£32,565	£34,386

Key: ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin; R, rituximab
Notes: * Corrected Base Case ICER, IR versus R

Table 19: Sensitivity of the Corrected Base Case ICER, IR versus BSC, 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%	£37,615	£39,436	£41,257	£43,078	£44,899
	25%	£37,334	£39,155	£40,976	£42,797	£44,618
	30%	£37,053	£38,874	£40,695	£42,516	£44,337
	35%	£36,771	£38,592	£40,413	£42,234	£44,055
	40%	£36,490	£38,311	£40,132	£41,953	£43,774
	45%	£36,209*	£38,030	£39,851	£41,672	£43,493

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin
Notes: * Corrected Base Case ICER, IR versus best supportive care

Table 20: Sensitivity of the Corrected Base Case ICER, IR versus ofatumumab, 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%	£12,356	£14,177	£15,998	£17,819	£19,640
	25%	£12,075	£13,896	£15,717	£17,538	£19,359
	30%	£11,794	£13,615	£15,436	£17,257	£19,078
	35%	£11,513	£13,334	£15,155	£16,976	£18,797
	40%	£11,231	£13,052	£14,873	£16,694	£18,515
	45%	£10,950*	£12,771	£14,592	£16,413	£18,234

Key: ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin
Notes: * Corrected Base Case ICER, IR versus ofatumumab

Table 21: Corrected Base Case ICERs, assuming zero IvIG use

ICER assuming zero IvIG Therapy Use, idelalisib with rituximab versus		
Rituximab	**BSC**	**Ofatumumab**
£29,633	£38,740	£13,481

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IvIG, intravenous immunoglobulin

1.2.4 Sensitivity analysis exploring the length of treatment benefit assumed for idelalisib with rituximab

Table 22 shows the sensitivity of Corrected Base Case ICERs to restrictions in predicted survival for idelalisib plus rituximab, replicating similar analyses for the Revised Base Case presented in Section 1.1.4. Due to the fall in the relative on-progression disease management cost for responders versus non-responders implied by a lower unit cost for IvIG, Corrected Base Case ICERs are slightly more sensitive to survival restrictions for the intervention arm of the model. Despite this, estimated ICERs remain below £50,000, even when conditional survival in the intervention arm is assumed equal to the comparator arm from 3 years onwards, an assumption considered highly unlikely given the data, as discussed in Section 1.1.4.

Table 22: The sensitivity of Corrected 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	£35,055	£47,299	£13,339
4 years	£30,003	£40,255	£11,822
5 years	£27,102*	£36,209*	£10,950*
No relative limit applied	£21,750	£28,746	£9,343

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin; OS, overall survival
Notes: * Corrected Base Case ICERs

1.2.5 Sensitivity analysis using clinical data from the subgroup of patients from Study 116 whose disease was refractory

Sensitivity analysis results for the Corrected Base Case using Weibull extrapolations of clinical effectiveness data from the subgroup of Study 116 patients whose disease is defined as refractory, described in Section 1.1.5. Predicted survival is reduced for both model arms when only the subgroup of patients with refractory disease are considered. In comparison to Corrected Base Case results in Section 1.2.1, the incremental QALYs associated with idelalisib plus rituximab are reduced and ICERs increase across comparisons, though remain well below an end-of-life threshold of £50,000 per QALY gained.

Table 23: Subgroup analysis for patients with refractory disease, Corrected Base Case, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	0.80	0.56				
Idelalisib with rituximab	[redacted]	2.46	1.66	£35,654	1.66	1.11	£32,207
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 24: Subgroup analysis for patients with refractory disease, Corrected Base Case, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	0.80	0.56				
Idelalisib with rituximab	[redacted]	2.46	1.66	£47,496	1.66	1.11	£42,904
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 25: Subgroup analysis for patients with refractory disease, Corrected Base Case, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	0.80	0.56				
Idelalisib with rituximab	[redacted]	2.46	1.66	£14,368	1.66	1.11	£12,979
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

1.3 Further additional analyses: the Proposed Base Case

Paragraph 4.14 of the ACD states the following as rationale for using HRQL data reported in the study by Dretzke et al instead of Study 116 EQ-5D data:

"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."

The inconsistency referred to involves the estimated mean EQ5D value for patients in the comparator arm of Study 116 (0.748) being lower than the HRQL value for pre-progressive CLL reported by Dretzke et al (0.80). Patient EQ5D data were not collected beyond treatment withdrawal in Study 116, so it was necessary to make assumptions about patient HRQL from this point. The study reported by Dretzke et al was identified the best available literature source for HRQL in a similar patient group to those considered, as reported in the submission, and reported HRQL values for pre- (utility value 0.80) and post-progressive patients (utility value 0.60).

For the "Pre-progression, Off Treatment" health state, a choice was made between the two utility values from Dretzke et al. Though assuming utility of 0.80 is inconsistent in its implications, clinical advice suggested this was the more appropriate value for patients whose disease had not yet progressed. Importantly, the choice of value used for this health state is not a key driver of model results. In our factual inaccuracy check of the ERG Report, we demonstrated the unsubstantial effect upon results of assuming patients in

this state have a utility of 0.60 (Issue 19, relating to Section 1.4 of the ERG report).

Perhaps the most appropriate assumption is to assume patients in the “Pre-progression, Off Treatment” health state have a utility of 0. 748 that reported by patients in the comparator arm of Study 116. This implies that patients who withdraw from an effective treatment (idelalisib) will experience an initial fall in HRQL, and a further fall when their disease progresses, while HRQL for patients who withdraw from an ineffective treatment (placebo) will remain unchanged until disease progression.

Having dealt with the inconsistency, using the two values from Dretzke et al to capture HRQL in all model states, in preference to using patient-reported EQ5D data where possible, is in contravention of the NICE reference case.[12]

Further, paragraph 4.18 of the ACD states:

“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.”

All HRQL benefits patients of idelalisib plus rituximab cannot be said to be captured if equal utility values are assumed for patients receiving an effective treatment (idelalisib plus rituximab) and patients receiving an ineffective treatment (rituximab plus placebo).

In this section, we present results from analyses which differ from those presented in Section 1.2 for the Corrected Base Case only in that EQ5D data from Study 116 are used to inform utility assumptions for pre-progression health states. The HRQL assumptions follow those in the Company base case submitted in February 2015, with the exception that the utility value for the “Pre-progression, Off Treatment” health state is that estimated for patients receiving treatment in the comparator arm of Study 116.

The assumptions implicit in the results presented in this section are proposed as the most appropriate for decision making, and this analysis is referred to throughout as the **Proposed Base Case**.

1.3.1 Proposed base case results

Table 26, Table 27 and Table 28 show Proposed Base Case deterministic results. Relative to Corrected Base Case results, total QALYs are increased on the intervention arm and reduced on the comparator arm, reflecting to a degree the preferable patient experience of receiving an effective, tolerable treatment, as opposed to an ineffective treatment, resulting in lower estimated ICERs across each comparison.

For decision making, Proposed Base Case ICERs are reduced relative to Corrected Base Case ICERs, and they remain far below the £50,000 level. Again, in only the conservative comparison to BSC is the ICER higher than £30,000 per QALY gained.

Table 26: Proposed base case deterministic results, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	1.39	0.89				
Idelalisib with rituximab	[redacted]	3.66	2.36	£38,933	2.27	1.47	£26,403
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 27: Proposed base case deterministic results, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	1.39	0.89				
Idelalisib with rituximab	[redacted]	3.66	2.36	£52,016	2.27	1.47	£35,275
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 28: Proposed base case deterministic results, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	1.39	0.89				
Idelalisib with rituximab	[redacted]	3.66	2.36	£15,731	2.27	1.47	£10,668
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

1.3.2 Probabilistic sensitivity analysis

Detailed PSA results for the Proposed Base Case are reported in the Appendix, Section 4.3.1. Results indicate that the probability that idelalisib plus rituximab is cost-effective versus at a willingness to pay threshold of £50,000 remains 97% versus rituximab, 88% versus BSC and 100% versus ofatumumab.

1.3.3 Sensitivity analysis exploring the proportion of patients assumed to receive intravenous immunoglobulin therapy

Table 29, Table 30 and Table 31 illustrate the robustness of Proposed Base Case ICERs to IvIG use assumptions, replicating the analyses presented in Sections 1.1.3 and 1.2.3.

In line with the Corrected Base Case analysis, results are robust to assumptions regarding the proportions of patients receiving IvIG therapy, though even more so given the higher incremental QALY gain associated with idelalisib plus rituximab using the Proposed Base Case approach. Again, in the most extreme deviation from base case assumptions, in which 20% of all patients are assumed to receive IvIG therapy, ICERs are less than £9,000 higher than base case results.

As observed for the Corrected Base Case, none of the IvIG scenarios explored produce ICERs close to or above £50,000. With corrected assumptions regarding IvIG costs, uncertainty around IvIG use is of far less importance from a decision-making perspective. Using HRQL data from Study 116 to inform pre-progression utility assumptions, such uncertainty is of even less significance.

Table 29: 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

Key: ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin; R, rituximab
Notes: * Proposed Base Case ICER, IR versus R

Table 30: Sensitivity of the Proposed Base Case ICER, IR versus BSC, 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%	£36,645	£38,419	£40,193	£41,967	£43,742
	25%	£36,371	£38,145	£39,919	£41,693	£43,468
	30%	£36,097	£37,871	£39,645	£41,419	£43,194
	35%	£35,823	£37,597	£39,371	£41,145	£42,920
	40%	£35,549	£37,323	£39,097	£40,871	£42,646
	45%	£35,275*	£37,049	£38,823	£40,597	£42,372

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin
Notes: * Proposed Base Case ICER, IR versus best supportive care

Table 31: Sensitivity of the Proposed Base Case ICER, IR versus ofatumumab, 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%	£12,038	£13,812	£15,586	£17,360	£19,134
	25%	£11,764	£13,538	£15,312	£17,086	£18,860
	30%	£11,490	£13,264	£15,038	£16,812	£18,586
	35%	£11,216	£12,990	£14,764	£16,538	£18,312
	40%	£10,942	£12,716	£14,490	£16,264	£18,038
	45%	£10,668*	£12,442	£14,216	£15,990	£17,764

Key: ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin
Notes: * Proposed Base Case ICER, IR versus ofatumumab

Table 32: Proposed Base Case ICERs, assuming zero IvIG use

ICER assuming zero IvIG therapy use, idelalisib with rituximab versus		
Rituximab	**BSC**	**Ofatumumab**
£28,869	£37,741	£13,134

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IvIG, intravenous immunoglobulin

1.3.4 Sensitivity analysis exploring the length of treatment benefit assumed for idelalisib with rituximab

Table 33 shows the sensitivity of Proposed Base Case ICERs to restrictions in predicted survival for idelalisib plus rituximab, replicating the analyses presented in Sections 1.1.4 and 1.2.4. Again, these results are slightly more sensitive to survival restrictions for the intervention arm of the model, in comparison to Revised Base Case results shown in Section 1.1.4. In comparison to respective results from the Corrected Base Case reported in Section 1.2.4 however, the results are less sensitive to survival-limiting impositions on the intervention arm, with the Study 116 EQ5D data reflecting to a degree the preferable patient experience of receiving an effective, tolerable treatment, as opposed to an ineffective treatment. Estimated ICERs remain well below £50,000, even when conditional survival in the intervention arm is assumed equal to the comparator arm from 3 years onwards, an assumption considered highly unlikely given the data, as discussed in Section 1.1.4.

Table 33: 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

Key: BSC, best supportive carel; ICER, incremental cost-effectiveness ratio; IR, idelalisib plus rituximab; IvIG, intravenous immunoglobulin; OS, overall survival
Notes: * Proposed Base Case ICERs

1.3.5 Sensitivity analysis using clinical data from the subgroup of patients from Study 116 whose disease was refractory

Sensitivity analysis results for the Proposed Base Case using Weibull extrapolations of clinical effectiveness data from the subgroup of Study 116 patients whose disease is defined as refractory, described in Section 1.1.5. Predicted survival is reduced for both model arms when only the subgroup of patients with refractory disease are considered. In comparison to Proposed Base Case results in Section 1.3.1, the incremental QALYs associated with idelalisib plus rituximab are reduced and ICERs increase across comparisons, though remain well below an end-of-life threshold of £50,000 per QALY gained.

Table 34: Subgroup analysis for patients with refractory disease, Proposed Base Case, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	0.80	0.54				
Idelalisib with rituximab	[redacted]	2.46	1.68	£35,654	1.66	1.14	£31,244
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 35: Subgroup analysis for patients with refractory disease, Proposed Base Case, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	0.80	0.54				
Idelalisib with rituximab	[redacted]	2.46	1.68	£47,496	1.66	1.14	£41,621
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 36: Subgroup analysis for patients with refractory disease, Proposed Base Case, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	0.80	0.54				
Idelalisib with rituximab	[redacted]	2.46	1.68	£14,368	1.66	1.14	£12,591
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

2 Factual inaccuracies identified by Gilead in the ACD

The following factual inaccuracies were identified in the ACD:

Paragraph number in ACD	Comment
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…"
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."
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."
3.1	The document states "…whose disease was relapsed and refractory." Please reword to read "…whose disease was relapsed or refractory."
3.3	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.
3.3	At the end of point 3.3, the document states "Patients were excluded if their disease had progressed to more aggressive malignancies"

Paragraph number in ACD	Comment
	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).”
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.”
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 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.
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.”
3.7	The document states “The results showed a statistically significant

Paragraph number in ACD	Comment
	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)."
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)."
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.
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."
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 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

Paragraph number in ACD	Comment
	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."
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.
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 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.
3.35	The document states "The company estimated that the cost of intravenous immunoglobulin therapy, incorporating the acquisition cost

Paragraph number in ACD	Comment
	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]
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 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.

3 References

1. Oscier D, Dearden C and Erem E. British Committee for Standards in Haematology: Guideline on the diagnosis and management of Chronic Lymphocytic Leukaemia. 2013 (Updated: 2013). Available at: http://www.bcshguidelines.com/documents/Revised_CLL_guideline_july_13.pdf Accessed: 6 July 2015.

2. Eichhorst B, Dreyling M, Robak T, et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2011; 22 Suppl 6:vi50-4.

3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008; 111(12):5446-56.

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10. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007; 25(35):5616-23.

11. Department of Health. Clinical guidelines for immunoglobulin use: Update to second edition. 2011. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf Accessed: 6 July 2015.

12. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013 (Updated: 4 April 2013). Available at: http://publications.nice.org.uk/pmg9 Accessed: 1 September 2014.

13. Ghia P, Hillmen P, Kim Y, et al. Overall survival ananlysis adjusting for treatment effect after crossover in a Phase III study evaluating idelalisib in combination with rituximab in relapsed chronic lymphocytic leukaemia. European Haematological Association 20th Annual Congress. Vienna, Austria. 11-14 June 2015. Oral Presentation.

4 Appendix

4.1 Appendix to Section 1.1

4.1.1 PSA results for the Revised Base Case

Mean PSA results for Revised Base Case comparisons to rituximab, BSC and ofatumumab, using 1000 probabilistic model runs, are shown in Table 40, Table 41 and Table 42.

Figure 8 shows the PSA scatterplot for the comparison to rituximab; Figure 9 and Table 37 show analyses of cost-effectiveness acceptability by different willingness to pay thresholds, using these results.

Mean PSA ICERs are fair approximations to the deterministic ICERs presented in Section 1.1.1, while the estimated probabilities that idelalisib plus rituximab is cost effective for patients similar to those in Study 116, at a willingness to pay threshold of £50,000 per QALY gained, are 99% versus rituximab, 95% versus BSC and 100% versus ofatumumab.

Figure 8: PSA scatterplot, Revised Base Case, IR versus R

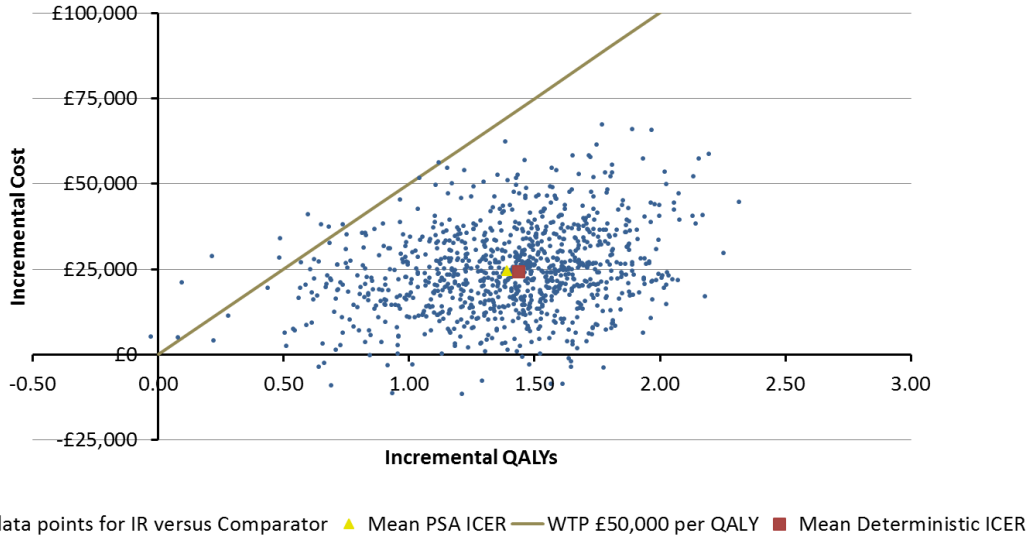

Figure 9: CEAC, Revised Base Case, IR versus R

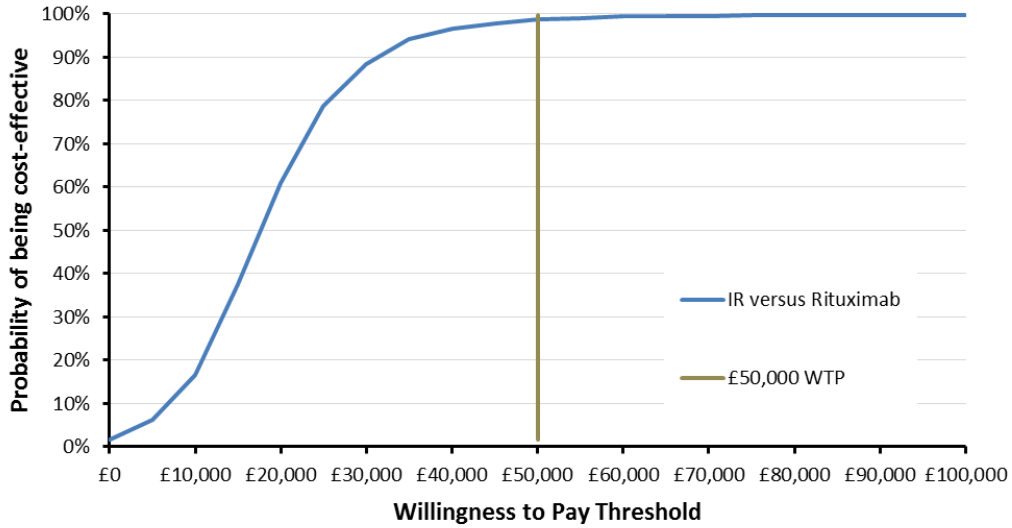

Table 37: CEAC table, Revised Base Case, IR versus R

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**R**
£0	2%	98%
£5,000	6%	94%
£10,000	17%	83%
£15,000	38%	62%
£20,000	61%	39%
£25,000	79%	21%
£30,000	88%	12%
£35,000	94%	6%
£40,000	97%	4%
£45,000	98%	2%
£50,000	99%	1%
£55,000	99%	1%
£60,000	99%	1%
£65,000	100%	1%
£70,000	100%	0%
£75,000	100%	0%
£80,000	100%	0%
£85,000	100%	0%
£90,000	100%	0%
£95,000	100%	0%
£100,000	100%	0%

Figure 10: PSA scatterplot, Revised Base Case, IR versus BSC

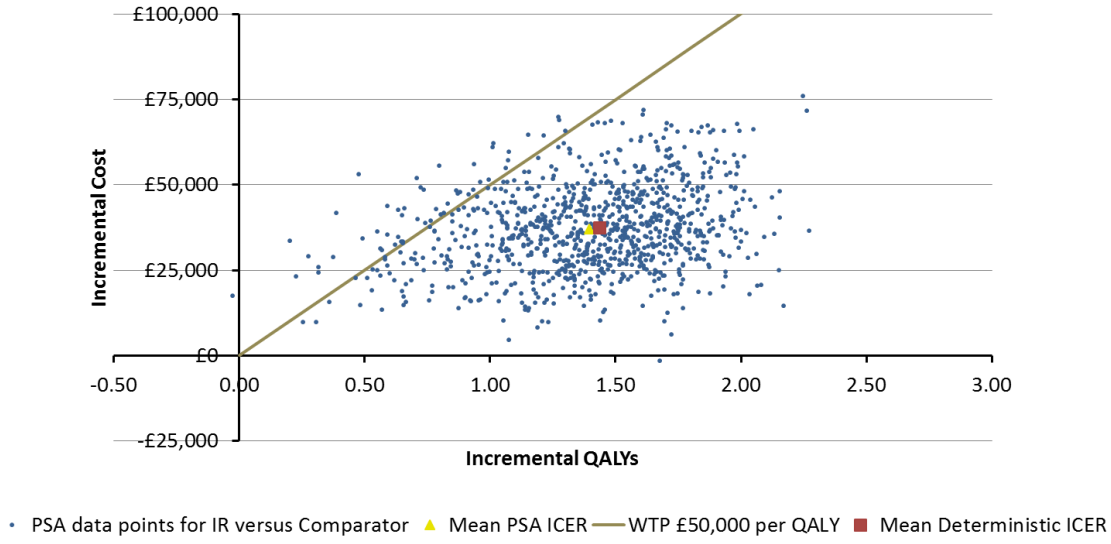

Figure 11: CEAC, Revised Base Case, IR versus BSC

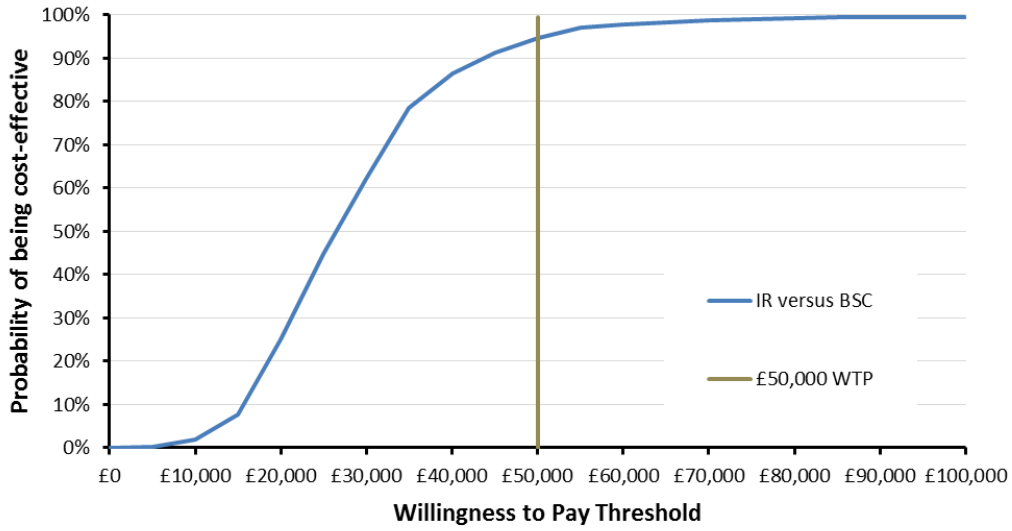

Table 38: CEAC table, Revised Base Case, IR versus BSC

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**BSC**
£0	0%	100%
£5,000	0%	100%
£10,000	2%	98%

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**BSC**
£15,000	8%	92%
£20,000	25%	75%
£25,000	45%	55%
£30,000	62%	38%
£35,000	79%	21%
£40,000	87%	14%
£45,000	91%	9%
£50,000	95%	5%
£55,000	97%	3%
£60,000	98%	2%
£65,000	98%	2%
£70,000	99%	1%
£75,000	99%	1%
£80,000	99%	1%
£85,000	99%	1%
£90,000	99%	1%
£95,000	99%	1%
£100,000	99%	1%

Figure 12: PSA scatterplot, Revised Base Case, IR versus ofatumumab

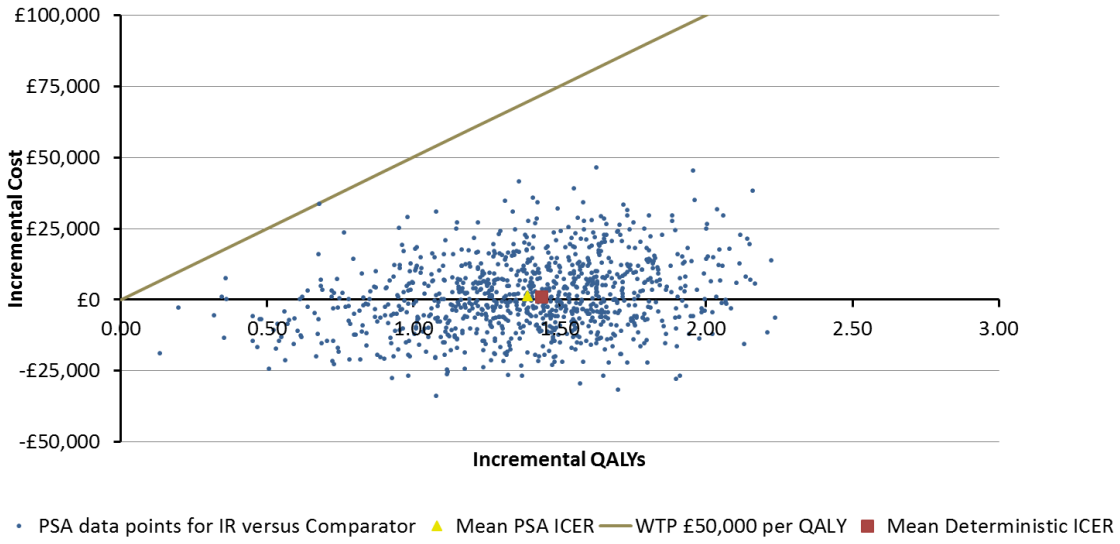

Figure 13: CEAC, Revised Base Case, IR versus ofatumumab

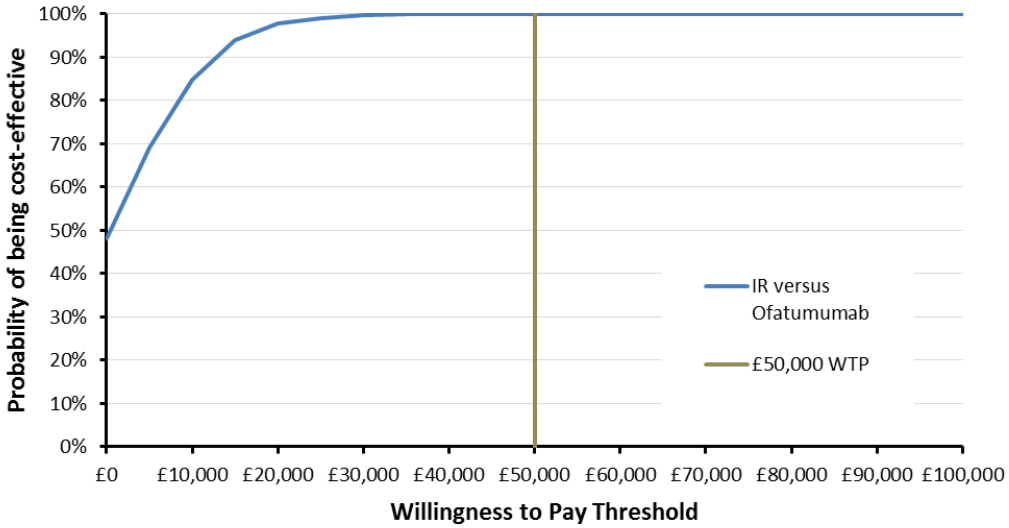

Table 39: CEAC table, Revised Base Case, IR versus ofatumumab

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**Ofatumumab**
£0	48%	52%
£5,000	69%	31%
£10,000	85%	15%
£15,000	94%	6%
£20,000	98%	2%
£25,000	99%	1%
£30,000	100%	0%
£35,000	100%	0%
£40,000	100%	0%
£45,000	100%	0%
£50,000	100%	0%
£55,000	100%	0%
£60,000	100%	0%
£65,000	100%	0%
£70,000	100%	0%
£75,000	100%	0%
£80,000	100%	0%
£85,000	100%	0%
£90,000	100%	0%
£95,000	100%	0%
£100,000	100%	0%

Table 40: Mean PSA results, Revised Base Case, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	1.52	1.41				
Idelalisib + rituximab	[redacted]	2.31	3.59	£24,649	1.39	2.18	£17,725
Key: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 41: Mean PSA results, Revised Base Case, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	1.52	1.42				
Idelalisib + rituximab	[redacted]	2.32	3.62	£37,158	1.40	2.20	£26,614
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life year							

Table 42: Mean PSA results, Revised Base Case, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	1.52	1.43				
Idelalisib + rituximab	[redacted]	2.32	3.60	£1,390	1.39	2.17	£1,000
Key: ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year							

4.2 Appendix to Section 1.2

4.2.1 PSA results for the Corrected Base Case

Table 46, Table 47 and Table 48 show mean PSA results for the three Corrected Base Case comparisons. Figure 15 to Figure 19 present the probabilistic results using PSA scatterplots and CEACs, while Table 43 to Table 45 show CEAC data in tabular form.

Despite the increased ICERs resulting from the correction to the Revised Base Case, results indicate that the probability that idelalisib plus rituximab is cost-effective at a willingness to pay threshold of £50,000 remains 94% versus rituximab, 84% versus BSC and 100% versus ofatumumab.

Figure 14: PSA scatterplot, Corrected Base Case, IR versus R

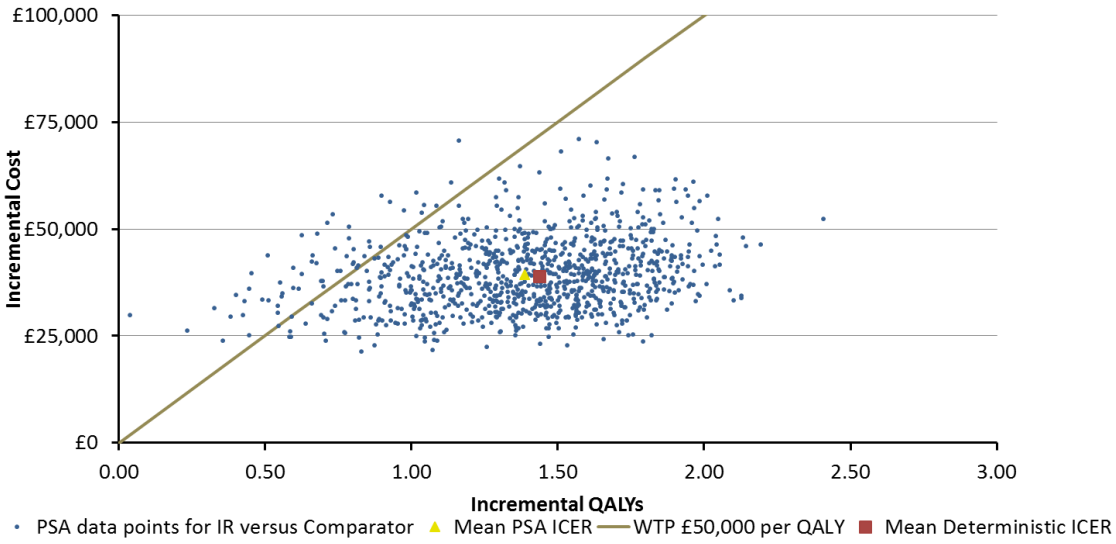

Figure 15: CEAC, Corrected Base Case, IR versus R

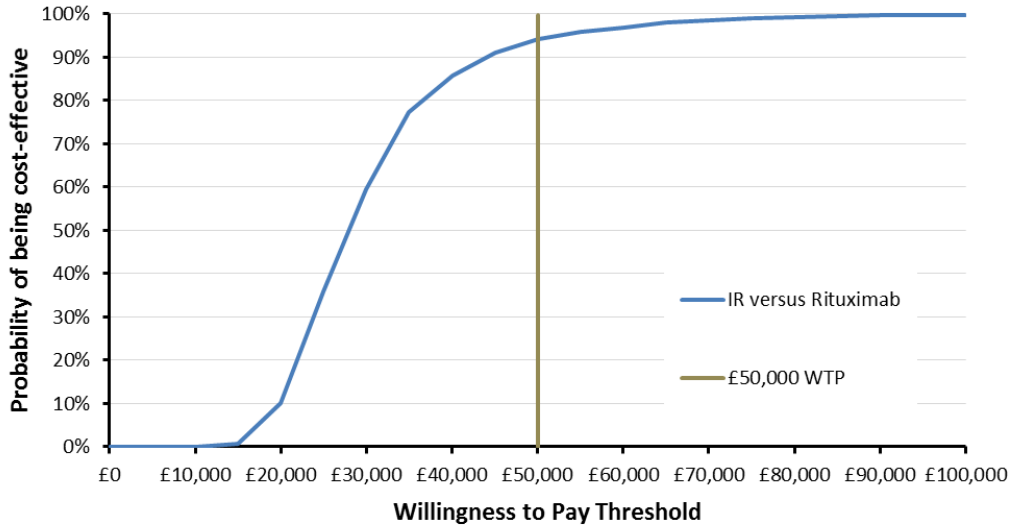

Table 43: CEAC table, Corrected Base Case, IR versus R

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**R**
£0	0%	100%
£5,000	0%	100%
£10,000	0%	100%
£15,000	1%	99%
£20,000	10%	90%
£25,000	36%	64%
£30,000	60%	41%
£35,000	77%	23%
£40,000	86%	14%
£45,000	91%	9%
£50,000	94%	6%
£55,000	96%	4%
£60,000	97%	3%
£65,000	98%	2%
£70,000	99%	1%
£75,000	99%	1%
£80,000	99%	1%
£85,000	99%	1%
£90,000	100%	0%
£95,000	100%	0%
£100,000	100%	0%

Figure 16: PSA scatterplot, Corrected Base Case, IR versus BSC

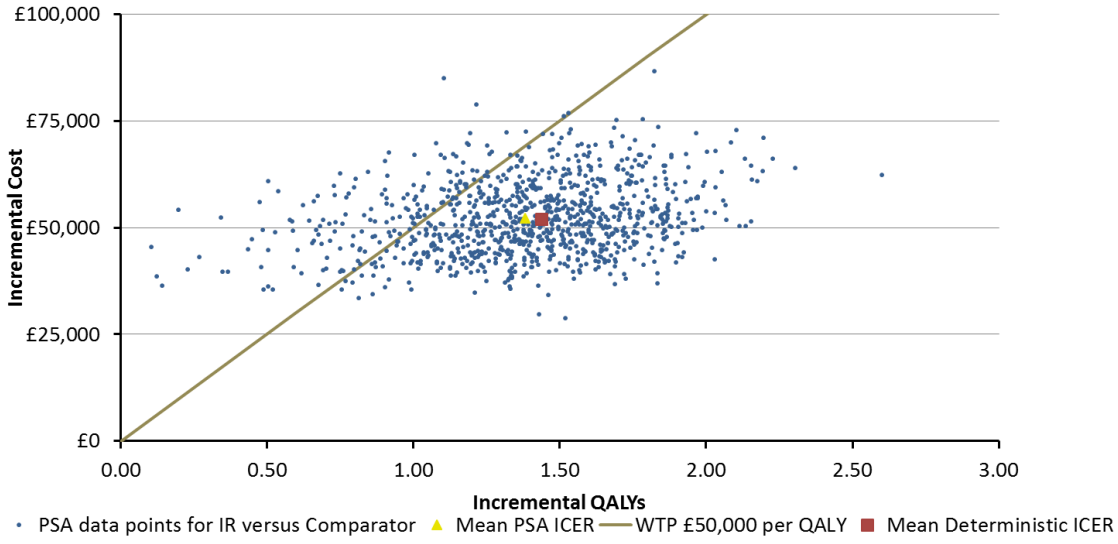

Figure 17: CEAC, Corrected Base Case, IR versus BSC

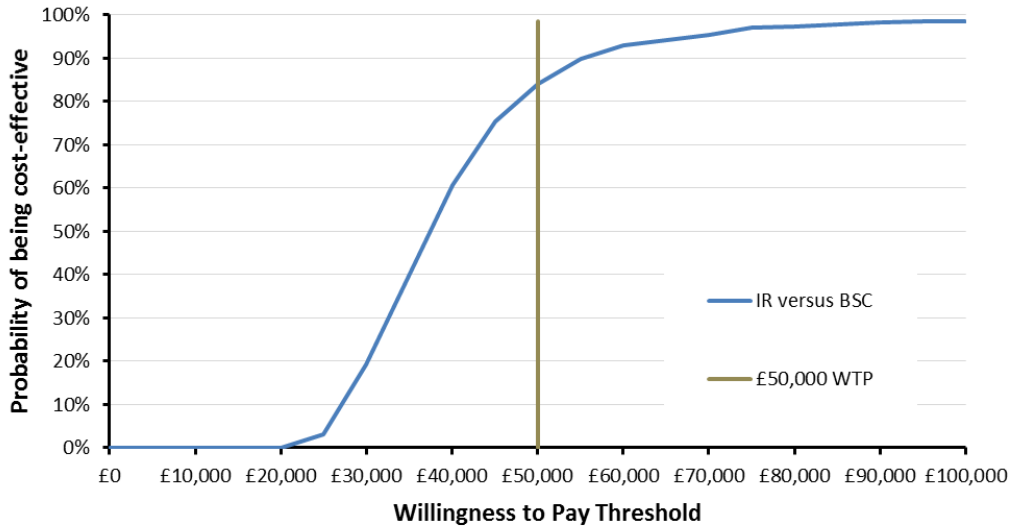

Table 44: CEAC table, Corrected Base Case, IR versus BSC

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**BSC**
£0	0%	100%
£5,000	0%	100%
£10,000	0%	100%

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	IR	BSC
£15,000	0%	100%
£20,000	0%	100%
£25,000	3%	97%
£30,000	19%	81%
£35,000	40%	60%
£40,000	61%	39%
£45,000	75%	25%
£50,000	84%	16%
£55,000	90%	10%
£60,000	93%	7%
£65,000	94%	6%
£70,000	95%	5%
£75,000	97%	3%
£80,000	97%	3%
£85,000	98%	2%
£90,000	98%	2%
£95,000	99%	2%
£100,000	99%	2%

Figure 18: PSA scatterplot, Corrected Base Case, IR versus ofatumumab

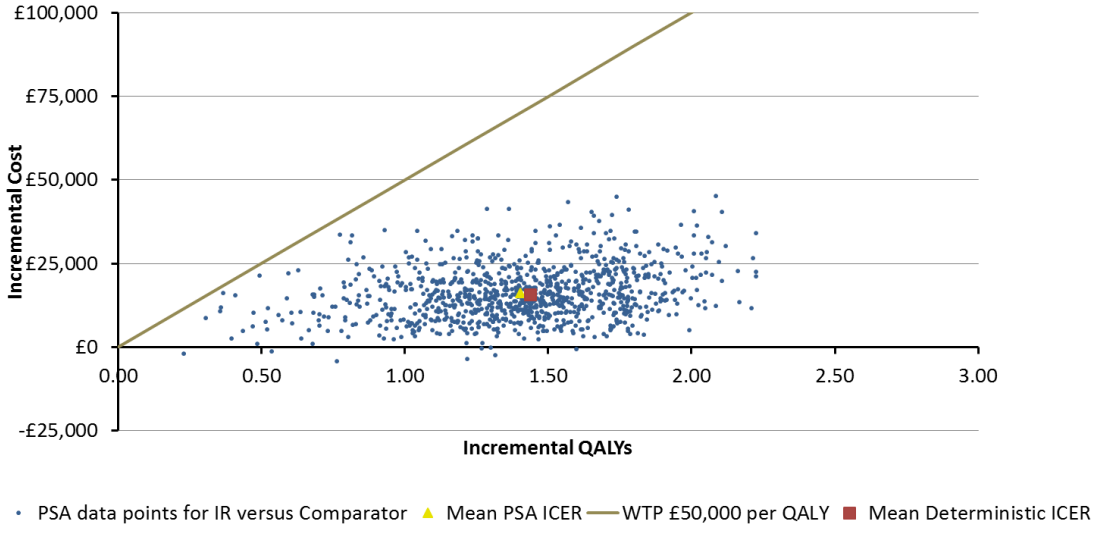

Figure 19: CEAC, Corrected Base Case, IR versus ofatumumab

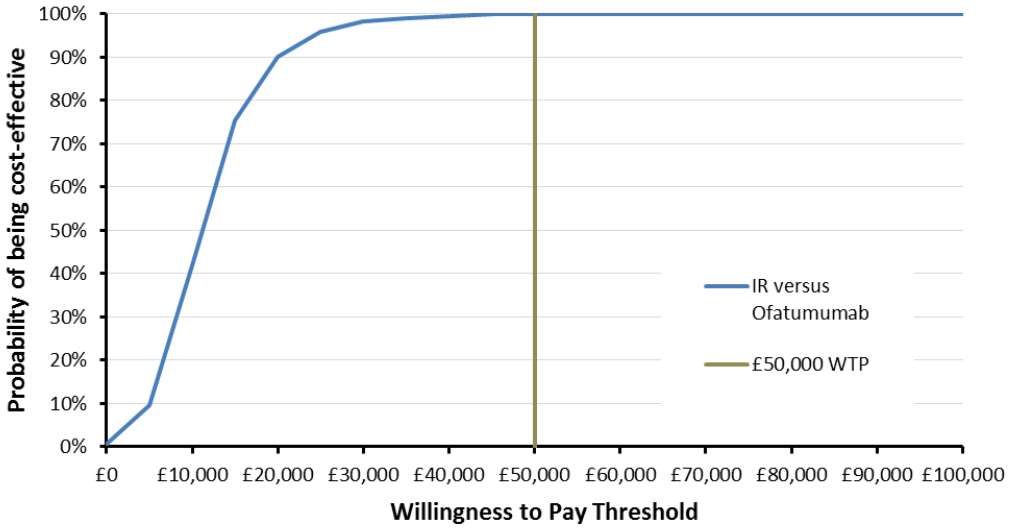

Table 45: CEAC table, Corrected Base Case, IR versus ofatumumab

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**Ofatumumab**
£0	1%	99%
£5,000	10%	90%
£10,000	42%	58%
£15,000	75%	25%
£20,000	90%	10%
£25,000	96%	4%
£30,000	98%	2%
£35,000	99%	1%
£40,000	100%	0%
£45,000	100%	0%
£50,000	100%	0%
£55,000	100%	0%
£60,000	100%	0%
£65,000	100%	0%
£70,000	100%	0%
£75,000	100%	0%
£80,000	100%	0%
£85,000	100%	0%
£90,000	100%	0%
£95,000	100%	0%
£100,000	100%	0%

Table 46: Mean PSA results, Corrected Base Case, IR versus R

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	1.52	1.41				
Idelalisib + rituximab	[redacted]	2.30	3.59	£39,263	1.39	2.18	£28,333
Key: ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year							

Table 47: Mean PSA results, Corrected Base Case, IR versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	1.52	1.43				
Idelalisib + rituximab	[redacted]	2.31	3.59	£52,122	1.38	2.16	£37,700
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year							

Table 48: Mean PSA results, Corrected Base Case, IR versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	1.52	1.41				
Idelalisib + rituximab	[redacted]	2.32	3.61	£16,150	1.40	2.20	£11,513
Key: ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year							

4.3 Appendix to Section 1.3

4.3.1 PSA results for the Proposed Base Case

Table 52, Table 53 and Table 54 show mean PSA results for the three Proposed Base Case comparisons. Figure 20 to Figure 25 present the probabilistic results using PSA scatterplots and CEACs, while Table 49 to Table 51 show CEAC data in tabular form.

Results indicate that the probability that idelalisib plus rituximab is cost-effective versus at a willingness to pay threshold of £50,000 remains 97% versus rituximab, 88% versus BSC and 100% versus ofatumumab.

Figure 20: PSA Scatterplot, Proposed Base Case, IR versus R

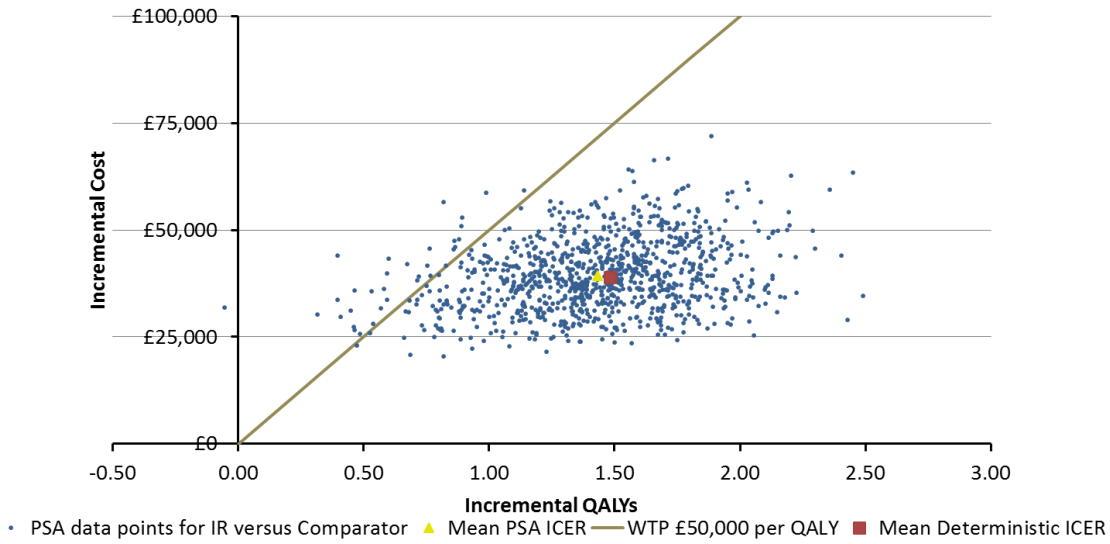

Figure 21: CEAC, Proposed Base Case, IR versus R

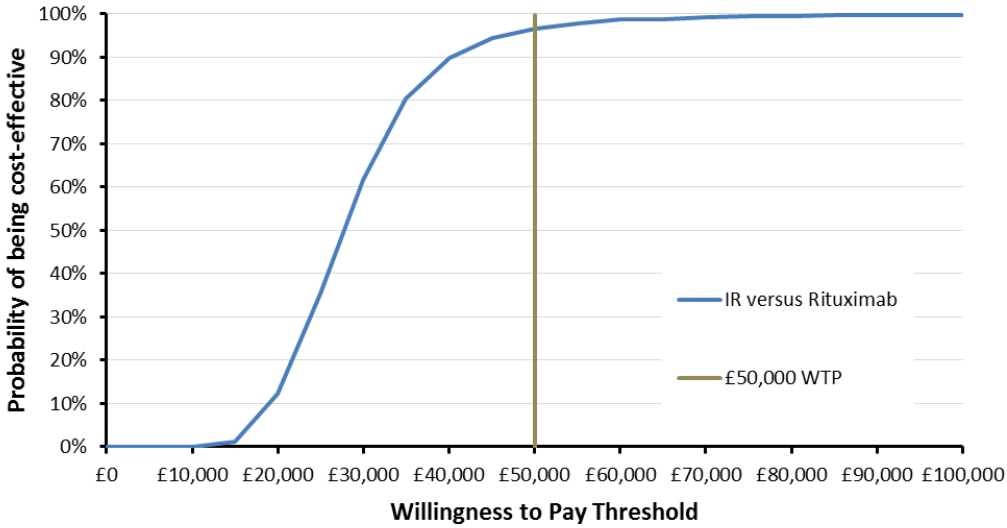

Table 49: CEAC Table, Proposed Base Case, IR versus R

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**R**
£0	0%	100%
£5,000	0%	100%
£10,000	0%	100%
£15,000	1%	99%
£20,000	12%	88%
£25,000	35%	65%
£30,000	62%	38%
£35,000	80%	20%
£40,000	90%	10%
£45,000	95%	6%
£50,000	97%	3%
£55,000	98%	2%
£60,000	99%	1%
£65,000	99%	1%
£70,000	99%	1%
£75,000	100%	1%
£80,000	100%	0%
£85,000	100%	0%
£90,000	100%	0%
£95,000	100%	0%
£100,000	100%	0%

Figure 22: PSA Scatterplot, Proposed Base Case, IR versus BSC

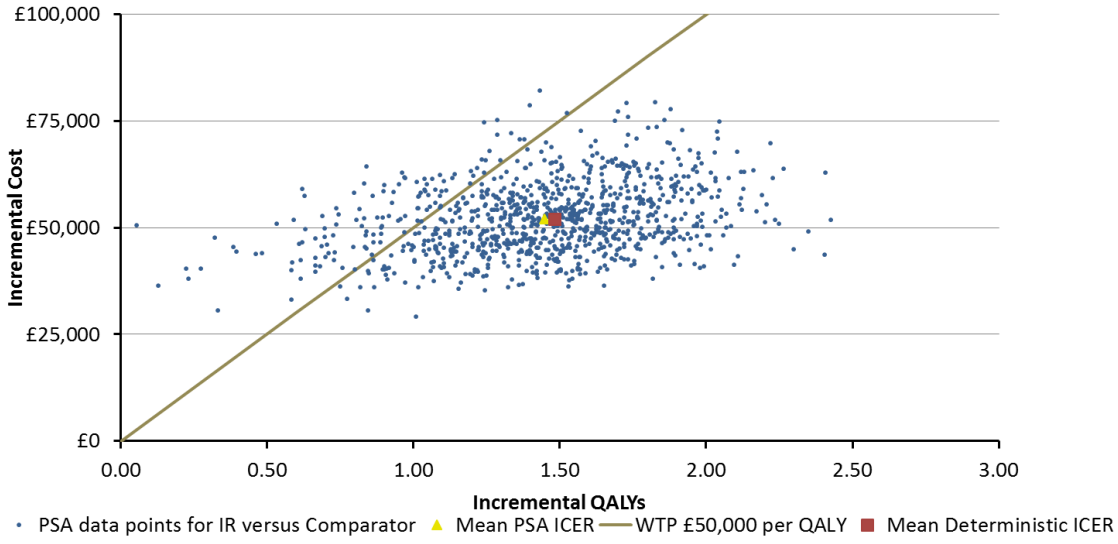

Figure 23: CEAC, Proposed Base Case, IR versus BSC

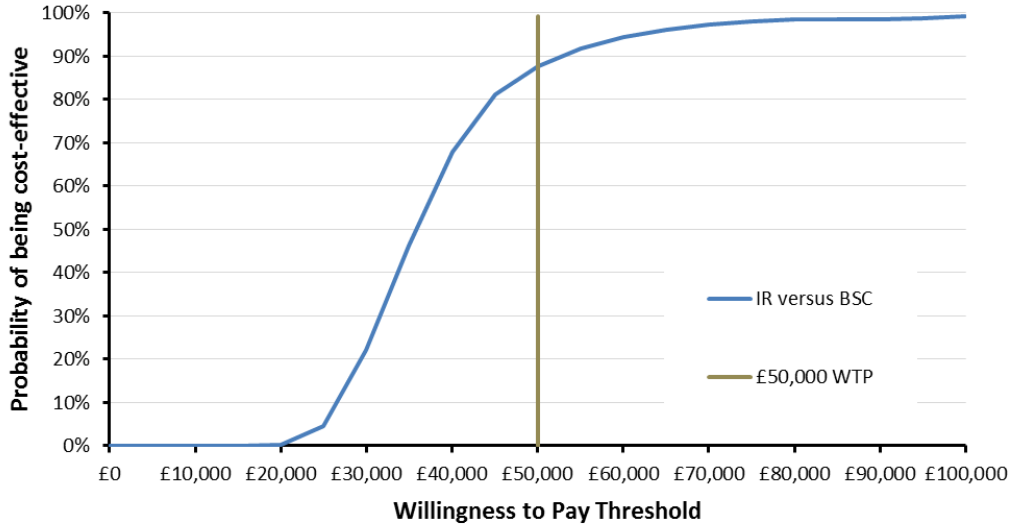

Table 50: CEAC Table, Proposed Base Case, IR versus BSC

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**BSC**
£0	0%	100%
£5,000	0%	100%
£10,000	0%	100%
£15,000	0%	100%
£20,000	0%	100%
£25,000	5%	95%
£30,000	22%	78%
£35,000	46%	54%
£40,000	68%	32%
£45,000	81%	19%
£50,000	88%	12%
£55,000	92%	8%
£60,000	95%	6%
£65,000	96%	4%
£70,000	97%	3%
£75,000	98%	2%
£80,000	99%	2%
£85,000	99%	2%
£90,000	99%	1%
£95,000	99%	1%
£100,000	99%	1%

Figure 24: PSA Scatterplot, Proposed Base Case, IR versus ofatumumab

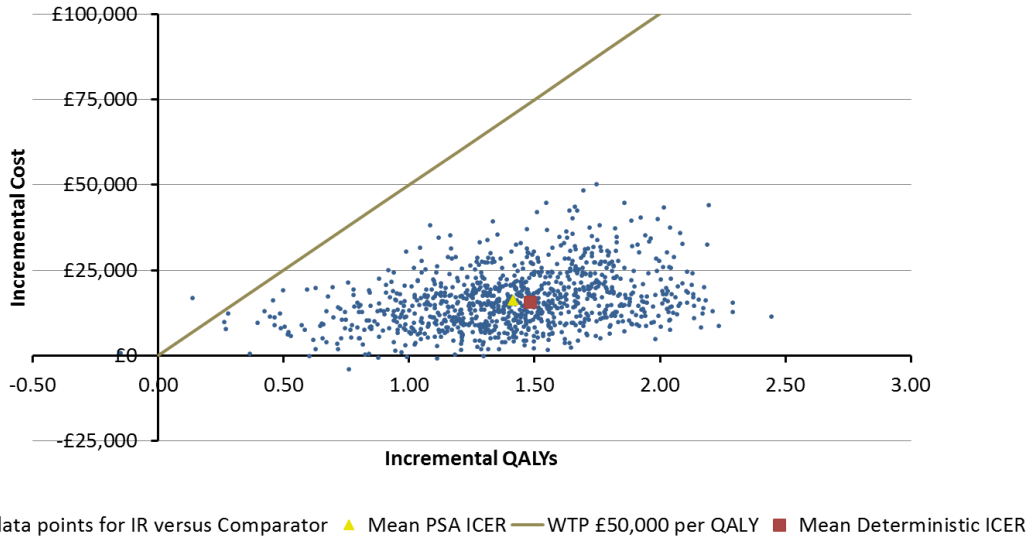

Figure 25: CEAC, Proposed Base Case, IR versus ofatumumab

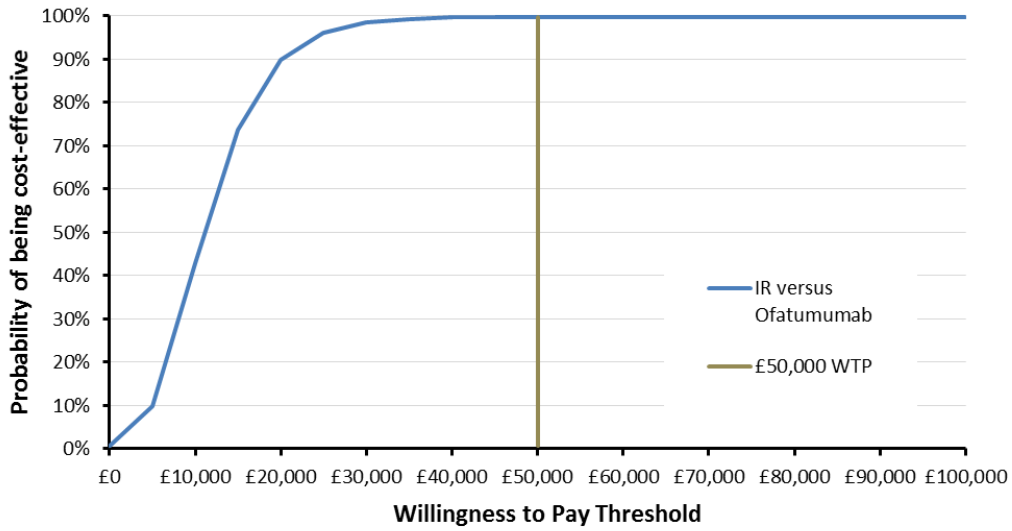

Table 51: CEAC Table, Proposed Base Case, IR versus ofatumumab

Cost-effectiveness acceptability		
Proportion of runs in which each treatment is the most cost effective		
Threshold	**IR**	**Ofatumumab**
£0	1%	99%
£5,000	10%	90%
£10,000	43%	57%
£15,000	74%	26%
£20,000	90%	10%
£25,000	96%	4%
£30,000	99%	1%
£35,000	99%	1%
£40,000	100%	0%
£45,000	100%	0%
£50,000	100%	0%
£55,000	100%	0%
£60,000	100%	0%
£65,000	100%	0%
£70,000	100%	0%
£75,000	100%	0%
£80,000	100%	0%
£85,000	100%	0%
£90,000	100%	0%
£95,000	100%	0%
£100,000	100%	0%

Table 52: Mean PSA results, Proposed Base Case, idelalisib with rituximab versus rituximab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Rituximab	[redacted]	1.52	1.42				
Idelalisib + rituximab	[redacted]	2.34	3.59	£39,390	1.43	2.17	£27,489
Key: ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year							

Table 53: Mean PSA results, Proposed Base Case, idelalisib with rituximab versus BSC

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
BSC	[redacted]	1.52	1.43				
Idelalisib + rituximab	[redacted]	2.36	3.62	£52,045	1.45	2.19	£35,977
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year; BSC, best supportive care							

Table 54: Mean PSA results, Proposed Base Case, idelalisib with rituximab versus ofatumumab

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ofatumumab	[redacted]	1.52	1.42				
Idelalisib + rituximab	[redacted]	2.31	3.55	£16,272	1.41	2.14	£11,501
Key: ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life year							