in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Idelalisib for treating refractory follicular lymphoma

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14	Sentence amended
18	Sentence deleted
36	Factual inaccuracy (carried over from the CS) amended: WHO PFS $\leq$ 2 for study 101-02/99
40-41	Baseline characteristics of CUP and HMRN patients amended in Table 4.4 of Page 40-41.
52	Baseline characteristics of HMRN adjusted population amended in Table 4.11 of Page 52
101	Sentence amended
102	Caption of Table 5.18 amended
107	Sentence deleted
113	Sentence amended
115	Typo amended
116	Sentence deleted
120	Sentence deleted

Table 4.3: Summary of methodology of included clinical effectiveness studies

Study	101-09[33]	101-02/99[34]	Compassionate use programme[35]
Location	41 sites in the US and Europe	Eight sites in the US	46 sites in UK and Ireland
Trial design	Single group, open label, Phase II study	Phase Ib dose escalation and extension study	Retrospective cohort study
Eligibility criteria for participants	Key criteria for eligibility included: • Confirmed diagnosis of B cell iNHL without evidence of histological transformation • Histological types included FL Grade 1, 2 or 3a; small lymphocytic lymphoma; splenic, nodal or extranodal marginal zone lymphoma; LPL/WM • Radiographically measurable disease (defined as ≥1 lymph node with perpendicular dimensions measuring ≥2.0 x ≥1.0cm) • Received at least two prior systemic therapies for iNHL • Refractory to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractory was defined as less than a partial response or progression of disease within 6 months after completion of a prior therapy • Karnofsky performance score of 60 or higher (on a scale of 0=death and 100=complete absence of symptoms) Exclusion criteria included: • Central nervous system lymphoma • Known histological transformation from iNHL to diffuse large B cell lymphoma • History of a non-lymphoma malignancy except for the following: adequately treated local basal cell or	Key criteria for eligibility included: • Histologically confirmed diagnosis of iNHL • Histologic types included follicular lymphoma Grade 1, 2 or 3a; small lymphocytic lymphoma; marginal zone lymphoma; lymphoplasmacytic lymphoma with or without WM • Measurable disease (defined as ≥1 lesion measuring >2cm in a single dimension by computed tomography • World Health Organization performance status ≤2 • Received at least 1 prior chemotherapy and prior rituximab Exclusion criteria included: • Active central nervous system lymphoma • Active serious infection requiring systemic therapy • Prior stem cell transplantation with active graft-versus-host disease	Refractory or relapsed FL: • Refractory defined as stable disease or progressive disease to the prior treatment, or relapse <6 months following a previous partial/complete response • Relapse defined as progressive disease followed a remission >6 months

Table 4.4: Baseline characteristics of patients in included studies

Baseline characteristic	Study 101-09[33]		Study 101-02/99 (n=64)[34]	CUP cohort (n=79)[35]	HMRN Patients ([redacted])[14]
	Overall population (n=125)	FL population (n=72)			
Median age, years (range)	64 (33–87)	62 (33–84)	64 (32–91)	64 (29–86)	[redacted]
Sex, male, n (%)	80 (64%)	39 (54.2%)	44 (69%)	40 (51%)	[redacted]
Performance status/Disease stage, n (%)	KPS 60: 2 (1.6%) KPS 70: 6 (4.8%) KPS 80: 27 (21.6%) KPS 90: 44 (35.2%) KPS 100: 46 (36.8%)	ECOG 2: 6 (8.3%) ECOG 1: 35 (48.6%) ECOG 0: 31 (43.1%)	NR	ECOG 2-4: 20 (25%) ECOG 0-1: 59 (75%)	Stage III or IV (%): [redacted]
Median time since diagnosis, years (range)	5.3 (0.4–18.4)	4.7 (0.8–18.4)	NR	NR	[redacted]
Disease subtype, n (%)					
Follicular lymphoma	72 (57.6%)	72 (100%)	38 (59%)	79 (100%)	[redacted]
Small lymphocytic lymphoma	28 (22.4%)	Not applicable	11 (17%)	NR	NR
Marginal zone lymphoma	15 (12.0%)	Not applicable	6 (9%)	NR	NR
Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinaemia	10 (8.0%)	Not applicable	9 (14%)	NR	NR
Health assessment, n (%)					
Disease Stage III or IV	111 (88.8)	60 (83.3)	NR	NR	NR
Elevated LDH	38 (30.4)	21 (29.2)	24 (38%)	NR	NR
Bulky disease (one or more nodes with at least one dimension of 7cm or more)	33 (26.4)	16 (22.2)	28 (44%)	NR	[redacted]
Baseline neutropenia (ANC <1,500 per mm^3)	17 (13.6)	9 (12.5)	7 (11%)	NR	NR
Baseline anaemia (haemoglobin <10 g/dL)	19 (15.2)	8 (11.1)	41 (64%)	NR	NR
Baseline thrombocytopenia (platelet count <75,000 per mm^3)	10 (8.0)	5 (6.9)	36 (56%)	NR	NR
High FLIPI risk score at baseline	Not applicable	39 (54.2)	NR	0-2: 19/78 (25%)	NR

Baseline characteristic	Study 101-09[33]		Study 101-02/99 (n=64)[34]	CUP cohort (n=79)[35]	HMRN Patients ([redacted])[14]
	Overall population (n=125)	FL population (n=72)			
				3-5: 59/78 (75%)	
FL grade	Not applicable	1: 21 (29.2) 2: 39 (54.2) 3A: 12 (16.7)	NR	NR	NR
Treatment history					
Median prior regimens (range)	4 (2–12)	4 (2–12)	4 (1–10)	3 (1–13)	[redacted]
Median time since completion of last treatment, months (range)	3.9 (0.7–41.4)	4.3 (0.7–39.1)	NR	8.6 (0.9–99.2)	NR
Prior therapy, n (%)					
Rituximab	125 (100)	72 (100)	62 (97%)	78 (99%)	[redacted]
Alkylating agent	125 (100)	72 (100)	58 (91%)	78 (99%)	[redacted]
Bendamustine	81 (64.8)	50 (69.4)	17 (27%)	NR	NR
Anthracycline	79 (63.2)	51 (72.2)	33 (52%)	NR	NR
Purine analogue	42 (33.6)	17 (23.6)	27 (42%)	NR	NR
Stem cell transplantation	14 (11.2)	12 (16.7)	NR	21 (27%)	[redacted]
Prior therapy to which the disease was refractory, n/total n (%)					
Rituximab	125/125 (100)	72/72 (100)	NR	NR	[redacted]
Alkylating agent	124/125 (99)[a]	72/72 (100)	NR	NR	[redacted]
R-bendamustine	47/60 (78.3)	23/36 (72.2)	NR	NR	NR
R-CHOP	40/56 (71.4)	23/35 (65.7)	NR	NR	NR
R-CVP	29/36 (80.6)	15/20 (75.0)	NR	NR	NR
Bendamustine	61/81 (75.3)	32/50 (64.0)	NR	NR	NR
Refractory to ≥2 regimens	99/125 (79.2)	57/72 (79.2)	NR	NR	NR
Refractory to most recent regimen	112/125 (89.6)	62/72 (86.1)	37 (58%)	NR	NR

Summary data for the FL population of Study 101-09 (June 2014 database lock), were compared with individual patient data (IPD) from HMRN. All variables which were common to both datasets were considered for inclusion in the MAIC. However, several variables were subsequently excluded. The variables included in the MAIC were therefore:

[redacted]

Patient characteristics pre- and post-matching are summarised in Table 4.11.

Table 4.11: Baseline characteristics of Study 101-09 patients and HMRN patients (pre- and post-matching), FL population with disease refractory to rituximab and an alkylating agent

Characteristic	Study 101-09 (n=72)	HMRN (n=[redacted])	Adjusted HMRN ([redacted])
Male, n (%)	39 (54.2)	[redacted]	[redacted]
Median age, years (range) Age ≥ 62 years (%)	62 (33–84) NR	NR [redacted]	[redacted]
Stage III or IV, n (%)	60 (83.3)	[redacted]	[redacted]
Bulky disease, n (%)	16 (22.2)	[redacted]	[redacted]
Median time since diagnosis, years (range) Time from diagnosis >=4.7 (%)	4.7 (0.8–18.4) NR	NR [redacted]	NR [redacted]
Median lines of prior therapy (range)	4 (2–12)	[redacted]	NR
Prior ASCT, n (%)	12 (16.7)	[redacted]	NR

Source: CS, Table 16, page 59, and Table 17, page 61.
ASCT = autologous stem cell transplantation; HMRN = Haematological Malignancy Research Network; FL = follicular lymphoma.

[redacted][37] The results for two-year OS and one-year PFS for the idelalisib patients in Study 101-09 and the HMRN patients before and after MAIC adjustment are summarised in Table 4.12.

Table 4.12: OS and PFS results for Study 101-09 patients and HMRN patients after adjustment, FL population with disease refractory to rituximab and an alkylating agent

Outcome	Study 101-09 (n=72)	Unadjusted HMRN (n=[redacted])	Adjusted HMRN [redacted]	Adjusted HMRN excluding time to diagnosis [redacted]
Two-year OS	69.8%	[redacted]	[redacted]	[redacted]
One year PFS	43%	[redacted]	[redacted]	[redacted]

Source: CS, Table 17, page 61; HMRN report, Tables 18 and 19
ASCT = autologous stem cell transplantation; HMRN = Haematological Malignancy Research Network; FL = follicular lymphoma.
*effective MAIC sample size calculated as the square of the summed weights divided by the sum of the squared weights.

Table 5.17: Comparison D: Study 101-09 vs. Study 101-09 (BSC) results, including idelalisib CCD

	Costs	QALYs	Life years	Incremental			ICER
				Costs	QALYs	Life years	
BSC	[redacted]	2.50	4.62	-	-	-	£25,272
Idelalisib	[redacted]	3.71	6.34	£30,473	1.21	1.72	

Source: Table 63 in the CS.[1]
BSC = best supportive care; CCD = confidential commercial discount; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.
*Note that the "Life years" results provided in the table are undiscounted

Other scenario analyses: alternative assumptions on Comparison A

Detailed cost effectiveness results for the remaining set of scenarios were not presented in the CS. However, based on the ICER change figures shown in Table 5.14 above, the ICER results from Comparison A did not change drastically with the scenarios tested by the company. The largest positive difference with respect to the base-case ICER was found in the scenario when the time horizon of 10 years was used (instead of a time horizon of 38 years in the base-case, using 10 years of time horizon resulted in an ICER increase of £5,462). The largest negative difference with respect to the base-case ICER was found in the scenario, which assumes a generalised gamma distribution for TTP (instead of using lognormal distribution for TTP in the base-case, using generalised gamma distributed TTP would lead to an ICER decrease of -£7,117).

ERG comments: Even though the results were presented in an appropriate way, the ERG discovered and corrected several errors in the model as described in Section 5.3.1. This had an impact on the results, as shown in sections 5.3.2 and 5.3.3. In the PSA, the ERG noted that normal distribution was used to sample cost related model inputs, and considers that using normal distribution has a probability, albeit small, to generate implausible (negative) sampled values, and therefore the ERG would have preferred gamma or lognormal distribution used while sampling for logically positive parameters. The ERG doubts if correlated variables like the survival coefficients should have been included in the one-way sensitivity analysis, since changing one parameter to its upper/lower bound while keeping the other correlated variable unchanged might lead to unrealistic combination of parameters.

Several structural uncertainties were tested by the company as scenario analyses. However, the ERG considered that the company could have conducted more scenario analyses, especially considering the substantial uncertainty in some of the model inputs related to resource use and utilities. Furthermore, in all scenario analyses, the uncertainties were explored individually and therefore a combined effect of changing multiple assumptions in the model on the ICER, is missing. This will be explored by the ERG in Section 5.3.

5.2.12 Model validation and face validity check

In the CS (on page 152), it was mentioned that the inputs and assumptions of the cost effectiveness analyses were reviewed during a meeting with Dr Robert Marcus. The meeting report was enclosed in the submission. Furthermore, it was stated that the economic model was reviewed for coding errors, inconsistencies, and the plausibility of inputs by an economist not involved in model building. In addition, in the CS, it was mentioned that a checklist of known modelling errors and questioning of assumptions was used to review the model. The details and results of the technical validation of the economic model were not reported.

The ERG has serious concerns on the lack of the reporting of the model validation efforts. The company declined to provide these, even this was requested. This, in combination with the spotted programming errors and the gap between trial outcomes and the model outcomes decreased our level of confidence in the economic model.

The ERG incorporated several changes to the comparisons provided in the CS: 1) fixing programming errors 2) Incorporating half cycle correction 3) Using the mean ToT estimate from the most recent data cut-off date while calculating AE cycle probabilities 4) Implementing wastage costs for idelalisib (i.e. when patients stop the treatment before the package is finished completely) 5) Implementing idelalisib mean dose intensity from Study 101-09 for chemotherapy (as a conservative estimate, as it was reported that the MDI for chemotherapy is expected to be lower) 6)Implementing age adjusted utility decline from Ara et al. 2010.[57]

After the ERG changes were implemented, in Comparison A, idelalisib resulted in [redacted] total (discounted) costs and 3.43 total QALYs, while chemotherapy resulted in [redacted] total (discounted) costs and 2.71 total QALYs, as presented in Table 5.19. Therefore, idelalisib produced 0.72 additional QALYs at an incremental cost of £23,599 when compared to chemotherapy, leading to an ICER of £32,882. This is higher than the company base-case ICER.

For Comparison B, after ERG changes, idelalisib resulted in [redacted] total (discounted) costs and 3.10 total QALYs, while chemotherapy resulted in [redacted] total (discounted) costs and 1.38 total QALYs, as presented in Table 5.20. Therefore, idelalisib produced 1.72 additional QALYs at an incremental cost of £37,164 when compared to chemotherapy, leading to an ICER of £21,559.

After the ERG changes were implemented, in Comparison C, idelalisib resulted in [redacted] total (discounted) costs and 3.21 total QALYs, while chemotherapy resulted in [redacted] total (discounted) costs and 2.82 total QALYs, as presented in Table 5.21. Therefore, idelalisib produced 0.39 additional QALYs at an incremental cost of £22,712 when compared to chemotherapy, leading to an ICER of £58,754.
For the chemotherapy ineligible patients, after ERG changes are implemented in Comparison D, idelalisib resulted in [redacted] total (discounted) costs, and 3.43 total QALYs, same as in Comparison A, while BSC resulted in [redacted] total (discounted) costs and 2.43 total QALYs, as presented in Table 5.22. Therefore, idelalisib produced 0.99 additional QALYs at an incremental cost of £29,426, when compared to BSC, leading to an ICER of £29,639.

The ERG conducted following additional scenario analyses: 1) 50% price reduction rituximab (due to biosimilar availability) 2) HR=1 for adjusting prior line treatment outcomes 3) Alternative utility inputs from Bec et al. 2014 or GADOLIN trial 4) 100% increase in CMV monitoring frequency 5) CHOP regimen costs for the chemotherapy costs 6) Applying minimum function instead of maximum to operationalise logical constraints on time to event extrapolation curves 7) Using alternative TTP (PFS for Comparison B), ToT and PPS (OS for Comparison B) extrapolations

In Comparison A, the ICER values range between £30,000 to £40,000. Incremental costs are between £22,500 to £27,500 and incremental QALYs are between 0.59 and 0.84. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73. The scenarios that had the most impact on the ICER seem to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and even comparison D (for chemotherapy ineligible patients, receiving BSC). This gap can be due to the difference in model inputs used (e.g. MAIC adjusted HMRN dataset) as well as the different underlying modelling assumptions made in comparison B (e.g. area under the curve approach).

In Comparison C, besides the one outlier (Scenario 7c), which generated rather implausible estimates in terms of LYs and QALYs, the ICER values range between £58,000 to £95,000. Incremental costs are between £21,500 to £26,500 and incremental QALYs are between 0.23 and 0.39. The scenarios that had the most impact on the ICER seem to be using an alternative distribution for TTP extrapolation (scenario 7a), and assuming an HR=1 to adjust for the prior-line treatment time-to-event outcomes (scenario 2). Less than these two scenarios, the other scenarios that still had a substantial impact on the ICER are assuming less expensive (i.e. same as the CHOP regimen) estimates for the chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a). The only difference of comparison C from comparison A was the TTP inputs, therefore, as expected, total LYs, QALYs and cost outcomes from comparison C seem to be in line with the outcomes from comparison A. The QALYs from the idelalisib arm are a bit lower and the QALYs from the chemotherapy arm are a bit higher than those in comparison A, which led to a higher ICER. The ERG considers that the TTP data used in comparison C might be more reflective of the UK population, as it was from a compassionate use program conducted in the UK and Ireland.

Finally, in Comparison D, the cost-effectiveness results are relatively robust. Incremental QALYs are around 0.99 and incremental costs are around £29,000, which lead to an ICER value around £30,000 per QALY gained in all scenarios. Scenarios that had some impact on the ICER are using an alternative distribution for TTP extrapolation (scenario 7a) and using utility inputs from Bec et al. 2014 or GADOLIN trial (Scenario 3a and 3b). However, one should interpret these comparison D results with caution since in this comparison, it is assumed that patients receiving BSC progress immediately, which leads to an underestimation for the BSC related outcomes.

In conclusion, the ERG analyses resulted in a range of ICERs between £16,800 and £95,000 per QALY gained. Most of the ICER estimates are larger than the £30,000 per QALY threshold. Especially in Comparison C, where the TTP data are potentially the most reflective of the UK clinical practice, the ICER estimates are all above the £50,000 per QALY threshold. These ranges are indicative of the substantial uncertainty inherent in the cost-effectiveness estimates, and with the inherent uncertainty, especially on the clinical effectiveness evidence, the ERG is doubtful whether idelalisib can be considered as cost-effective for the population it was indicated for.

5.3.3. Results from the ERG additional exploratory scenario analyses

The additional scenarios listed in Section 5.3.1 were performed after the ERG changes were implemented to all four comparisons. The results of these additional scenarios are going to be summarised from Table 5.23 to Table 5.26, for Comparisons A, B, C and D, respectively.

It can be seen that there is a substantial uncertainty surrounding the cost effectiveness of idelalisib.

When we look at Comparison A, the ICER values range between £30,000 to £40,000. Incremental costs are between £22,500 to £27,500 and incremental QALYs are between 0.59 and 0.84.

The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73.

The scenarios that had the most impact on the ICER seems to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a).

Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and D (for chemotherapy ineligible patients receiving BSC).

In Comparison C, besides the one outlier (Scenario 7c), which generated rathe implausible estimates in terms of Lys and QALYs, the ICER values range between £58,000 to £95,000. Incremental costs are between £21,500 to £26,500 and incremental QALYs are between 0.23 and 0.39.

The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), and assuming an HR=1 to adjust for the prior-line treatment time-to-event outcomes (scenario 2). Less than these two scenarios, the other scenarios that had still a substantial impact on the ICER are assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

Total LYs, QALYs and costs associated with the chemotherapy in Comparison C seem to be in line with the results from Comparison A. The QALYs from the idelalisib arm is a bit lower and the QALYs from the chemotherapy arm is a bit higher than those in Comparison A.

Finally, in Comparison D, the cost effectiveness results are relatively robust. Incremental QALYs are around 0.99 and incremental costs are around £29,000, which lead to an ICER value around £30,000 per QALY gained.

The scenarios that had some impact on the ICER are to be using an alternative distribution for TTP extrapolation (scenario 7a) and using utility inputs from Bec et al. 2014 or GADOLIN trial (Scenario 3a and 3b). However, one should interpret the results with caution since in this comparison, it is assumed that patients receiving BSC progress immediately, which is an underestimation for the BSC related outcomes.

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and D (for chemotherapy ineligible patients receiving BSC).

In Comparison C, besides the one outlier (Scenario 7c), which generated rather implausible estimates in terms of LYs and QALYs, the ICER values range between £58,000 to £95,000. Incremental costs are between £21,500 to £26,500 and incremental QALYs are between 0.23 and 0.39. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), and assuming an HR=1 to adjust for the prior-line treatment time-to-event outcomes (scenario 2). Less than these two scenarios, the other scenarios that had still a substantial impact on the ICER are assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy in Comparison C seem to be in line with the results from Comparison A. The QALYs from the idelalisib arm is a bit lower and the QALYs from the chemotherapy arm is a bit higher than those in Comparison A.

Finally, in Comparison D, the cost effectiveness results are relatively robust. Incremental QALYs are around 0.99 and incremental costs are around £29,000, which lead to an ICER value around £30,000 per QALY gained. The scenarios that had some impact on the ICER are using an alternative distribution for TTP extrapolation (scenario 7a) and using utility inputs from Bec et al. 2014 or GADOLIN trial (Scenario 3a and 3b). However, one should interpret the results with caution since in this comparison, it is assumed that patients receiving BSC progress immediately, which is an underestimation for the BSC related outcomes obviously.

In conclusion, the ERG analyses resulted in a range of ICER between £16,800 and £95,000 per QALY gained. Most of the ICER estimates are larger than the £30,000 per QALY threshold. Especially in Comparison C, where the TTP data that is potentially the most reflective of the UK clinical practice, the ICER estimates are above £50,000 per QALY threshold. These ranges are indicative of the substantial uncertainty inherent in the cost effectiveness estimates.

In the total population, 72 patients (57.6%) reported a serious adverse event (SAE); in the FL population, 36 patients (50.0%) reported an SAE. The most frequent SAEs in the total population (reported in ≥10% of patients) were pyrexia and pneumonia (both reported in 14 [11.2%] patients); pyrexia was also the only SAE reported in ≥10% of patients in the FL population (reported in 8 [11.1%] patients). In total, 13 (10.4%) patients had an AE that resulted in death.

No adverse events were reported for comparators. Therefore, it is not possible to say anything about the relative safety profile in comparison to usual care.

The base-case cost effectiveness analysis for Comparison A showed that idelalisib resulted in a total cost of [redacted] and 3.75 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 resulted in a total cost of [redacted] and 2.81 QALYs, resulting in an ICER of £26,076 per QALY gained. In Comparison B, idelalisib treatment resulted in a total cost of [redacted] and 3.19 QALYs, whereas chemotherapy regimens as observed in the HMRN database resulted in a total cost of [redacted] and 1.44 QALYs. In Comparison C idelalisib treatment resulted in a total cost of [redacted] and 3.41 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme resulted in a total cost of [redacted] and 2.92 QALYs. Lastly, in Comparison D idelalisib treatment resulted in a total cost of [redacted] and 3.71 QALYs, best supportive care in a total cost of [redacted] and 2.50 QALYs.

The company submission presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis for Comparison A, and a number of scenario analyses covering all comparisons. The estimated probability of idelalisib being cost effective compared to chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 was 68% at a threshold of £30,000 per QALY gained. The deterministic sensitivity analysis showed that model outcomes were most sensitive to changes in the time to progression under idelalisib treatment.

In the scenario analyses, the published survival data used in Comparison B and C was digitised, and parametric survival models were subsequently fitted and incorporated into the economic analysis. This scenario resulted in a reduced ICER in Comparison B (£19,872), but a large increase in the ICER in Comparison C (£47,011). Other scenarios assessed the impact of choosing different parametric survival models for TTP, PPS and ToT in Comparison A. These resulted in moderate changes in the ICER, changes ranging from -£7,117 to +£3,785.

In Comparison A, the ICER values range between £30,000 to £40,000. Incremental costs are between £22,500 to £27,500 and incremental QALYs are between 0.59 and 0.84. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and D (for chemotherapy ineligible patients receiving BSC).

The base-case cost effectiveness analysis for Comparison A showed that idelalisib resulted in a total cost of [redacted] and 3.75 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 resulted in a total cost of [redacted] and 2.81 QALYs, resulting in an ICER of £26,076 per QALY gained. In Comparison B, idelalisib treatment resulted in a total cost of [redacted] and 3.19 QALYs, whereas chemotherapy regimens as observed in the HMRN database resulted in a total cost of [redacted] and 1.44 QALYs. In Comparison C idelalisib treatment resulted in a total cost of [redacted] and 3.41 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme resulted in a total cost of [redacted] and 2.92 QALYs. Lastly, in Comparison D idelalisib treatment resulted in a total cost of [redacted] and 3.71 QALYs, best supportive care in a total cost of [redacted] and 2.50 QALYs.

The company submission presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis for Comparison A, and a number of scenario analyses covering all comparisons. The estimated probability of idelalisib being cost effective compared to chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 was 68% at a threshold of £30,000 per QALY gained. The deterministic sensitivity analysis showed that model outcomes were most sensitive to changes in the time to progression under idelalisib treatment.

In the scenario analyses, the published survival data used in Comparison B and C was digitised, and parametric survival models were subsequently fitted and incorporated into the economic analysis. This scenario resulted in a reduced ICER in Comparison B (£19,872), but a large increase in the ICER in Comparison C (£47,011). Other scenarios assessed the impact of choosing different parametric survival models for time to progression (TTP), post-progression survival (PPS) and time on treatment (ToT) in Comparison A. These resulted in moderate changes in the ICER, changes ranging from -£7,117 to +£3,785.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The model structure in the CS can be considered in line with other, commonly used, Markov models used in oncology. The population considered in the company's economic analyses is in line with the NICE scope. It was not obvious to the ERG to what extent the population from Study 101-09 was reflective of the double refractory FL population in the UK.

The comparators included in the cost effectiveness analyses were in line with the final scope. However, the ERG considered that obinutuzumab with bendamustine should have been one of the chemotherapy options constituting the umbrella treatment, as comparator in the model. The company did not consider this comparator based on the lack of evidence and the opinion of one clinical expert.

The company generated comparative clinical effectiveness inputs for the economic model from non-randomised evidence. This non-randomised evidence was obtained either from different single arm studies, or obtained from the same study but using data from different time-points. The ERG considered that the analyses conducted to derive these comparative effectiveness inputs were not fully in line with the recommendations outlined in NICE DSU TSD 17, which could have led to biased estimates. In line with the recommendations, the ERG considered that a covariate adjusted survival analysis might have provided a less biased, sounder and confounder-adjusted treatment effect of idelalisib for the relevant time-to-event endpoints. Additionally, the ERG had some concerns regarding the use of a hazard ratio (HR) of 0.75 for the chemotherapy arm, to adjust for the additional number of prior treatments received. The evidence source for this parameter value could not be verified, and it is not clear to the ERG why one HR should be used for all time-to-event outcomes.

Different health utilities were assigned to the pre- and post-progression health states. Input for utilities was derived from previously published poster using the EQ-5D questionnaire in FL patients. Utility decrements were applied to account for adverse events.

The model included the costs of treatment, drug administration costs, costs for monitoring and prophylaxis, costs for healthcare use in the form of visits, tests, and procedures, and costs for the treatment of adverse events. Chemotherapy proportions from Study 101-09 were used in the model. Separate estimates of healthcare utilisation for pre- and post-progressive disease are used. A separate cost estimate for the last eight weeks of life (palliative care phase) is used. Resource use was based on a combination of clinical sources and published literature, and NHS reference costs were used.

The base-case cost effectiveness analysis for Comparison A showed that idelalisib resulted in a total cost of [redacted] and 3.75 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 resulted in a total cost of [redacted] and 2.81 QALYs, resulting in an ICER of £26,076 per QALY gained. In Comparison B, idelalisib treatment resulted in a total cost of [redacted] and 3.19 QALYs, whereas chemotherapy regimens as observed in the HMRN database resulted in a total cost of [redacted] and 1.44 QALYs. In Comparison C idelalisib treatment resulted in a total cost of [redacted] and 3.41 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in the UK & Ireland compassionate use programme resulted in a total cost of [redacted] and 2.92 QALYs. Lastly, in Comparison D idelalisib treatment resulted in a total cost of [redacted] and 3.71 QALYs, best supportive care in a total cost of [redacted] and 2.50 QALYs.

The company submission presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis for Comparison A, and a number of scenario analyses covering all comparisons. The estimated probability of idelalisib being cost effective compared to chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 was 68% at a threshold of £30,000 per QALY gained. The deterministic sensitivity analysis showed that model outcomes were most sensitive to changes in the time to progression under idelalisib treatment.

In the scenario analyses, the published survival data used in Comparison B and C was digitised, and parametric survival models were subsequently fitted and incorporated into the economic analysis. This scenario resulted in a reduced ICER in Comparison B (£19,872), but a large increase in the ICER in Comparison C (£47,011). Other scenarios assessed the impact of choosing different parametric survival models for TTP, PPS and ToT in Comparison A. These resulted in moderate changes in the ICER, changes ranging from -£7,117 to +£3,785.

The model structure in the CS can be considered in line with other, commonly used, Markov models used in oncology. The population considered in the company's economic analyses is in line with the NICE scope. It was not obvious to the ERG to what extent the population from Study 101-09 was reflective of the double refractory FL population in the UK.

The comparators included in the cost effectiveness analyses were in line with the final scope. However, the ERG considered that obinutuzumab with bendamustine should have been one of the chemotherapy options constituting the umbrella treatment, as comparator in the model. The company did not consider this comparator based on the lack of evidence and the opinion of one clinical expert.

The company generated comparative clinical effectiveness inputs for the economic model from non-randomised evidence. This non-randomised evidence was obtained either from different single arm studies, or obtained from the same study but using data from different time. The ERG considered that

The company also provided an internal validation check (Table 35 in the Appendices), where the model base-case outcomes for mean PFS and mean OS were compared with median trial PFS and OS outcomes from Study 101-09. The ERG replaced the reported mean values from the model with the median PFS and OS outcomes from the model, which is given in Table 5.18 below.

Table 5.18: Comparison A: mean PFS and OS – model predictions vs. observed data

	Idelalisib		Chemotherapy	
	Median from base-case model	**Median from the trial**	**Median from base-case model**	**Median from the trial (prior line)**
PFS (months)	12.46	11.0	3.69	4.60
OS (months)	57.46	38.10	43.38	NA
Source: Table 35 in the Appendix of the CS and the electronic model submitted in the CS[1] PFS = progression free survival; OS = overall survival;				

From Table 5.18 above, a gap between the trial and model outcomes can be seen, especially in the idelalisib arm. The gap between model and trial PFS outcomes is less pronounced in the chemotherapy arm, especially considering the HR=0.75 applied to adjust the trial PFS. The median OS for the prior line therapy was not reported from the Study 101-09, but it is expected to be higher than the median OS from the idelalisib, since no patient has reported dead during the prior line therapy. The potential causes for this gap were not discussed in the CS.

Also, in Table 27 of the CS, the features of the economic analysis were justified in comparison to the corresponding features of the NICE appraisal of obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab, completed in August 2017 (TA472).[50]

According to this table, the time horizon, utility source and resource use features of the CS of this appraisal and the CS of the TA472 appraisal seemed to be in line with each other.

ERG comments: The ERG requested the company to provide all details of the validation methods, using the AdvisHE validation tool.[75] In the response to the clarification letter, the company stated that the details of the model quality control process were confidential commercial property of the company and declined to provide these details.[29] It was not clear to the ERG why the company did not submit the reporting of their quality control efforts as a "commercial in confidence" document. Without any documentation of these efforts, the ERG considers that the validation section of the CS is clearly inadequate. The lack of the documenting of the validation efforts, the trust level of the ERG on the results of the cost effectiveness analyses is very low, which is reinforced by the gap between the median OS from the economic model and median trial OS from Study 101-09 for idelalisib, as depicted in Table 5.18.

Finally, in Table 27 of the CS, "the treatment effect waning" features were compared between the CS model and the TA472 model. It was not clear how the company handles the "treatment effect waning" in its model. The separate modelling of time to event outcomes for idelalisib and prior line therapy does not assume a constant HR between two treatment arms (unless exponential distribution is chosen), however there is some level of OS surrogacy, as the gain in TTP is transferred into a gain in OS, since the PPS of both arms were modelled identically. This OS surrogacy issue was reviewed in Davis et al. 2012, and was discussed thoroughly in previous cancer appraisals (e.g. TA496).[76, 77]