NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Idelalisib for treating refractory follicular lymphoma

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

[redacted]

Follicular lymphoma disease background

- Most common indolent non-Hodgkin lymphoma (iNHL) in the UK
- Median age at diagnosis in UK 60-65 years
- Male: Female ratio: 0.9
- Median life expectancy: 18 years in rituximab era
- Approximately 10-15% of people with follicular lymphoma have aggressive disease and lower life expectancy.
- Aim of treatment is to extend remission and control symptoms, treatment is characterised by recurrent remissions and relapses.

Idelalisib (Zydelig®, Gilead)

Mechanism	• Phosphatidylinositol 3-kinase p110δ (PI3Kδ) inhibitor. • Blocks signalling pathways that drive the growth and metabolism of malignant cells in lymphoid tissue and bone marrow
Marketing authorisation	• Marketing authorisation (September 2014): "Monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment"
Administration and dose	• 150mg tablet, administered orally twice daily
List price	• £3,114.75 per pack of 60 150mg tablets. • Confidential price discount has been agreed.

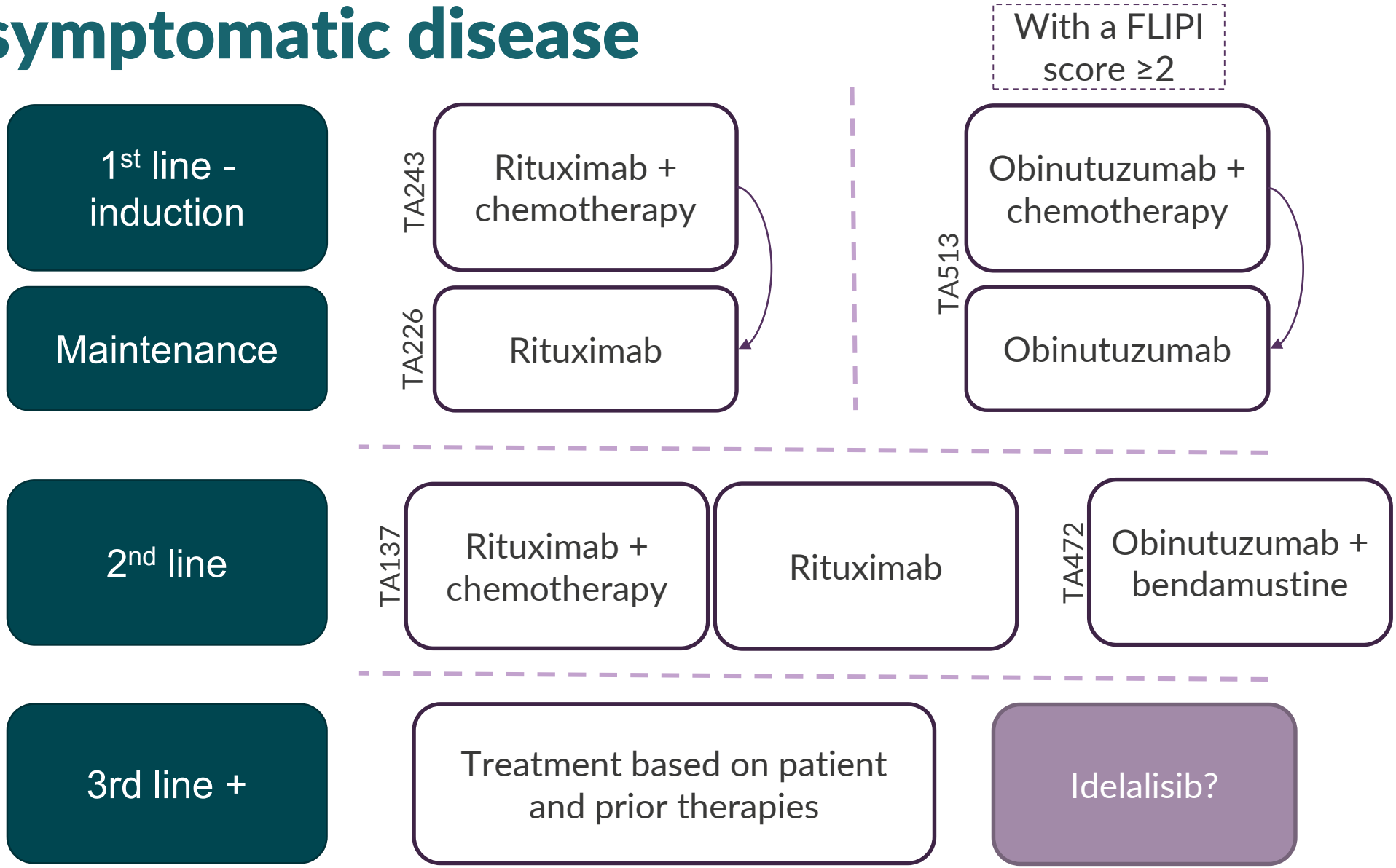
[redacted]

Follicular Lymphoma International Prognostic Index (FLIPI)

- Current NICE guidelines use FLIPI classification system for stratification of risk in assessment of treatment options
- FLIPI score combines patient characteristics with the Ann Arbor staging system to predict survival as low, intermediate or high.

FLIPI score (1 point for each factor)	Ann Arbor classification system
• Age >60 years • Haemoglobin level <12g/dl • Lactate dehydrogenase level > upper limit of normal • ≥ 4 nodal sites of disease • Ann Arbor Stage III-IV	**Stage I:** Single lymph node **Stage II**: Multiple lymph node groups on same side of diaphragm. **Stage III**: Multiple lymph nodes on both sides of diaphragm. **Stage IV**: Multiple extranodal sites or lymph nodes and extranodal disease. For all stages: **A/B:** Absence or presence of B symptoms including weight loss >10%, fever, drenching night sweats.
Risk category	
• Low (0 or 1) • Intermediate (2) • High (≥3)	

Treatment Pathway – advanced stage symptomatic disease



Professional expert feedback

Population

- 3 key populations of unmet need
  - Patients whose disease progresses after 1st line therapy within 2 years
  - Patients that relapse after autologous stem cell transplant in 2nd remission
  - **Patients that are 'double-refractory' to anti-CD20 antibodies and alkylating agents**

Setting

- Idelalisib would be used in specialist clinics in secondary care.
- Idelalisib may be used as a bridge to allogenic stem cell transplantation.

Complications

- Idelalisib has a well known toxicity profile that requires careful monitoring
- Grade 3-4 immuno-related toxicities are likely to impair quality of life significantly
- Close monitoring for cytomegalovirus and PJP prophylaxis are necessary
- Important to educate physicians around excess infections and death

[redacted]

Current treatment options/patient perspective

- The most common symptom is a painless swelling in the lymph nodes but can extend to B-symptoms including weight loss, fever, night sweats, fatigue and the complications of bone marrow diseases.
- Depression and stress from reduced life expectancy are commonly reported.
- The aim of treatment is to control symptoms and extend remission in order to improve quality of life.

- There is a lack of standard of care, current treatment consists of a variety of chemotherapies and other treatment options including radiotherapy, palliative options and salvage treatment with the aim to perform allogenic stem cell transplant.
- Re-treatment with rituximab or rituximab-containing regimens is an option, depending on response to rituximab, time since relapse and patient characteristics.
- Most common UK chemotherapies include cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil but choice depends on clinician and patient preference and may vary considerably between countries.

[redacted]

Decision problem

	Final scope issued by NICE	Decision problem in the company submission	ERG comment
Population	Follicular lymphoma refractory to 2 prior lines of therapy	No change	-
Intervention	Idelalisib	No change	-

Comparators	• Chemotherapy regimens
	  • cyclophosphamide- or fludarabine-containing regimens
	  • bendamustine
	  • chlorambucil
	When chemotherapy is unsuitable:
	• Best supportive care
		No change	No clinical effectiveness evidence for best supportive care as a comparator.

Outcomes	• overall survival • progression-free survival • response rates • duration of response/remission • adverse effects of treatment • health-related quality of life	Additionally: • time to progression • post-progression survival • time on treatment	Only overall survival and progression free survival reported for comparator.

[redacted]

Clinical evidence: overview

Study	DELTA (Study 101-09) (n=72/125)	101-2/99 (n=38/64)	Compassionate use programme (CUP) (n=79)
Study design	Phase II, open label, **single arm** study	Phase Ib dose escalation and extension study	Retrospective observational convenience data
Population	Relapsed indolent non-Hodgkin's lymphoma refractory to rituximab and chemotherapy containing an alkylating agent.	Relapsed indolent non-Hodgkin's lymphoma, refractory to or relapsed after at least one prior chemotherapy regimen and rituximab.	Refractory or relapsed follicular lymphoma.
Intervention	Idelalisib	Idelalisib variable dose (10/64 with licensed dose)	Idelalisib
Comparison	None	None	None
Outcomes	• Overall survival • Progression-free survival • Response rates • Duration of response/remission • Adverse effects of treatment • Health-related quality of life	• Adverse effects of treatment • Response rate • Progression-free survival	• Overall response rate • Progression-free survival • Overall survival • Adverse effects of treatment

[redacted]

DELTA Study design – no control group

- Phase II, open label study
- 72 people aged ≥ 18 years with follicular lymphoma with 53 other indolent non-Hodgkin lymphoma subtypes
- Prior treatment with ≥ 2 prior regimens and refractory to both rituximab and an alkylating agent.

↓

Idelalisib

↓

Minimum 31.5 months follow up (2015 database lock)

↓

Outcomes:

- Overall response rate (primary)
- Progression-free survival
- Overall survival
- Health related quality of life (FACT-Lym questionnaire)
- Adverse event and safety data

CUP cohort study design

- Observational retrospective design from patient data collected between 2015-2016
- Data collected from 46 UK and Ireland centres
- 79 people with relapsed or refractory follicular lymphoma treated with idelalisib made available via the expanded access programme

Median follow up 6.1 months

Outcomes:

- Overall response rate (primary)
- Progression-free survival
- Overall Survival

Baseline characteristics

Baseline characteristic	DELTA (n=72)	CUP Cohort (n=79)
Median age, years (range)	62 (33–84)	64 (29-86)
Sex, male, n (%)	39 (54.2)	40 (51)
Median time since diagnosis, years (range)	4.7 (0.8–18.4)	4.5 (0.4-24.6)
Performance status, n (%)	ECOG 0-1: 66 (91.7) ECOG 2-4: 6 (8.3)	ECOG 0-1: 59 (75) ECOG 2-4: 20 (25)
High (≥3) FLIPI risk score at baseline, n (%)	39 (54.2)	59 (75)
Prior therapy		
Median prior regimens (range)	4 (2–12)	3 (1-13)
Median time since completion of last treatment, months (range)	4.3 (0.7–39.1)	8.6 (0.9-99.2)
Rituximab, n (%)	72 (100)	78 (99)
Alkylating agent, n (%)	72 (100)	78 (99)
Refractory to ≥2 regimens , n (%)	57 (79.2)	NR
Refractory to most recent regimen, n (%)	62 (86.1)	NR
Stem cell transplantation , n (%)	12 (16.7)	21 (27)

Results summary

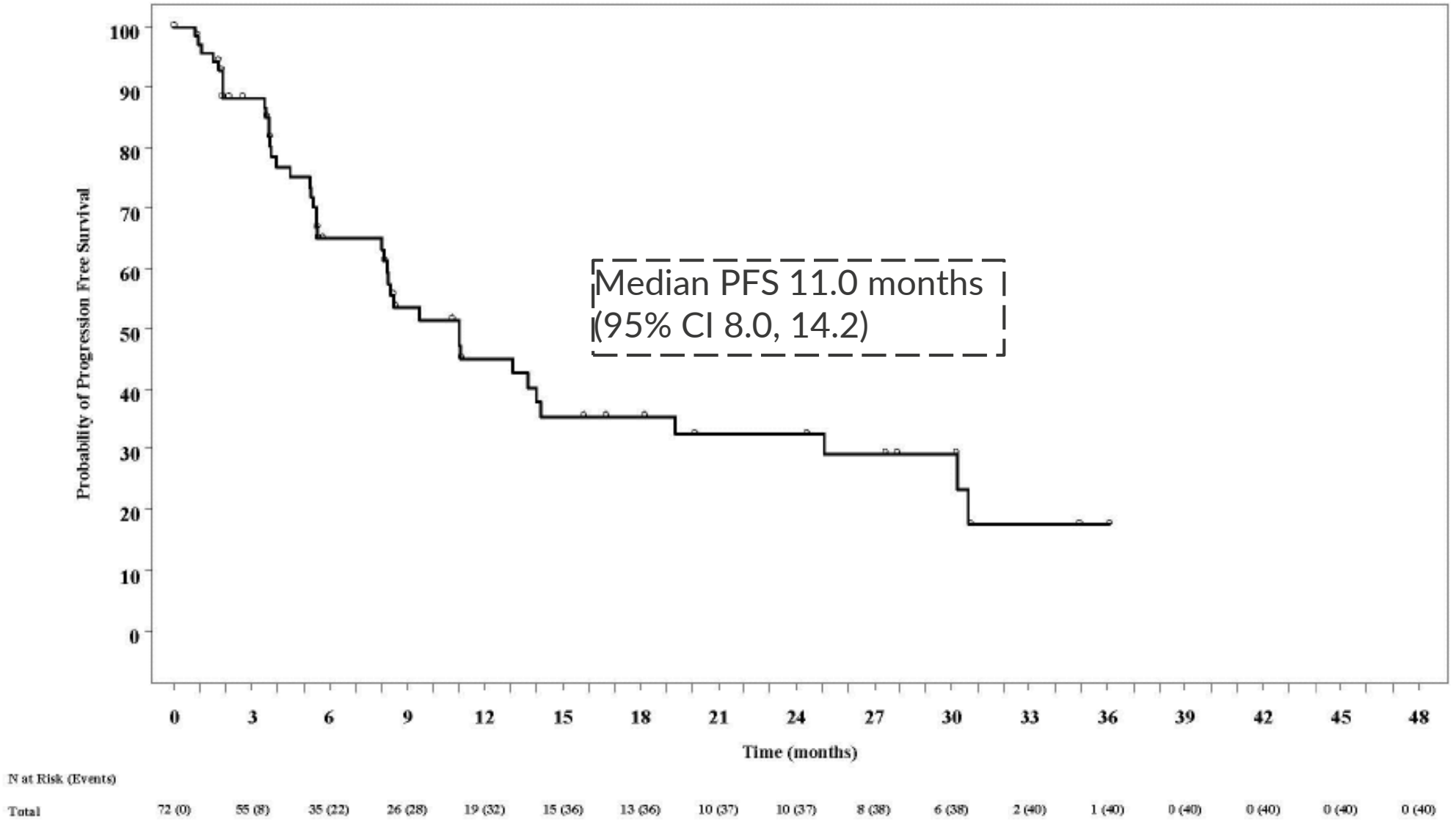
	DELTA (n=72)	CUP cohort (n=65/79)	Used in modelling?
Overall response n (%)	40 (55.6)	37 (57)	x
Complete response	10 (13.9)	10 (15)	x
Partial response	30 (41.7)	27 (42)	x
Stable disease	23 (31.9)	NR	x
Progressive disease	8 (11.1)	NR	x
Survival, months (95% CIs)			
Median progression free survival	11.0 (8.0, 14.2)	7.1 (5.0, 9.1)	To estimate time to progression
Median overall survival	Not reached. Estimated 38.1 (37.8, not reached)	Not reached (13.7, not reached)	DELTA study in comparison B only

ERG comment

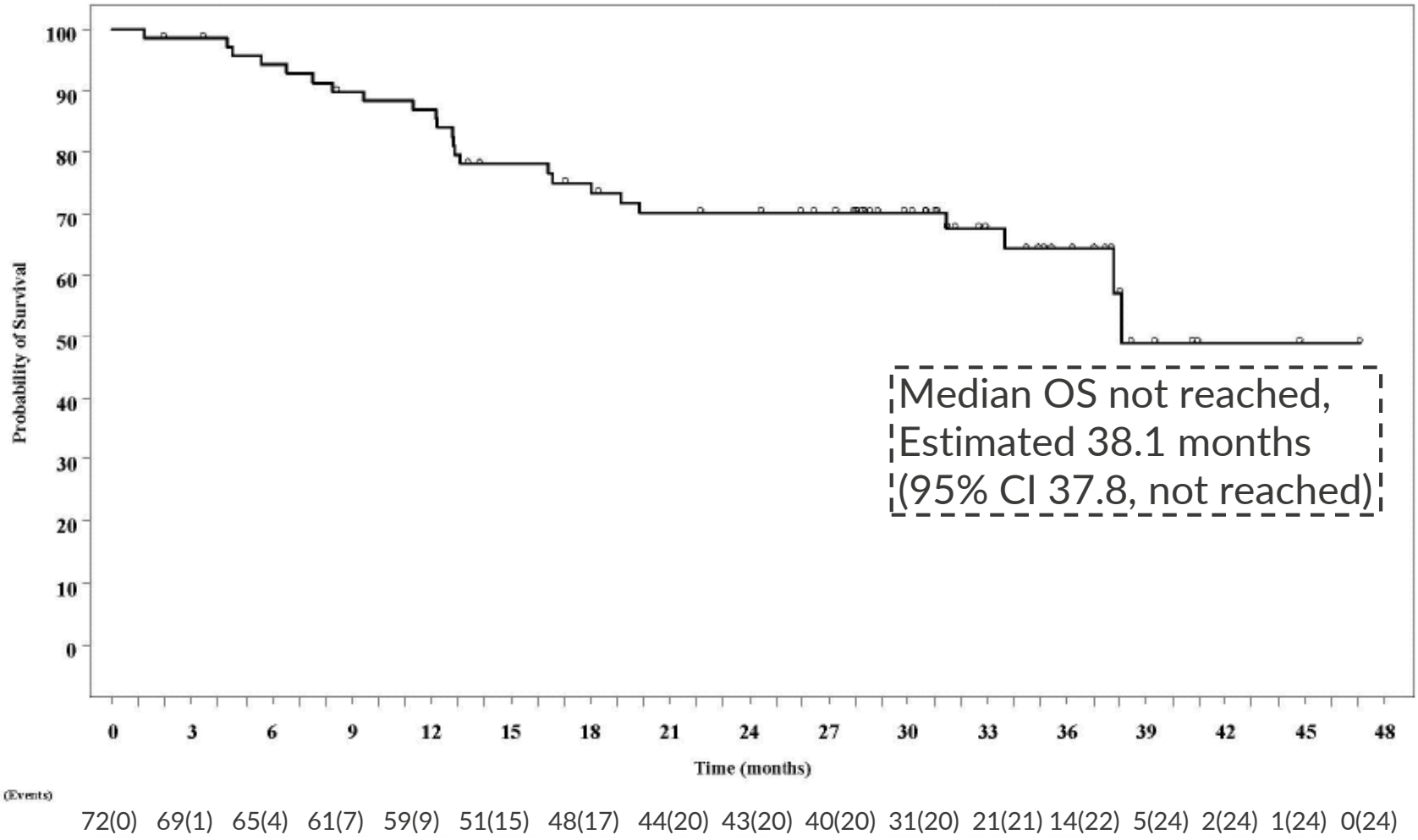
- Only 65 participants were included in the response data for CUP cohort.
- Unconfirmed complete responses presented for the CUP cohort.

[redacted]

DELTA: Progression-free survival

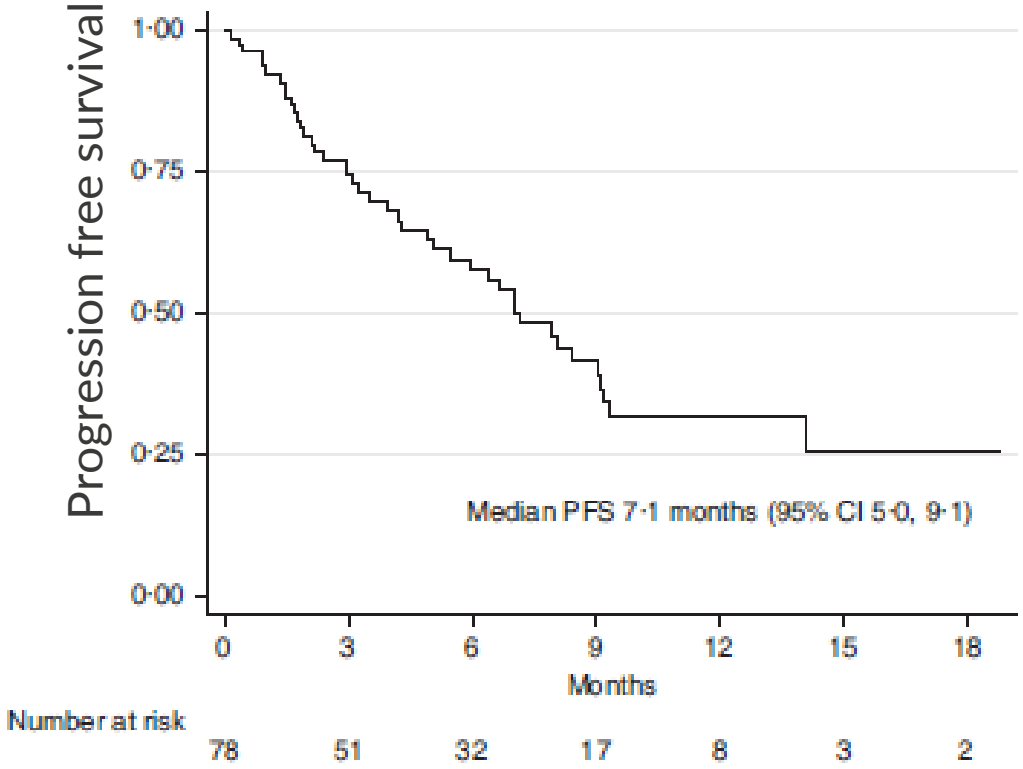


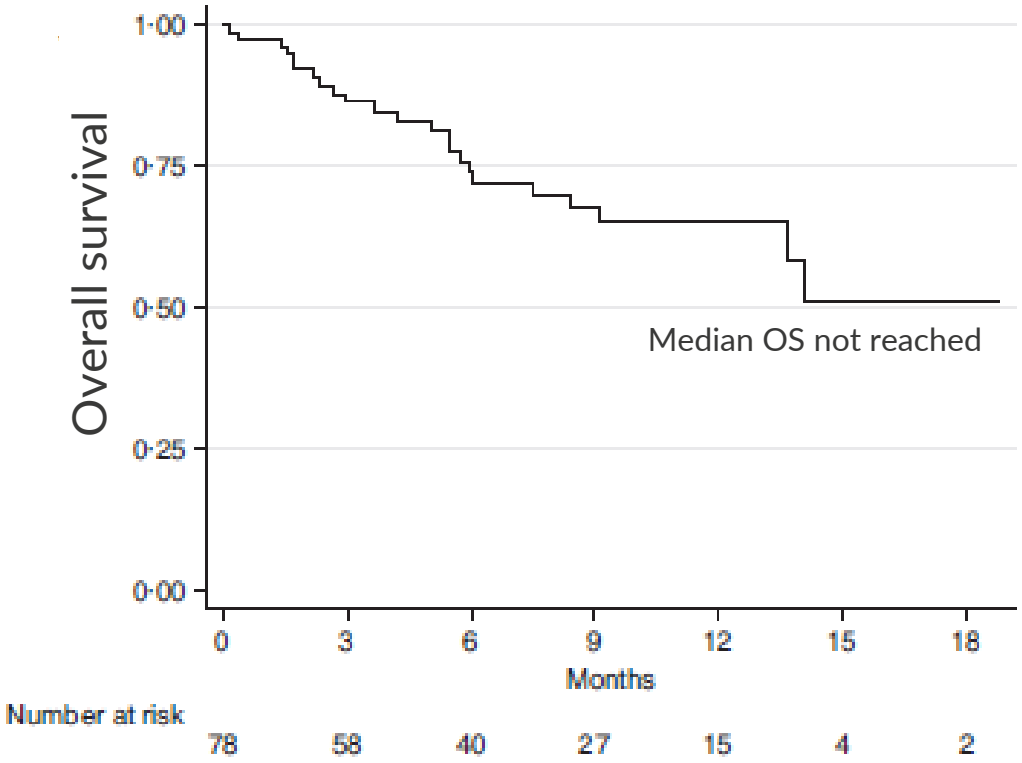
DELTA: Overall survival



N at Risk (Events)																	
Total	72(0)	69(1)	65(4)	61(7)	59(9)	51(15)	48(17)	44(20)	43(20)	40(20)	31(20)	21(21)	14(22)	5(24)	2(24)	1(24)	0(24)

Compassionate Use Programme (CUP) cohort progression-free and overall survival





- 24 people received treatment post-idelalisib including 8 people who went on to receive allogenic or autologous stem cell transplant.

Comparison methods

- Both studies created single-arm data. In order to address the decision problem, the company used two types of comparison data.

Intra-patient comparison – last previous line of therapy

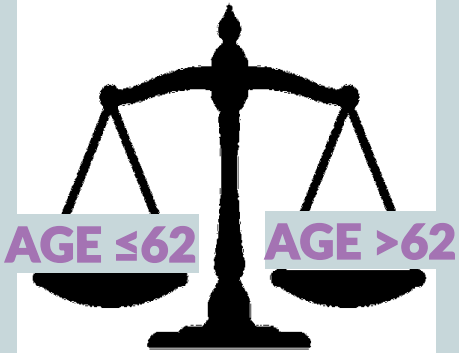
- Progression free survival data from the last previous line of therapy directly before idelalisib treatment were collected for each study participant.
- These data were pooled to create a 'cohort' reflecting the distribution of potential chemotherapy treatments immediately preceding idelalisib for each study.
- Data from idelalisib was compared with the pooled data from the 'cohort' for each study.

Matching adjusted indirect comparison

- The Haematological Malignancy Research Network (HMRN) identified a cohort of patients that were used in an indirect comparison. Baseline patient characteristics were matched to adjust for prognostic factor and treatment effect modifier differences between studies.

Individual patient data

Need to increase weighting of younger participants to match distribution of summary patient data



Summary patient characteristics

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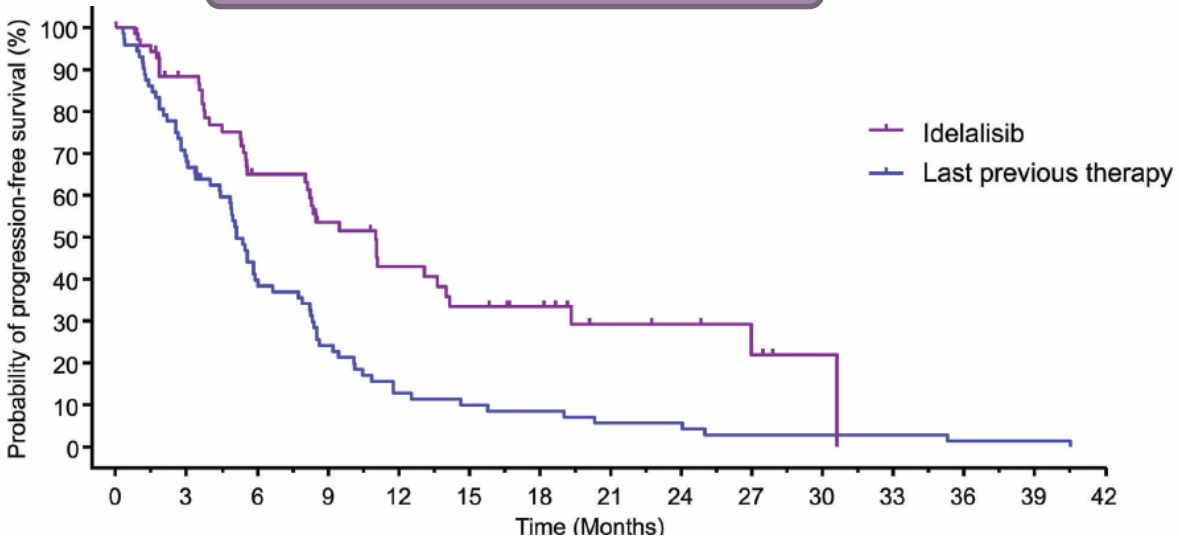
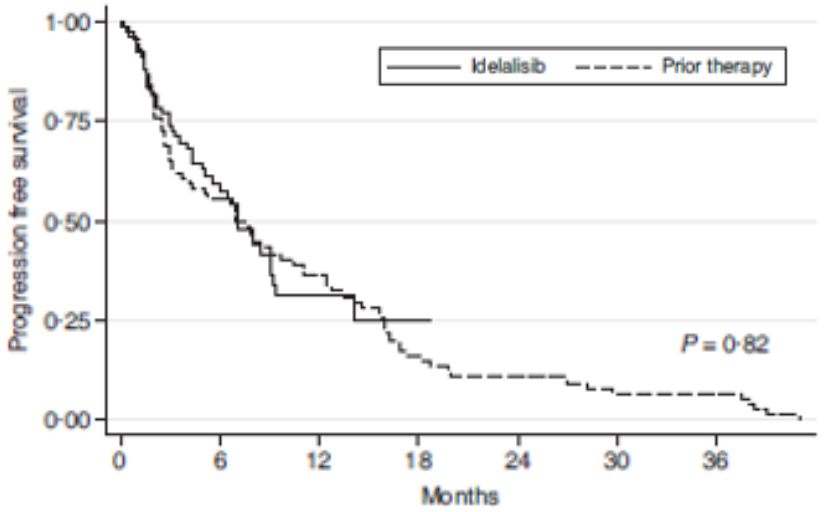
Previous line of therapy progression free survival comparison

DELTA



CUP cohort



ERG comment

- The difference in results may be due to the differences between populations or the different methods of progression assessment. DELTA previous therapy progression is primarily based on clinician recall and may be subject to selection bias and error. CUP cohort idelalisib and previous therapy do not use objective measures of progression due to the clinical practice setting.
- These comparisons are highly unreliable and should be interpreted with extreme caution.

[redacted]

Matching adjusted indirect comparison - Haematological Malignancy Research Network (HMRN) cohort

- HMRN population-based cohort comprises 3.8 million people from former adjacent UK Cancer Networks of Yorkshire and the Humber & Yorkshire Coast from September 2004.
- [redacted] matched the criteria in the scope of being refractory to 2 lines of prior therapy and treated with rituximab and chemotherapy at first or second line.
- Each patient had varying treatment histories and current chemotherapy regimen, reflective of current UK standard of care.

[redacted]

Matching adjusted indirect comparison - direction of adjustment

Matching adjusted indirect comparison to compare idelalisib with equivalent line chemotherapy - results

[redacted]

Matching adjusted indirect comparison – progression free survival for chemotherapy

[redacted]

Matching adjusted indirect comparison – overall survival for chemotherapy

ERG comments on HMRN matching adjusted indirect comparison

[redacted]

DELTA Health related quality of life

- Health related quality of life was measured by a disease specific Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) questionnaire, administered at baseline and follow up on a 4-weekly basis. Data are presented from minimum 20 months follow-up.

Median FACT-Lym score (range)	People with follicular lymphoma treated with idelalisib (n=72)	
	Best change from baseline	Minimally important difference
Physical Well-being	1.0 (-12.0 to 11.0)	2–3
Total Outcome Index	6.0 (-34.0 to 35.0)	7–8
FACT-G total score	4.0 (-29.7 to 31.0)	3–7
FACT-Lym total score	7.5 (-39.0 to 47.0)	10–11

ERG comment

- The company only present best change from baseline and did not provide mean or median change from baseline.
- This data is not used in the economic model to inform utilities because no mapping algorithm from FACT-Lym to EQ-5D was identified for this population. FACT-G data can be mapped to EQ-5D data but this analysis was not performed.
- There is insufficient evidence presented to understand the impact of idelalisib on health related quality of life.

[redacted]

Safety profile overview – DELTA

Adverse event	DELTA population (N=72)
Any adverse event, n (%)	71 (98.6)
Grade ≥3 adverse event, n (%)	48 (66.7)
Treatment-related adverse event	61 (84.7)
Treatment-related Grade ≥3 adverse event, n (%)	41 (56.9)
Any serious adverse event, n (%)	36 (50.0)
Treatment-related serious adverse event, n (%)	24 (33.3)
Adverse event leading to dose reduction, n (%)	22 (30.6)
Adverse event leading to study drug discontinuation, n (%)	18 (25.0)
Adverse event leading to death, n (%)	6 (8.3)
Death on study drug or within 30 days of last study drug dose, n (%)	7 (9.7)
All deaths, n (%)	24 (33.3)

ERG comment

- Immune related adverse events were anticipated *a priori* in light of common risks associated with idelalisib and an extensively pre-treated population.
- No adverse events were reported for chemotherapy so it is not possible to comment on the relative safety profile.

[redacted]

Key issues – clinical effectiveness

- Which patients would receive idelalisib in clinical practice?
- Which population is most representative of UK population?
- What is the role of stem-cell transplantation in this population?
- Can same-patient prior therapy be used as a comparator in the absence of comparator arms?
- Is the matching-adjusted indirect comparison performed on the HMRN cohort a reliable source of comparator data?
  - Should the effect be estimated in DELTA or HMRN?
- Which variables should be matched in the matching adjusted indirect comparison?
- Is the evidence robust enough to determine the clinical effectiveness of idelalisib compared to established practice?

[redacted]

Cost effectiveness

Modelling approach

- The company presented 4 comparisons that varied clinical inputs for deriving model transition probabilities. (Comparisons A-D)
- Because of the lack of standard of care, it is challenging to define the relevant comparator treatments.
  - Comparisons A and C used prior line of therapy intra-patient data as a proxy for current line of therapy
  - Comparison B used matching adjusted indirect comparison with HMRN cohort data
  - Comparison D estimated outcomes for chemotherapy ineligible patients
- The company argued that using prior line of therapy as a proxy for current comparator likely biases against the intervention because people have disease that is likely to be more severe further from time of diagnosis. To account for this, a hazard ratio of 0.75 was applied to prior therapy data in the economic models. This hazard ratio was estimated from time to next treatment data by a consultant haematologist.

ERG comment

- The clinical inputs were generated from non-randomised evidence from different single arm studies or different time points within the same study.
- A covariate adjusted survival analysis would have reduced bias from the confounding variable 'number of prior lines of therapy' but this approach was not used.
- The ERG could not verify the source of the hazard ratio estimate and note that the estimate was 0.9 in other health technology assessment submissions.

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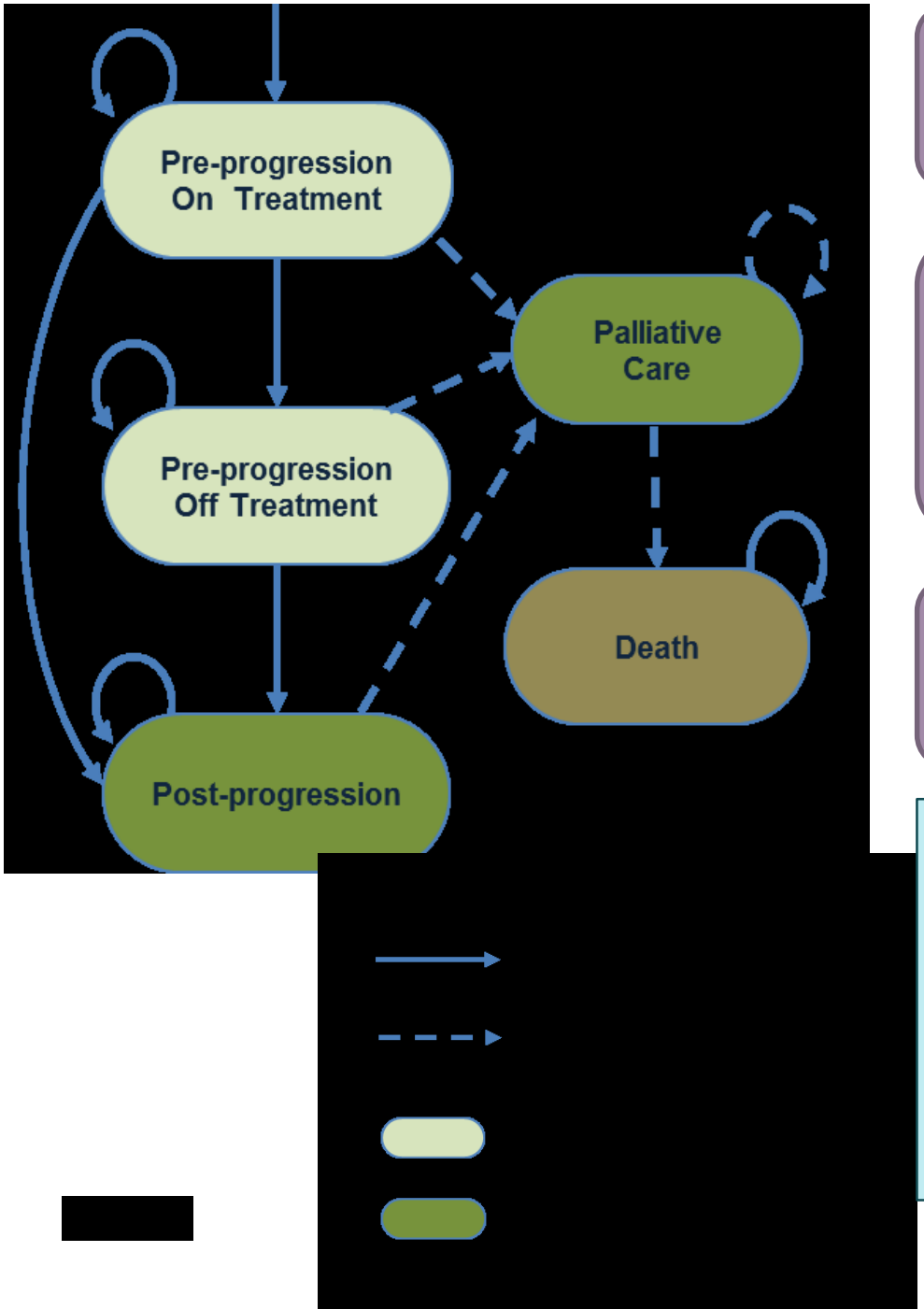
Company's general economic model structure



- Pre-progression state divided into on and off treatment because patients can withdraw from active treatment before disease progression

- It is possible to transition to death from any of the health states via the transitory palliative care health state. This captures the heightened cost of palliative care for cancer patients in the 8 weeks immediately preceding death.

- 1-week cycle length
- Time horizon =38 years, assumed to be lifetime
- Discount rate of 3.5% for costs and QALYs

ERG comment

- The model structure can be considered in line with other commonly used Markov models used in oncology.
- Choice of time horizon and discounting are appropriate. Half cycle correction is necessary for consistent application of costs and QALYs

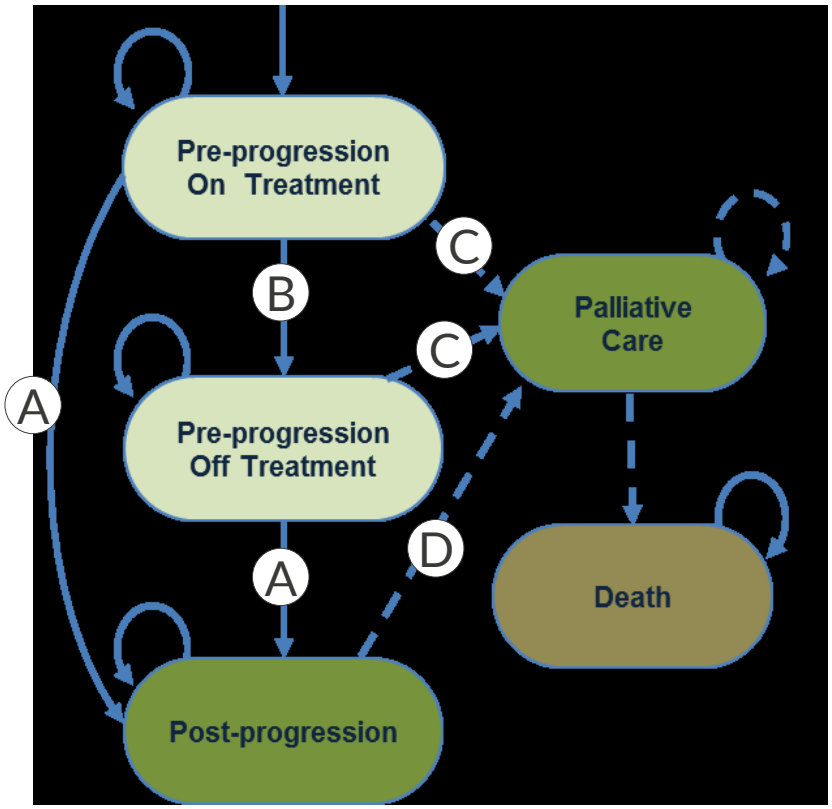
Choice of comparison in economic model

Comparison	Idelalisib data source	Comparator data source	Model type
Comparison A (company base case)	Data from DELTA study idelalisib	Data from 'intra-patient' previous line of treatment as a proxy for current chemotherapy. Hazard ratio applied	Markov cohort-transition state
Comparison B	Data from DELTA study idelalisib	Matching adjusted survival data from chemotherapy regimens of HMRN cohort	Partitioned survival model
Comparison C	Data from CUP cohort and DELTA idelalisib.	Time to progression data from 'intra-patient' previous line of treatment as a proxy for current chemotherapy. Hazard ratio applied	Markov cohort-transition state
Comparison D	Data from DELTA study idelalisib	No treatment costs because instant disease progression is assumed	Markov cohort-transition state

[redacted]

Comparison A structure

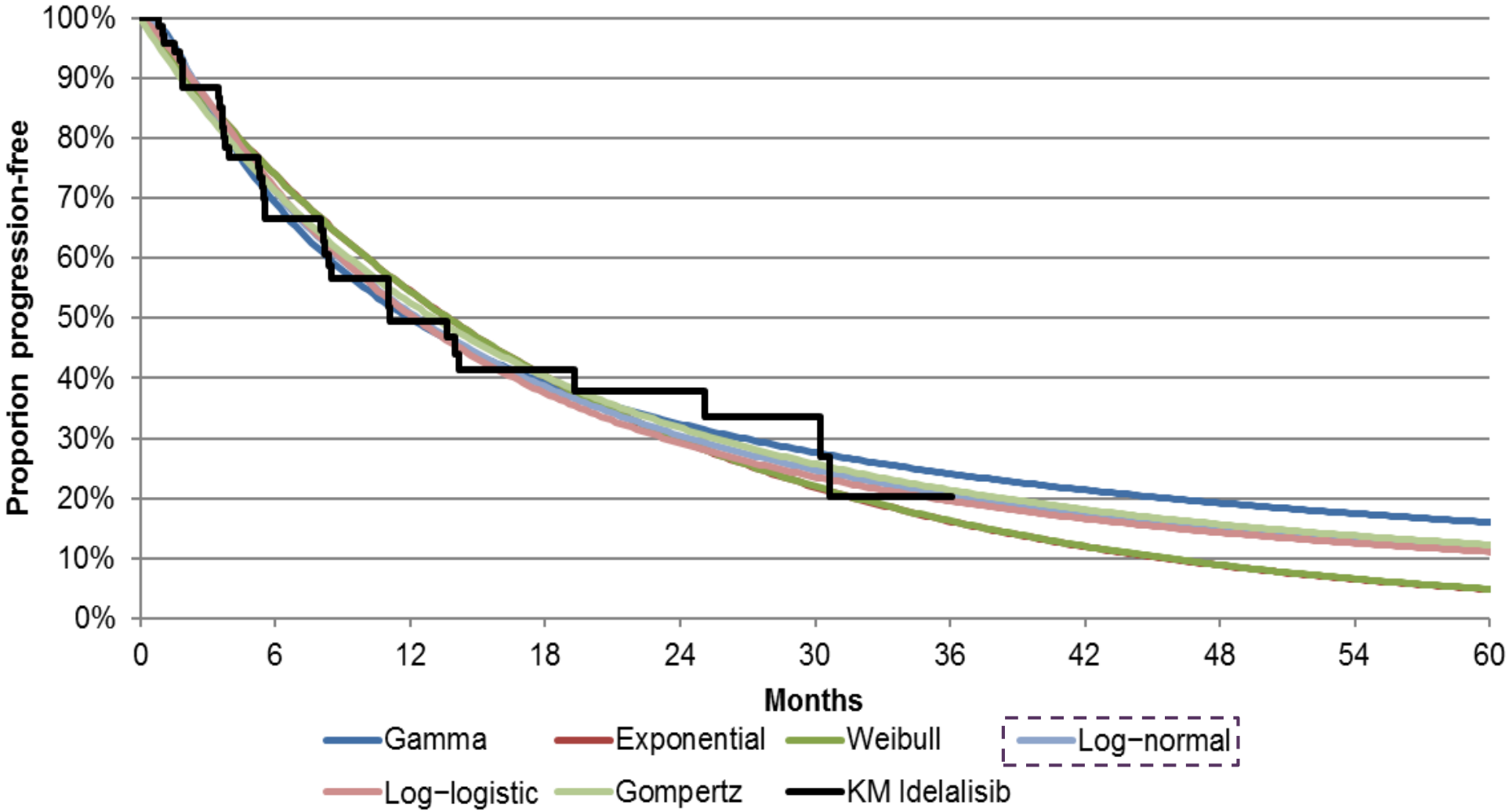
- Cohort level state transition model
- Used intra-patient data from previous line of treatment from DELTA study as comparator
- Hazard ratio is applied to prior treatment outcomes
- Because pre- and post-progression survival are considered equivalent for both arms, the key driver of the model is the difference in time to progression between the arms.



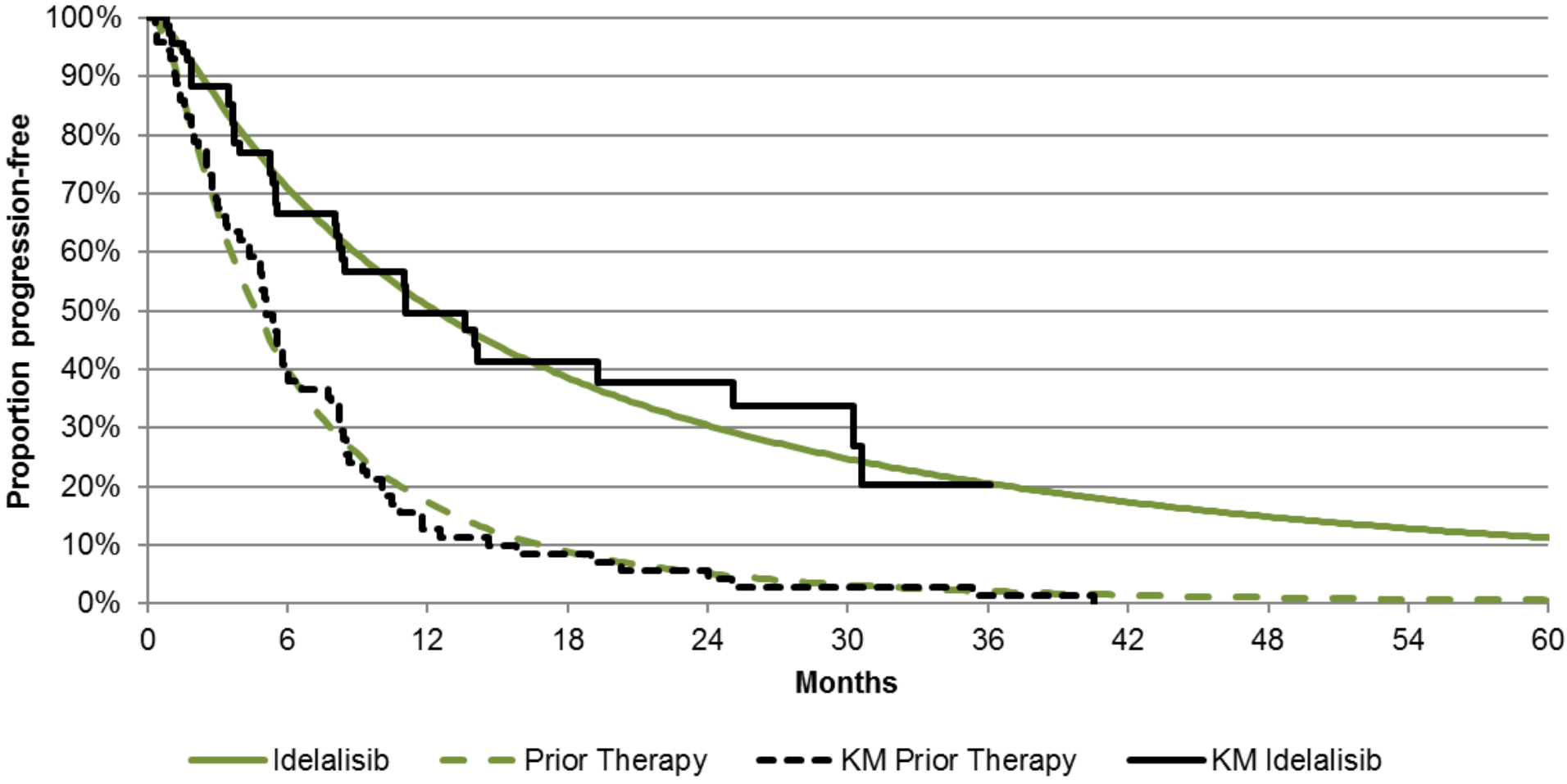
Idelalisib	Chemotherapy regimens
Dataset used: DELTA	Dataset used: DELTA (prior line of treatment)
A. Idelalisib time to progression	A. Prior treatment time to progression (hazard ratio adjusted)
B. Idelalisib time on treatment	B. Prior treatment time on treatment (hazard ratio adjusted)
C. Idelalisib pre-progression survival	C. Idelalisib pre-progression survival
D. Idelalisib post-progression survival	D. Idelalisib post-progression survival

[redacted]

DELTA Idelalisib time to progression



Comparison A: DELTA Time to progression



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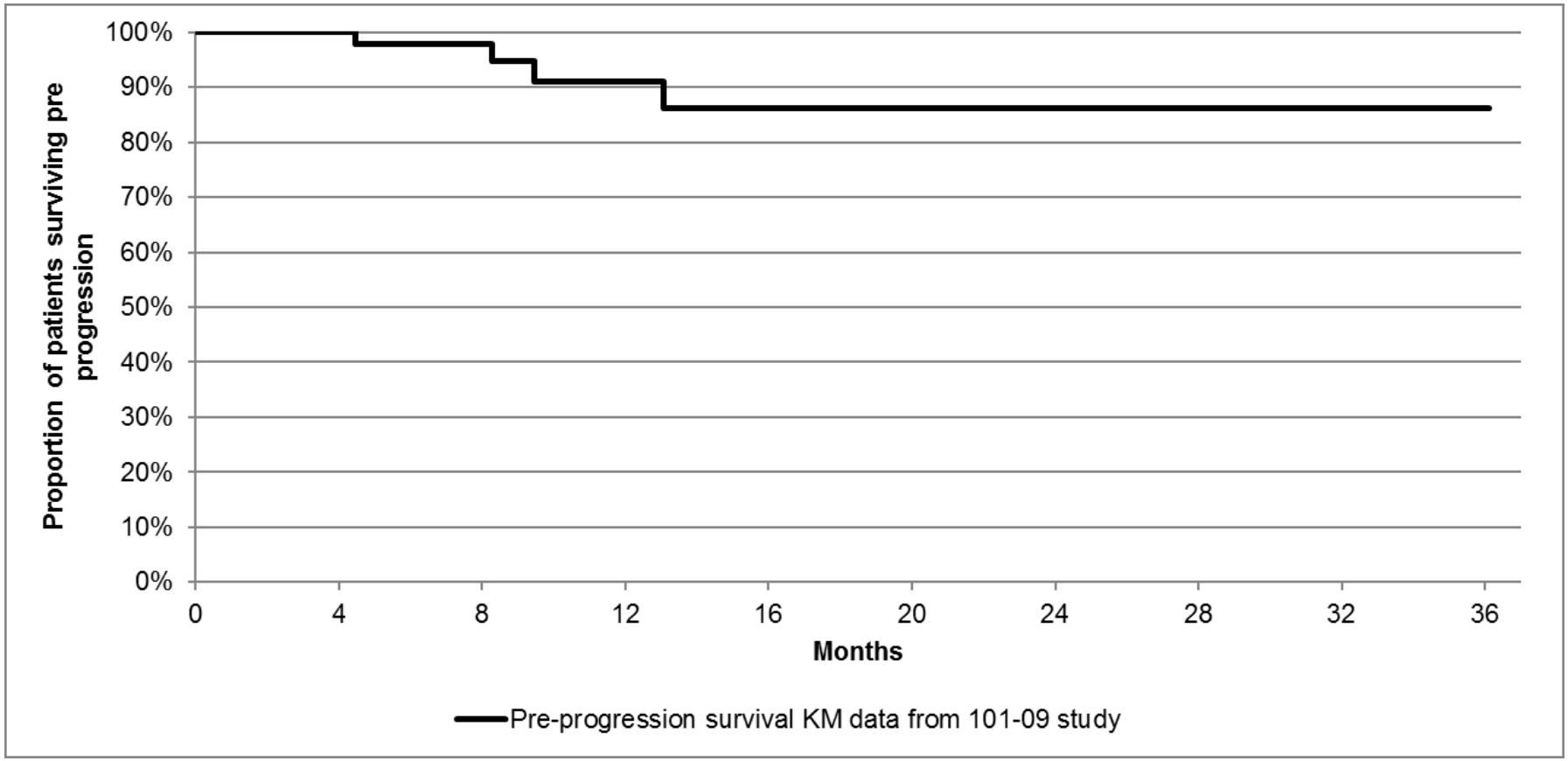
Comparison A: DELTA Time on treatment

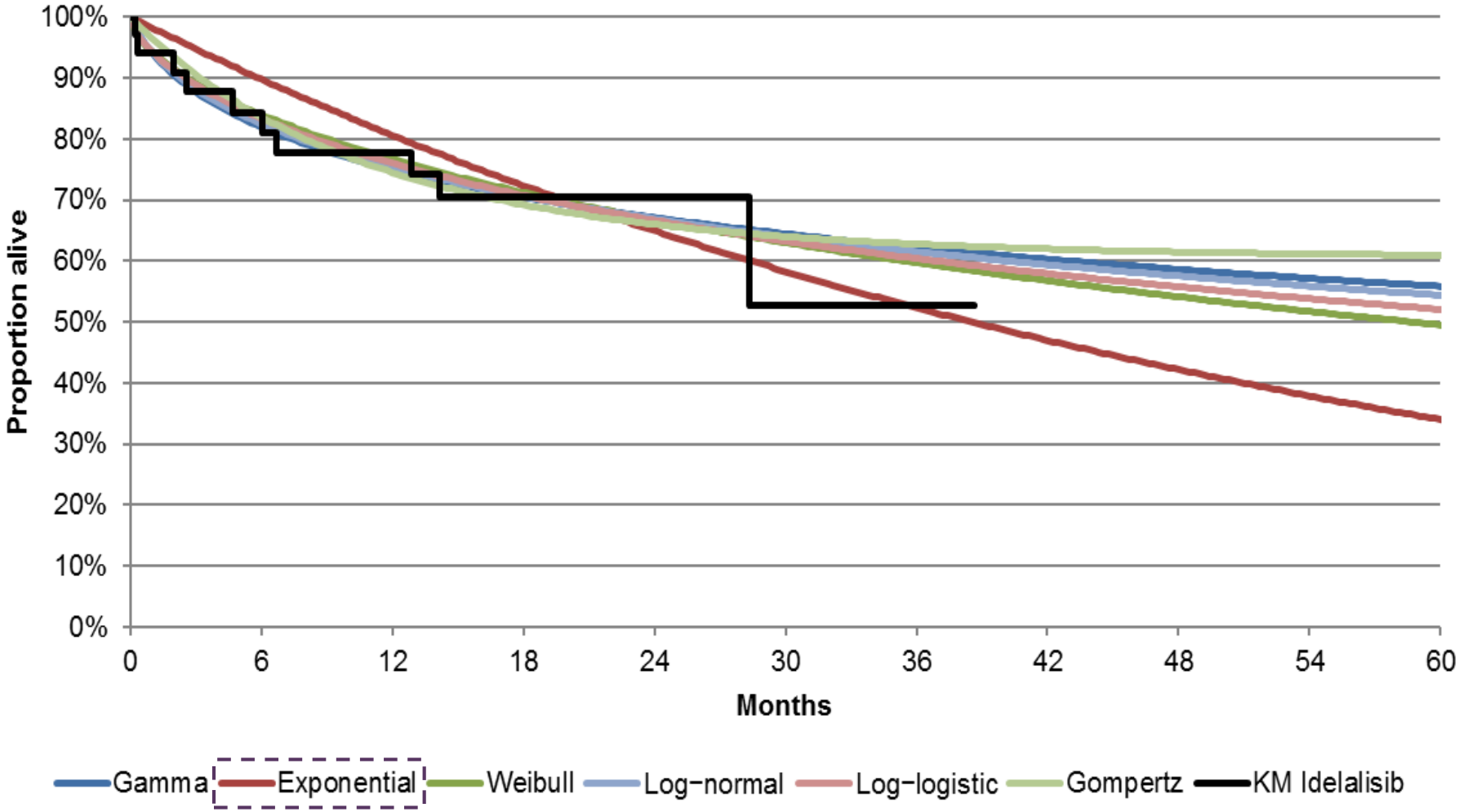
DELTA Idelalisib pre-progression survival



- Pre-progression survival is based on only 4 events (at 82% population progressed), therefore a hazard ratio of 5.71 was estimated for double refractory follicular lymphoma pre-progression survival vs age and sex adjusted general population survival.

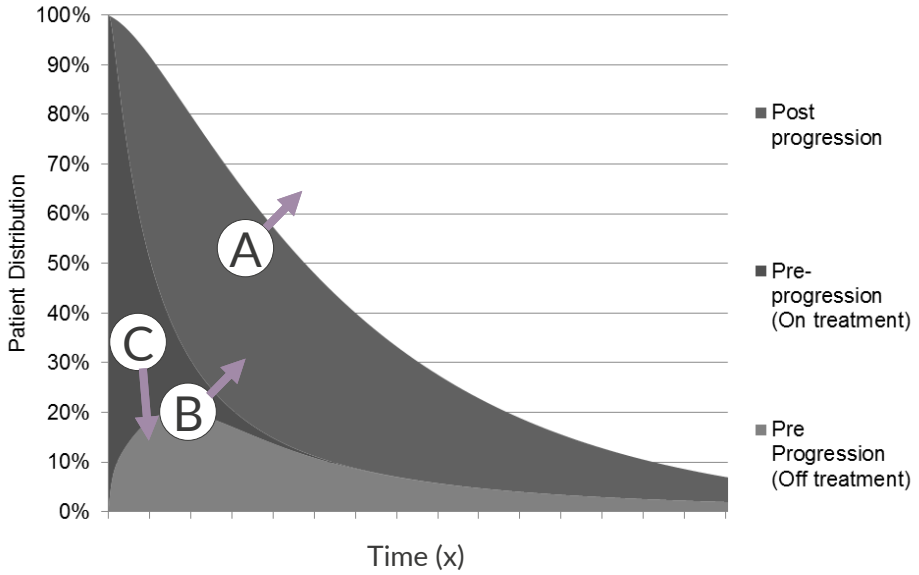
[redacted]

DELTA Idelalisib post-progression survival



Comparison B structure

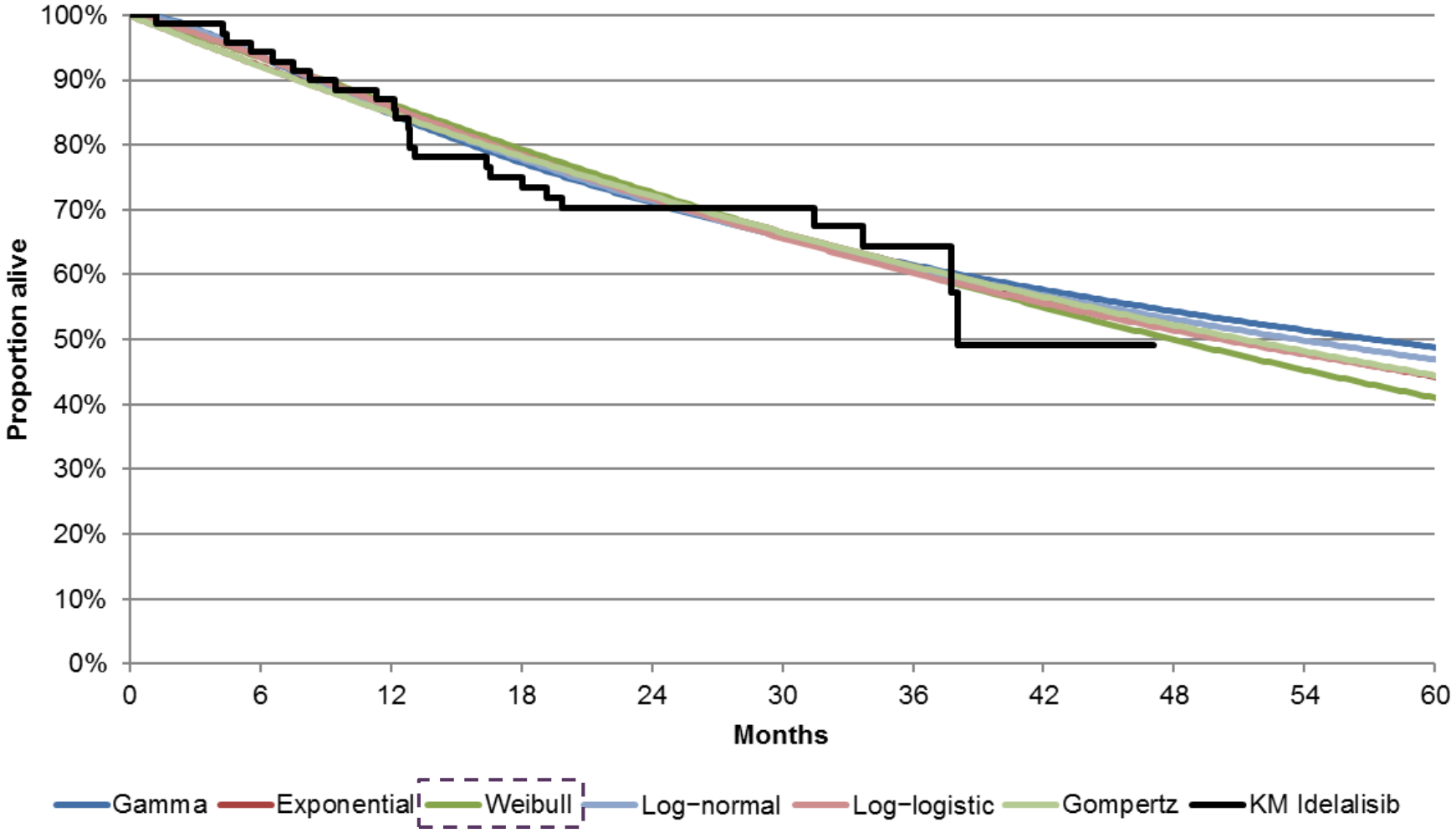
- Partitioned survival analysis
- Used area-under-the-curve from overall survival data
- Matching adjusted indirect comparison (company preferred) with HMRN cohort survival data
- Overall survival is much more influential to QALY-gain than progression-free survival in this model so the overall survival difference between the two treatment arms is the key driver of the model



Idelalisib	Chemotherapy regimens
Dataset used: DELTA A. Idelalisib overall survival B. Idelalisib progression free survival C. Idelalisib time on treatment	Dataset used: HMRN A. MAIC adjusted "chemotherapy" overall survival B. MAIC adjusted "chemotherapy" progression free survival Dataset used: DELTA C. Prior treatment time on treatment

[redacted]

Comparison B: DELTA Overall survival



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Comparison B: HMRN MAIC-adjusted Overall survival

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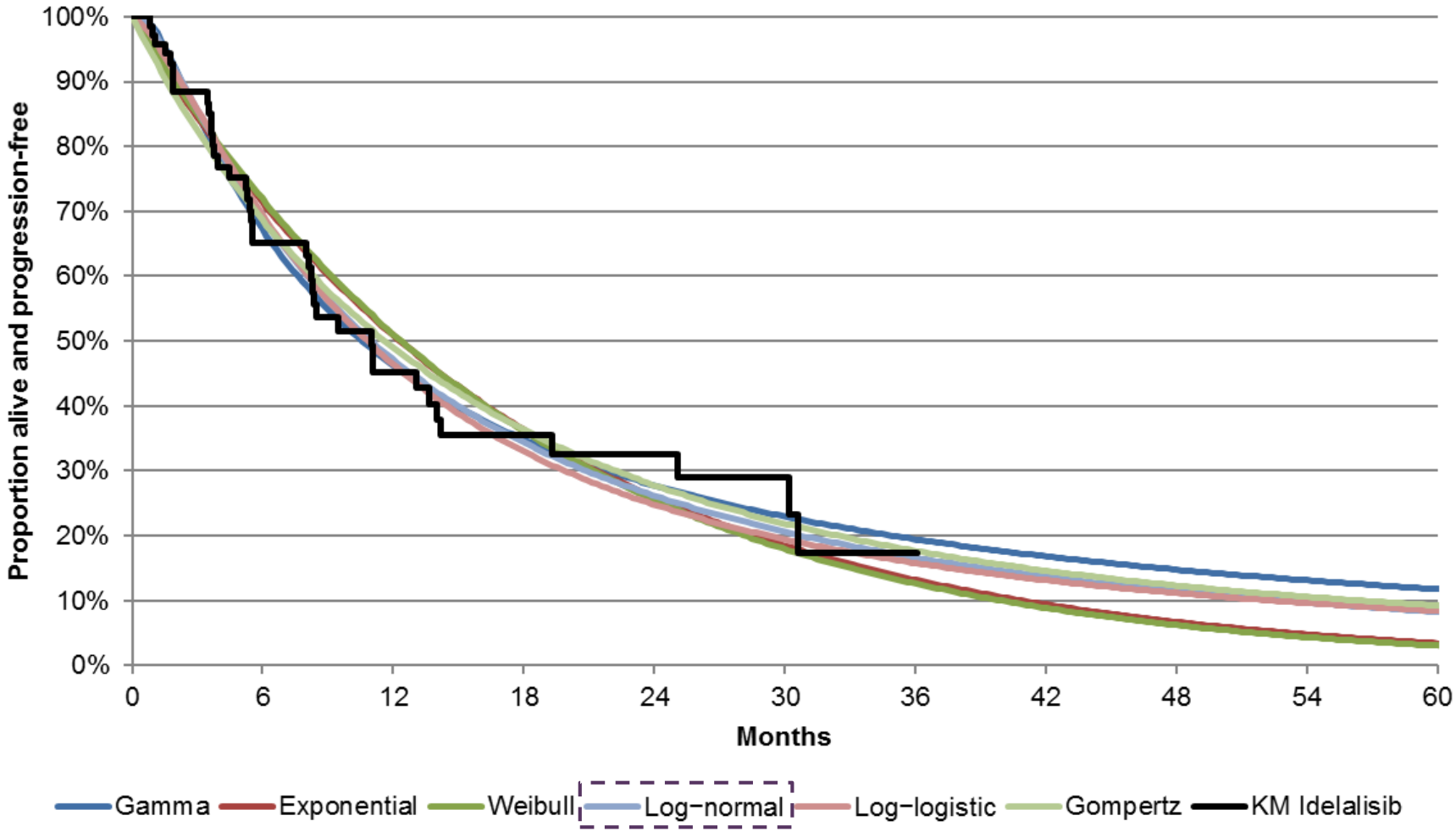
Comparison B: DELTA Progression-free survival



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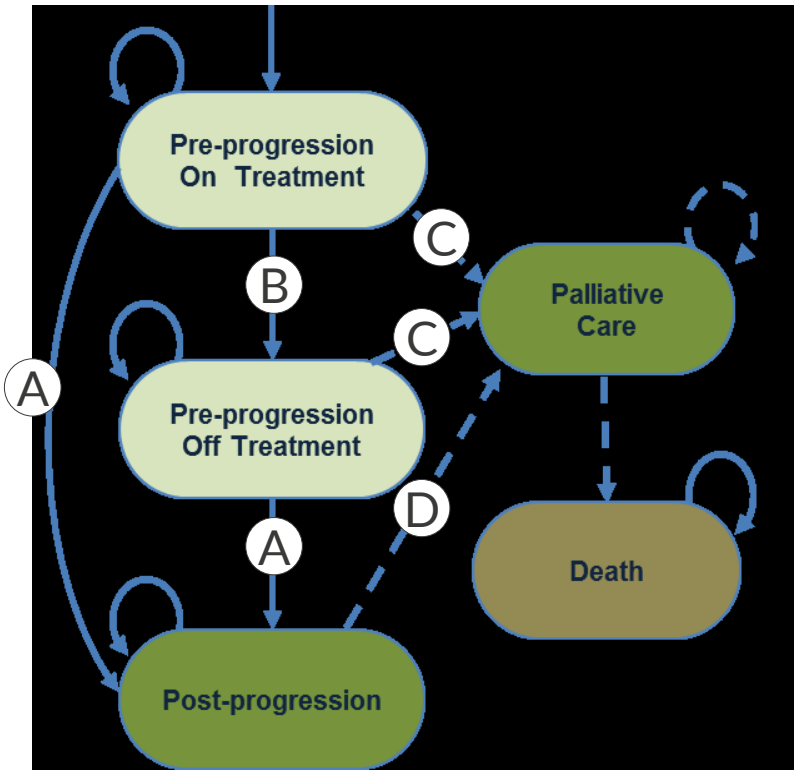
Comparison B: HMRN MAIC-adjusted Progression-free survival

[redacted]

Comparison C structure

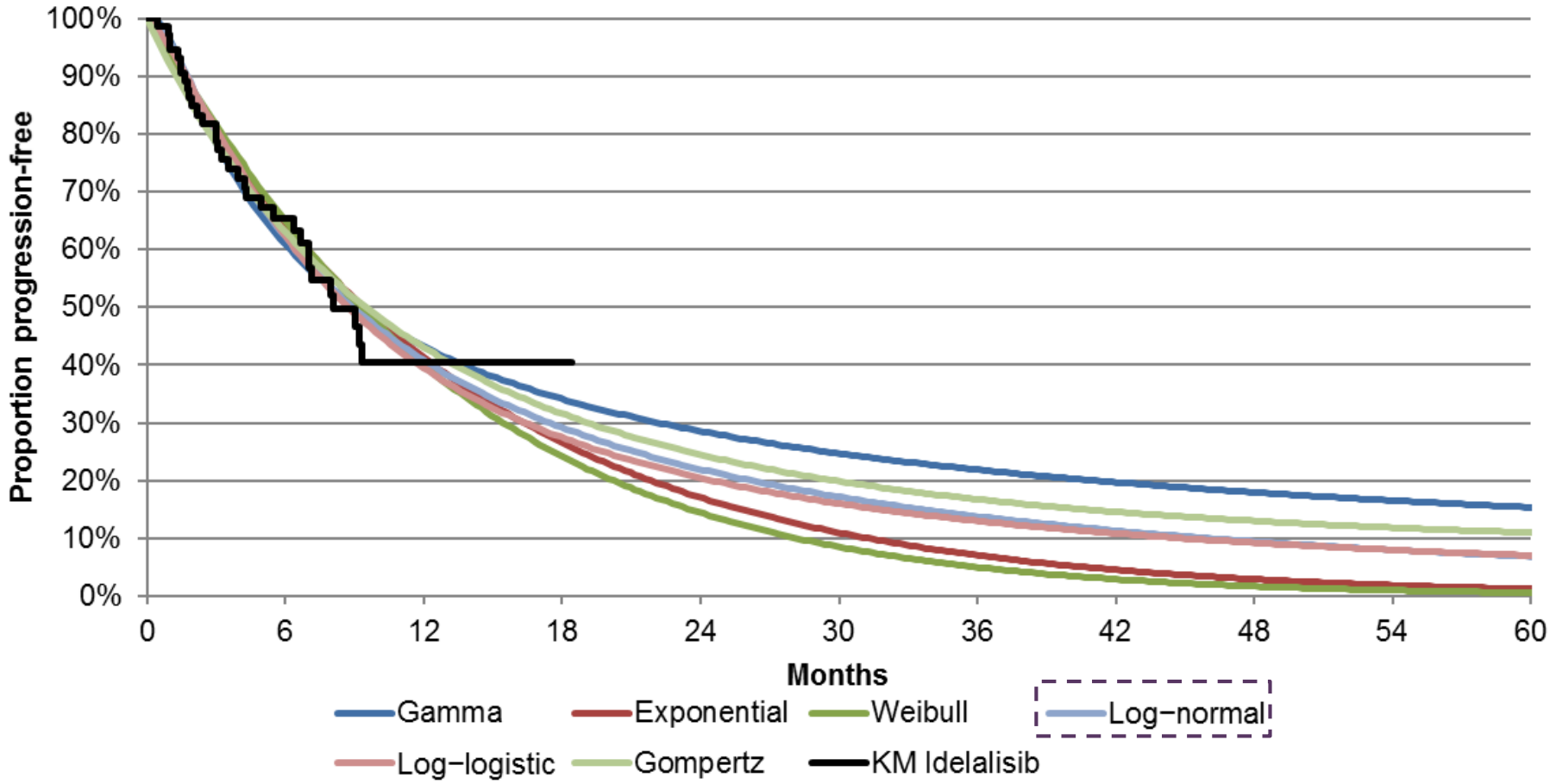
- Cohort level state transition model
- Used intra-patient data from previous line of therapy from CUP cohort as comparator
- Similar limitations to Comparison A and the key driver of the model is the difference in time to progression
- The model is sensitive to the hazard ratio adjustment.



Idelalisib	Chemotherapy regimens
Dataset used: CUP cohort A. Idelalisib time to progression Dataset used: DELTA B. Idelalisib time on treatment C. Idelalisib pre-progression survival D. Idelalisib post-progression survival	Dataset used: CUP cohort A. Prior treatment time to progression (hazard ratio adjusted) Dataset used: DELTA B. Prior treatment time on treatment (hazard ratio adjusted) C. Idelalisib pre-progression survival D. Idelalisib post-progression survival

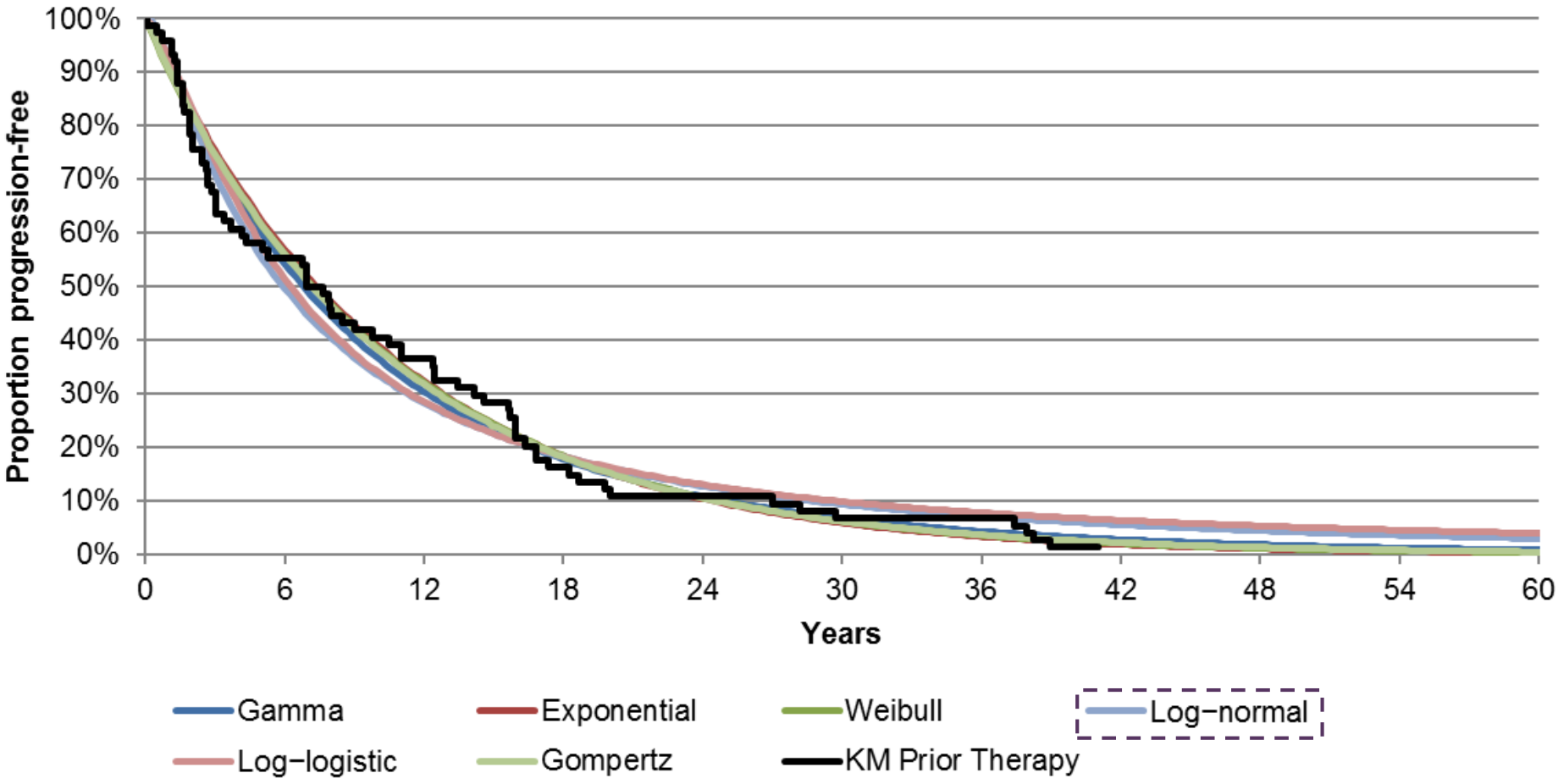
[redacted]

CUP Time to progression – idelalisib

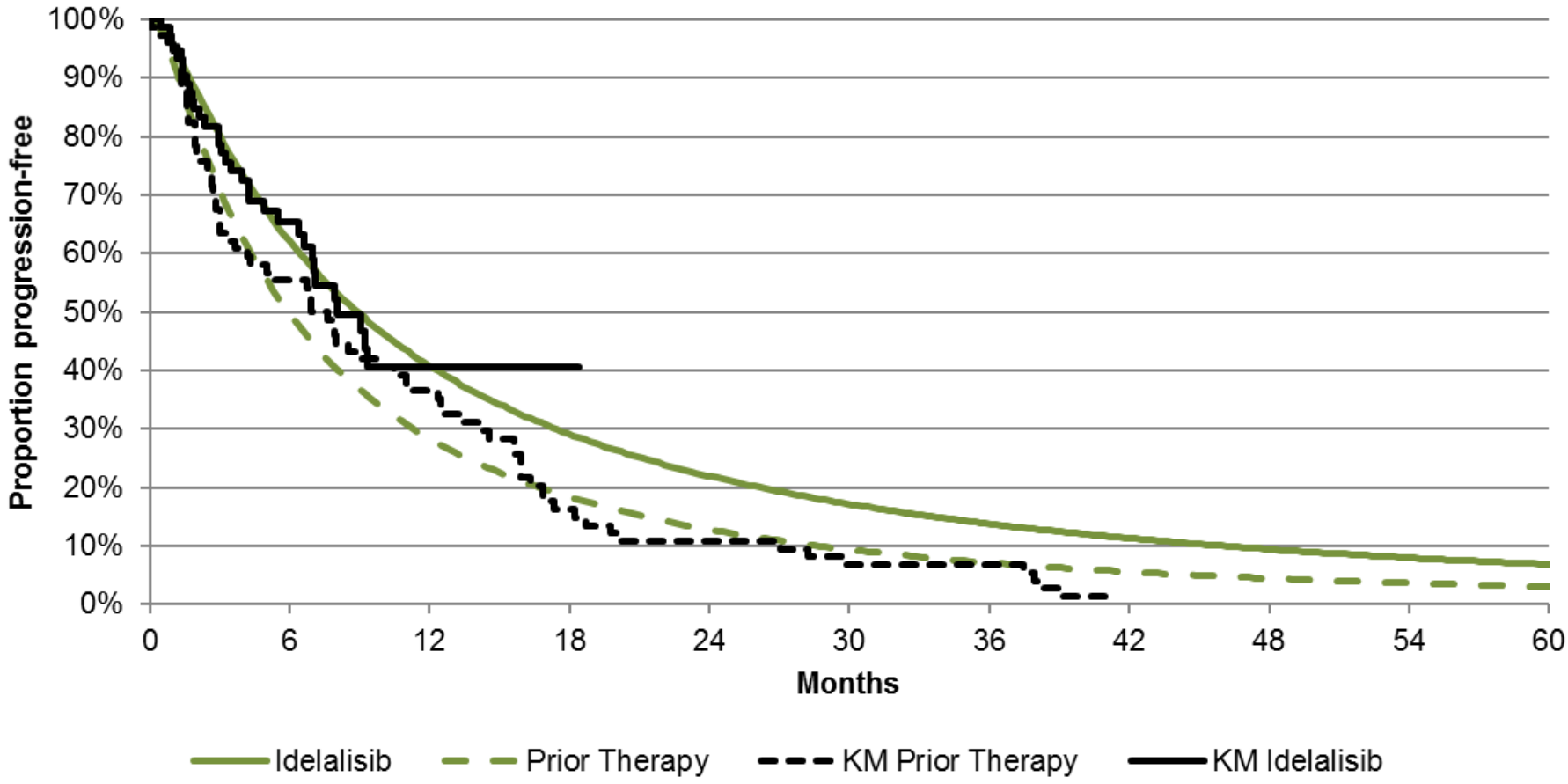


[redacted]

CUP Time to progression – prior therapy

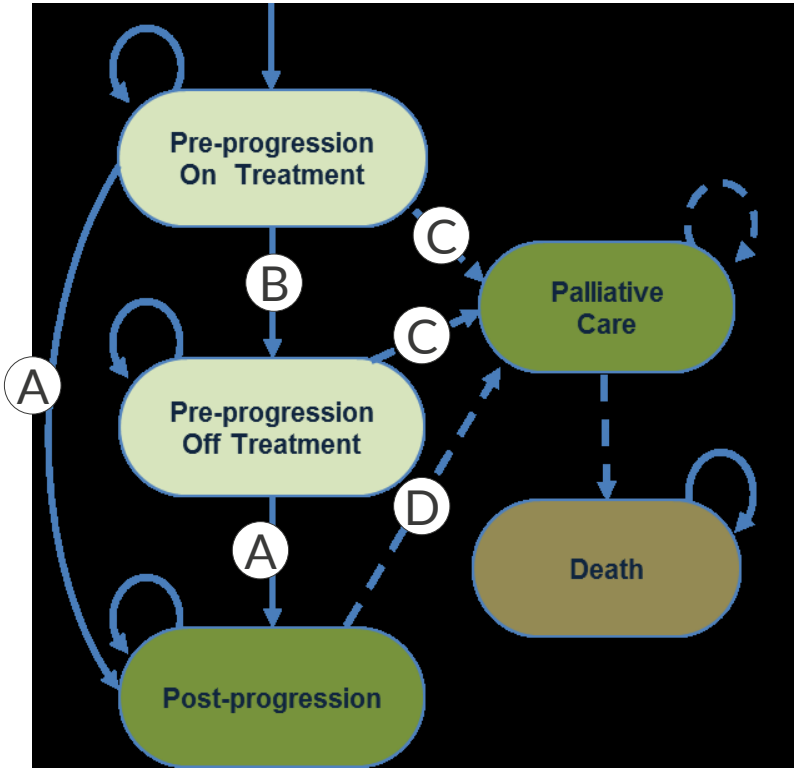


Comparison C: CUP Time to progression



Comparison D structure

- Cohort level state transition model
- Comparison is with best supportive care, for those that are not eligible for chemotherapy
- Key driver in difference is the idelalisib time to progression



Idelalisib	Best Supportive Care
Dataset used: DELTA (A) Idelalisib time to progression (B) Idelalisib time on treatment (C) Idelalisib pre-progression survival (D) Idelalisib post-progression survival	• No treatment costs since instant disease progression is assumed. Dataset used: DELTA (D) Idelalisib post-progression survival

[redacted]

Choice of comparison in economic model

	Pros	Cons
Comparison A	• Consistent use of data from the pivotal trial • Prior treatment as approximation for standard care may minimise individual heterogeneity	• Intra-patient comparison is a methodologically weak form of comparison • Use of hazard ratio adjustment creates additional structural uncertainty • Use of Markov cohort transition model does not incorporate overall survival data
Comparison B	• Representative UK population comparator chemotherapy treatments • Most appropriate modelling method	• Uncertainty around the MAIC adjustment performed including small sample size [redacted] and variable-choice sensitivity • No sensitivity analysis available for other MAIC adjustment choices
Comparison C	• CUP Cohort is representative of current UK population and clinical need	• As Comparison A but additionally uses data from different sources without adjustment which may lead to bias
Comparison D (BSC)	• Gives approximation of best supportive care	• Strong assumption that all people receiving palliative care progress immediately

ERG comment

- The ERG considers that since the evidence underlying each comparison has different problems, the decision should be based on the cost effectiveness estimates considering all comparisons, hence the cost effectiveness threshold should be satisfied in all comparisons.

[redacted]

Utility values

- Company used published literature (Pettengell et al, 2007) for progression-free survival and post-progression survival states. Pettengell et al assessed HRQL using FACT-Lym, Hospital Anxiety and Depression Scale (HADS) to measure psychological morbidity and Work Productivity and Impairment Scale (WPAI) to assess influence of the disease on activity and productivity.
- Patients were categorised into two broad groups to represent "progression-free" and "progression".

Mean Progression free EQ-5D utility (SD)
0.81 (0.02)

Mean Progression EQ-5D utility (SD)
0.62 (0.06)

ERG comment

- The ERG would have preferred to see utility data derived from FACT-G data collected in DELTA mapped to EQ-5D.
- The ERG was unable to verify the reported utilities from the references provided but identified two other sources of utility data which are used and presented as scenario analyses.

Health state	Bec et al. 2014 UK Sample	GADOLIN
Progression free (on treatment)	0.71	0.82
Progression free (off treatment)		0.81
Progressed disease	0.51	0.76

[redacted]

Utility values – adverse events

Adverse Event	Utility Decrement	Duration (days)	Cost per cycle
Acute kidney injury	-0.06	35	£2.38
Anaemia	-0.12	16	£3.78
Asthenia	-0.12	35	£0.15
Colitis	-0.05	35	£1.29
Dehydration	-0.10	8	£1.94
Diarrhoea	-0.05	35	£6.76
Dyspnoea	-0.05	13	£1.18
Febrile neutropenia	-0.15	7	£7.29
Hypokalaemia	-0.12	35	£0.68
Hypotension	-0.06	8	£1.94
Neutropenia	-0.09	15	£11.31
Pneumonia	-0.20	14	£8.49
Pyrexia	-0.11	12	£1.36
Thrombocytopenia	-0.11	23	£0.91

ERG comment

- The company uses the same incidence of adverse events for idelalisib and chemotherapy arms, implicitly assuming no difference in utilities for Comparisons A-C which is not supported by comparative safety evidence.

[redacted]

Costs and resource use

Cost/Resource	Source
Drug costs	eMIT, MIMS UK
Administration costs	NHS National Schedule of Reference Costs 2016-17
Monitoring costs	NHS National Schedule of Reference Costs 2016-17, Unit Costs of Health and Social Care 2017 (PSSRU)
Chemotherapy regimen resource use	West London Cancer Network, Derby-Burton Local Cancer Network, South East London Cancer Network, various journal articles.
Disease management resource use	UK-based key opinion leader
Palliative care costs	King's Fund report – Improving choice at end of life, 2008
Adverse event costs	NHS National Schedule of Reference Costs 2016-17, ERG report for NICE appraisal guidance TA306

Company base-case cost-effectiveness results

Deterministic base case

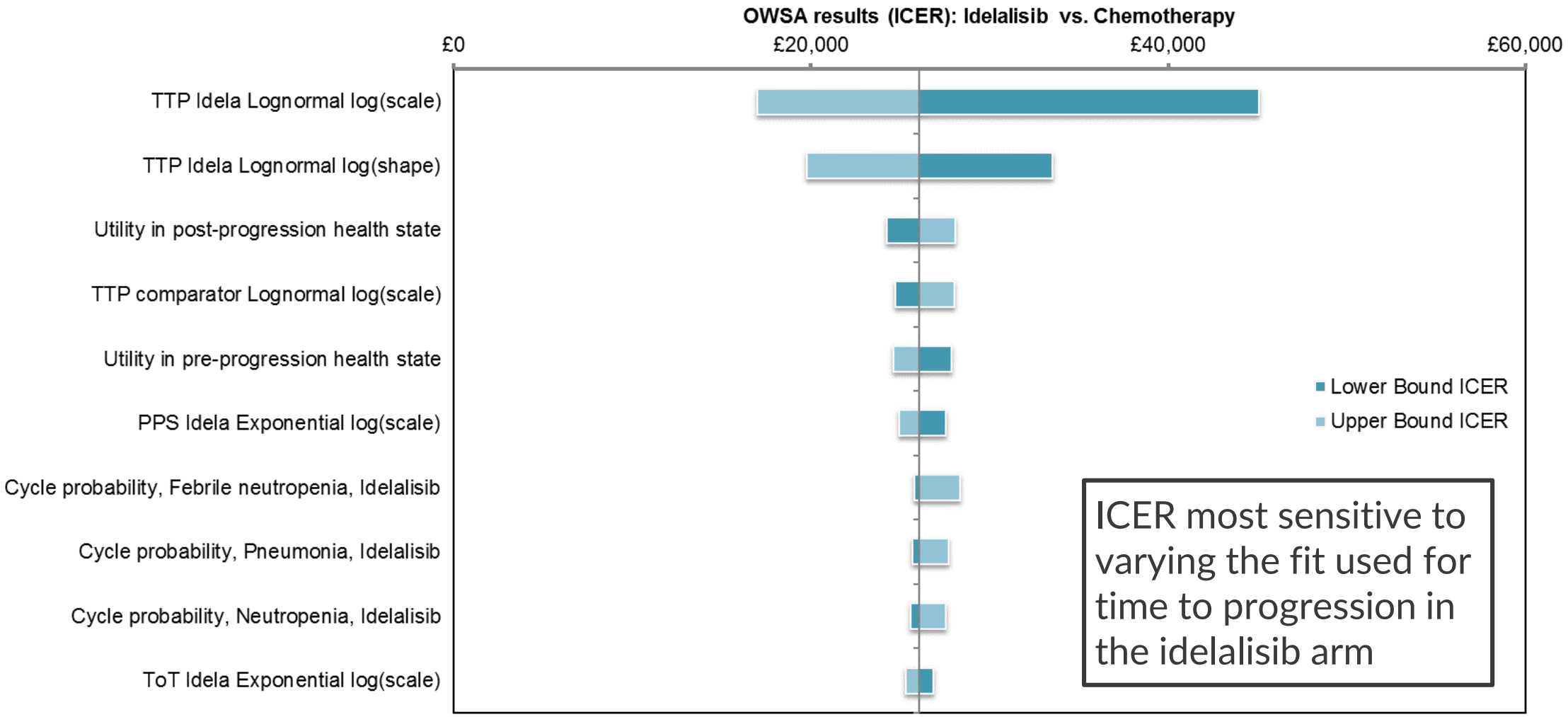
	Technologies	Total			Incremental			ICER (£/QALY)
		Costs	LYG	QALYs	Costs	LYG	QALYs	
Comparison A	Chemotherapy Regimens	£XXXX	5.01	2.80	-	-	-	£26,076
	Idelalisib	£XXXX	6.34	3.71	£23,762	1.33	0.91	

Probabilistic base case

	Technologies	Mean		Incremental Mean		Probabilistic ICER versus baseline
		Costs	QALYs	Costs	QALYs	
Comparison A	Chemotherapy Regimens	£XXXXX	2.81	-	-	£25,364
	Idelalisib	£XXXXX	3.75	£23,821	0.94	

[redacted]

Deterministic sensitivity analysis



[redacted]

Company base case scenario analysis

Scenario detail	ICER (£/QALY)	% change
Base case	£26,076	-
Hazard ratio set to 1 implying no drop in time to progression in the next line of treatment for chemotherapy.	£27,893	7.0%
Costs and benefits are discounted at 6%.	£28,876	10.7%
Costs and benefits are not discounted.	£21,957	-15.8%
Costs and benefits are accumulated for 10 years.	£31,538	20.9%
Mortality hazard is assumed to be equal to that of a general population to model no risk of higher mortality in the pre-progression population.	£22,868	-12.3%
A generalised gamma parametric survival model fitted to the time to progression data.	£18,959	-27.3%
A lognormal parametric survival model fitted to the post-progression survival data.	£29,861	14.5%
A lognormal parametric survival model fitted to the time on treatment data.	£28,099	7.8%
Adjustment for general population age utility decline.	£27,158	4.1%
Biosimilar prices used for rituximab.	£26,288	0.8%
Inclusion of idelalisib drug wastage costs.	£27,516	5.5%
Applying mean dose intensity estimate of 93.75% to chemotherapy arm.	£26,354	1.1%

[redacted]

Company cost-effectiveness results – alternative comparisons

	Technologies	Total			Incremental			ICER (£/QALY)
		Costs	LYG	QALYs	Costs	LYG	QALYs	
Comparison B	Chemotherapy Regimens	£XXXXX	1.44	2.29	-	-	-	£19,872
	Idelalisib	£XXXXX	3.19	5.33	£34,924	1.76	3.04	
Comparison C	Chemotherapy Regimens	£XXXXX	2.92	5.18	-	-	-	£47,011
	Idelalisib	£XXXXX	3.41	5.88	£22,712	0.48	0.70	
Comparison D	Best supportive care	£XXXXX	2.50	4.62	-	-	-	£25,272
	Idelalisib	£XXXXX	3.71	6.34	£30,473	1.21	1.72	

[redacted]

ERG corrections and scenarios

Errors
- Correcting the transition probabilities from pre-progression state to include the conditional probability of surviving previous cycle
- Correctly implementing the post-progression survival extrapolation
- Applying hazard ratio to time on treatment for Comparison B

Violations
- Incorporating half cycle correction.
- Updating to June 2015 database lock for adverse event cycle data

Judgement
- Implementing idelalisib wastage costs
- Implementing age-adjusted utility decline
- Using mean dose intensity estimate from DELTA for chemotherapy

Scenarios

1. 50% reduction in rituximab price from use of rituximab biosimilar
2. A hazard ratio of 1 used to adjust for prior therapy as proxy for current comparator
3. Alternative utility data identified in literature search
4. Cytomegalovirus monitoring costs doubled from clinical expert estimates
5. Drug costs for chemotherapy based on cheaper CHOP regimen only
6. Other plausible distributions are chosen for relevant time to event curves

[redacted]

ERG corrected cost-effectiveness results

	Technologies	Total			Incremental			ICER (£/QALY)
		Costs	LYG	QALYs	Costs	LYG	QALYs	
Comparison A	Chemotherapy Regimens	£XXXX	4.99	2.71	-	-	-	£32,882
	Idelalisib	£XXXX	6.03	3.43	£23,599	1.04	0.72	
Comparison B	Chemotherapy Regimens	£XXXX	2.28	1.38	-	-	-	£21,559
	Idelalisib	£XXXX	5.32	3.10	£37,164	3.04	1.72	
Comparison C	Chemotherapy Regimens	£XXXX	5.14	2.82	-	-	-	£58,754
	Idelalisib	£XXXX	5.70	3.21	£22,712	0.56	0.39	
Comparison D	Best supportive care	£XXXX	4.62	2.43	-	-	-	£29,639
	Idelalisib	£XXXX	6.03	3.43	£29,426	1.41	0.99	

ERG exploratory analyses – all comparisons

	Comparison A	Comparison B	Comparison C	Comparison D
Scenarios	ICER (£)	ICER (£)	ICER (£)	ICER (£)
Company base-case	£26,076	£19,872	£47,011	£25,272
ERG corrected	£32,882	£21,559	£58,754	£29,639
Scenario 1 – Rituximab price reduction	£35,202	£22,091	£62,922	£29,789
Scenario 2 – Hazard Ratio=1 for adjusting prior line treatment outcomes	£35,980	£21,004	£92,801	£29,639
Scenario 3a –Utility inputs from Bec et al. 2014	£36,526	£26,081	£65,305	£32,979
Scenario 3b –Utility inputs from GADOLIN trial	£35,893	£17,766	£64,103	£32,081
Scenario 4 – Increased CMV monitoring	£33,416	£21,787	£59,746	£30,025
Scenario 5 – Cheaper chemotherapy costs	£37,953	£22,740	£67,870	£29,961
Scenario 6a – Using different time to progression extrapolation (exponential)	£39,542	-	£95,120	£33,771
Scenario 6b – Using different time on treatment extrapolation (lognormal)	£34,542	£22,560	£61,772	£30,596
Scenario 6c – Using different post progression survival extrapolation (lognormal)	£29,455	-	£41,131	£27,990
Scenario 6d – Using different progression free survival extrapolation (loglogistic)	-	£21,791	-	-

[redacted]

Innovation and Equality

Innovation

- Company comments
  - Idelalisib is the first PI3Kδ inhibitor to be licensed for follicular lymphoma
  - Offers a different mode of action to patients that have poor response to immunotherapy and chemotherapy
  - Convenience of an oral treatment compared to intravenous chemotherapy
  - Adverse event profile contrasts to chemotherapy
- Professional comments
  - Idelalisib could be used in a key area of unmet need in the follicular lymphoma treatment pathway

Equality

- No equality concerns have been identified

[redacted]

End of life considerations

Criterion	Data source	Overall survival	
		Median (months)	Mean
Short life expectancy, normally < 24 months	HMRN cohort data	XXX	-
	HMRN MAIC-adjusted data	XXX	-
	Base case economic analysis standard of care	-	60.1
Extension to life, normally of a mean value of ≥ 3 months		Increase with idelalisib	
		Median (months)	Mean
	DELTA difference to HMRN MAIC adjusted overall survival	XXXX	-
	Base case economic analysis difference to standard of care	-	16.0

ERG comment

- The most plausible life expectancy of [redacted] the number of life years gained for standard of care in all economic analyses was never less than 24 months.

[redacted]

Key issues – cost effectiveness

- Which comparison (A-D) gives the most appropriate data for the comparator?
- What is the most appropriate distribution for extrapolation of time to progression in the DELTA idelalisib arm?
- What is the most appropriate utility data for people with progression free and progressed follicular lymphoma?
- Is it appropriate to assume adverse events are equivalent for idelalisib and chemotherapy?
- What is the most plausible ICER?
- Are the end of life criteria met?

[redacted]

Authors

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with input from the Lead Team (Amanda Adler, Stephen Palmer, Diar Fattah, Nigel Westwood)

ERG exploratory analysis – Comparison A

Scenarios	Idelalisib		Chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	£XXXXX	3.71	£XXXXX	2.8	£23,762	0.91	£26,076
ERG corrected Comparison A	£XXXXX	3.43	£XXXXX	2.71	£23,599	0.72	£32,882
Scenario 1 – Price reduction rituximab	£XXXXX	3.43	£XXXXX	2.71	£25,264	0.72	£35,202
Scenario 2 – Hazard Ratio=1 for adjusting prior line treatment outcomes	£XXXXX	3.43	£XXXXX	2.80	£22,454	0.62	£35,980
Scenario 3a –Utility inputs from Bec et al. 2014	£XXXXX	2.89	£XXXXX	2.24	£23,599	0.65	£36,526
Scenario 3b –Utility inputs from GADOLIN trial	£XXXXX	3.93	£XXXXX	3.27	£23,599	0.66	£35,893
Scenario 4 – Increased CMV monitoring	£XXXXX	3.43	£XXXXX	2.71	£23,983	0.72	£33,416
Scenario 5 – Cheaper chemotherapy costs	£XXXXX	3.43	£XXXXX	2.71	£27,239	0.72	£37,953
Scenario 6a – Using different time to progression extrapolation (exponential)	£XXXXX	3.30	£XXXXX	2.71	£23,329	0.59	£39,542
Scenario 6b – Using different time on treatment extrapolation (lognormal)	£XXXXX	3.43	£XXXXX	2.71	£24,785	0.72	£34,542
Scenario 6c – Using different post progression survival extrapolation (lognormal)	£XXXXX	4.76	£XXXXX	3.91	£24,843	0.84	£29,455

[redacted]

ERG exploratory analysis – Comparison B

Scenarios	Idelalisib		Chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company Comparison B	£XXXXX	3.19	£XXXXX	1.44	£34,924	1.76	£19,872
ERG corrected Comparison B	£XXXXX	3.10	£XXXXX	1.38	£37,164	1.72	£21,559
Scenario 1 – Price reduction rituximab (due to biosimilar)	£XXXXX	3.10	£XXXXX	1.38	£38,082	1.72	£22,091
Scenario 2 – Hazard ratio =1 for adjusting prior line treatment outcomes	£XXXXX	3.10	£XXXXX	1.38	£36,155	1.72	£21,004
Scenario 3a –Utility inputs from Bec et al. 2014	£XXXXX	2.63	£XXXXX	1.20	£37,164	1.42	£26,081
Scenario 3b –Utility inputs from GADOLIN trial	£XXXXX	3.52	£XXXXX	1.43	£37,164	2.09	£17,766
Scenario 4 – Increased cytomegalovirus monitoring frequency	£XXXXX	3.10	£XXXXX	1.38	£37,558	1.72	£21,787
Scenario 5 – Cheaper chemotherapy costs	£XXXXX	3.10	£XXXXX	1.38	£39,201	1.72	£22,740
Scenario 6d – Using different progression free survival extrapolation – (loglogistic)	£XXXXX	3.13	£XXXXX	1.45	£36,725	1.69	£21,791
Scenario 6b – Using different time on treatment extrapolation – (lognormal)	£XXXXX	3.10	£XXXXX	1.38	£38,851	1.72	£22,560
Scenario 6e – Using different overall survival extrapolation – (lognormal)	£XXXXX	4.20	£XXXXX	1.47	£46,066	2.73	£16,855

ERG exploratory analysis – Comparison C

Scenarios	idelalisib		chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company Comparison C	£XXXX	3.41	£XXXXX	2.92	£22,712	0.48	£47,011
ERG corrected Comparison C	£XXXX	3.21	£XXXXX	2.82	£22,712	0.39	£58,754
Scenario 1 – Price reduction rituximab (due to biosimilar)	£XXXX	3.21	£XXXXX	2.82	£24,323	0.39	£62,922
Scenario 2 – Hazard ratio =1 for adjusting prior line treatment outcomes	£XXXX	3.21	£XXXXX	2.97	£21,408	0.23	£92,801
Scenario 3a –Utility inputs from Bec et al. 2014	£XXXX	2.69	£XXXXX	2.34	£22,712	0.35	£65,305
Scenario 3b –Utility inputs from GADOLIN trial	£XXXX	3.72	£XXXXX	3.37	£22,712	0.35	£64,103
Scenario 4 – Increased cytomegalovirus monitoring frequency	£XXXX	3.21	£XXXXX	2.82	£23,095	0.39	£59,746
Scenario 5 – Cheaper chemotherapy costs	£XXXX	3.21	£XXXXX	2.82	£26,236	0.39	£67,870
Scenario 6a – Using different time to progression extrapolation (exponential)	£XXXX	3.06	£XXXXX	2.82	£22,332	0.23	£95,120
Scenario 6b – Using different time on treatment extrapolation (lognormal)	£XXXX	3.21	£XXXXX	2.82	£23,900	0.39	£61,772
Scenario 6c – Using different post progression survival extrapolation (lognormal)	£XXX	4.60	£XXXXX	4.00	£24,710	0.60	£41,131

ERG exploratory analysis – Comparison D

Scenarios	idelalisib		Best supportive care		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company Comparison D	£XXXXX	3.71	£XXXXX	2.5	£30,473	1.21	£25,272
ERG corrected Comparison D	£XXXXX	3.43	£XXXXX	2.43	£29,426	0.99	£29,639
Scenario 1 – Price reduction rituximab (due to biosimilar)	£XXXXX	3.43	£XXXXX	2.43	£29,575	0.99	£29,789
Scenario 2 – Hazard ratio =1 for adjusting prior line treatment outcomes	£XXXXX	3.43	£XXXXX	2.43	£29,426	0.99	£29,639
Scenario 3a –Utility inputs from Bec et al. 2014	£XXXXX	2.89	£XXXXX	2.00	£29,426	0.89	£32,979
Scenario 3b –Utility inputs from GADOLIN trial	£XXXXX	3.93	£XXXXX	3.01	£29,426	0.92	£32,081
Scenario 4 – Increased cytomegalovirus monitoring frequency	£XXXXX	3.43	£XXXXX	2.43	£29,809	0.99	£30,025
Scenario 5 – Cheaper chemotherapy costs	£XXXXX	3.43	£XXXXX	2.43	£29,746	0.99	£29,961
Scenario 6a – Using different time to progression extrapolation (exponential)	£XXXXX	3.30	£XXXXX	2.43	£29,145	0.86	£33,771
Scenario 6b – Using different time on treatment extrapolation (lognormal)	£XXXXX	3.43	£XXXXX	2.43	£30,371	0.99	£30,596
Scenario 6c – Using different post progression survival extrapolation (lognormal)	£XXXXX	4.76	£XXXXX	3.69	£29,914	1.07	£27,990

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Idelalisib for treating refractory follicular lymphoma [ID1379]

Document B

Company evidence submission

June 2018

File name	Version	Contains confidential information	Date
ID1379 Document B	V1	Yes	7 June 2018

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are

summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

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Contents

Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BID	Twice a day
BSA	Body surface area
BSC	Best supportive case
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CR	Complete response
CUP	Compassionate use programme
DBL	Database lock
DHAP	Dexamethasone, cytarabine, cisplatin
DOR	Duration of response
DSU	Decision Support Unit
EAP	Early access programme
ECOG	European Cooperative Oncology Group
EMA	European Medical Agency
ERG	Evidence Review Group
FACT-Lym	Functional Assessment of Cancer Therapy: Lymphoma
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
iNHL	Indolent non-Hodgkin’s lymphoma
IPD	Individual patient data
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intent-to-treat
KM	Kaplan–Meier
LDH	Lactate dehydrogenase

Abbreviation	Definition
MAIC	Matching-adjusted indirect comparison
N/A	Not applicable
NCPE	National Centre for Pharmacoeconomics
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PJP	*Pneumocystis jirovecii* pneumonia
PPS	Post-progression survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-CVP	Rituximab, cyclophosphamide, vincristine, prednisone
RCT	Randomised controlled trial
RS	Relative survival
RWE	Real world evidence
SAE	Serious adverse event
SCT	Stem cell transplantation
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
ToT	Time on treatment
TSD	Technical Support Document
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response

Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, as shown alongside further details of the decision problem in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with follicular lymphoma that is refractory to 2 prior lines of therapy	People with follicular lymphoma that is refractory to 2 prior lines of therapy	N/A
Intervention	Idelalisib	Idelalisib	N/A
Comparator(s)	• Chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil) In people for whom chemotherapy is unsuitable: • Best supportive care	• Chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil) In patients for whom chemotherapy is unsuitable: • Best supportive care	N/A
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response/remission • adverse effects of treatment	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response/remission • time-to-progression	The additional outcome measures are necessary for economic analysis.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• health-related quality of life	• post-progression survival • time on treatment • adverse effects of treatment health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	Incremental cost per QALY gained analysis, with a lifetime NHS and Personal Social Services perspective on costs and health effects on the individual perspective on benefits.	N/A
Subgroup considerations	If the evidence allows, a subgroup of people suitable to receive stem cell transplantation and for whom idelalisib could be used to induce remission before transplantation will be considered.	-	The use of idelalisib to induce remission before transplantation has not been formally investigated. Observations from trials are provided where available but evidence is not sufficient for full consideration of this subgroup.
Key: N/A, not applicable; PSS, personal social services; QALY, quality-adjusted life years.			

B.1.2. Description of the technology being appraised

A description of idelalisib (Zydelig®) is presented in Table 2.

The summary of product characteristics (SmPC) and European Public Assessment Report (EPAR) is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Idelalisib (Zydelig®)
Mechanism of action	Idelalisib is a selective inhibitor of adenosine-5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ (phosphatidylinositol 3-kinase p110δ), resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol and prevention of Akt (protein kinase B) phosphorylation. PI3Kδ is hyperactive in B cell malignancies and is central to multiple signalling pathways that drive the growth, differentiation, proliferation, survival, migration and metabolism of malignant cells in lymphoid tissue and bone marrow.[1] As a result, through the inhibition of PI3Kδ, idelalisib induces apoptosis and limits proliferation in cell lines derived from malignant B cells and in primary tumour cells. The high specificity of idelalisib for targeting the PI3K p110δ catalytic domain makes it a promising treatment option for prolonging efficacy and reducing toxicity compared to chemotherapy-containing regimens.[2]
Marketing authorisation/CE mark status	On 24th July 2014, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product idelalisib (both indications detailed below), 100mg and 150mg, film-coated tablets. The marketing authorisation for the UK was issued on 18th September 2014.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Indications** Zydelig is indicated as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment. Zydelig is also indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with CLL: • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies **Summary of restrictions** • Treatment should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal or viral infection – Prophylaxis for PJP should be administered to all patients throughout treatment and for a period of 2 to 6 months after

	discontinuation.
Method of administration and dosage	The recommended dose of idelalisib is one 150mg tablet to be taken orally twice a day.
Additional tests or investigations	• Regular clinical and laboratory monitoring for CMV infection is recommended in patients with positive CMV serology at the start of treatment with idelalisib or with other evidence of a history of CMV infection. • Patients with CMV viraemia, without associated clinical signs of CMV infection, should be carefully monitored. • Full blood counts should be monitored in all patients at least every 2 weeks for the first 6 months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm^3. • ALT, AST, and total bilirubin must be monitored in all patients every 2 weeks for the first 3 months of treatment, then as clinically indicated.
List price and average cost of a course of treatment	The list price for idelalisib is £3,114.75 per pack of 60 150mg film-coated tablets. Estimated average cost of a course of treatment of [redacted] from list-price deterministic base case economic analysis, no time-preference discounting.
Patient access scheme (if applicable)	There is an agreed commercial discount to the list price of idelalisib approved by the Department of Health that is applicable to this appraisal.
Key: AKT, protein kinase B; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CHMP, Committee for Medicinal Products for Human Use; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; FL, follicular lymphoma; PJP, *Pneumocystis jirovecii* pneumonia; SmPC, summary of product characteristics; TEN, toxic epidermal necrolysis; ULN, upper limit of normal. **Source:** Zydelig SmPC[3]	

B.1.3. Health condition and position of the technology in the treatment pathway

Disease overview

Follicular lymphoma (FL) is the most common of the low-grade lymphomas (also referred to as indolent non-Hodgkin's lymphoma [iNHL]) in the UK.[4] Its incidence increases with age, with a median presentation between 60 and 65 years and a slight female:male predominance.[4] FL is typically characterised by an indolent clinical course, with recurrent remissions and relapses and a median survival of 7–10 years in the pre-rituximab era.[5] FL is an incurable disease with a substantial

symptom burden, including B symptoms, fatigue and the local mass effects of lymph node enlargement and bone marrow failure.[5]

The course of FL is highly heterogeneous; approximately 10% to 15% of patients have aggressive disease and short survival, whereas others have more prolonged and subdued disease.[6] Nonetheless, with each relapse in FL, the disease becomes more resistant and/or refractory to treatment and each remission becomes shorter than the preceding one.[7] In a UK cohort study of patients with FL (N=212), the median length of response to treatment was 31 months at first remission, 13 months at second and third remission, and 6 months at fourth remission.[8] In a more recent US longitudinal study of patients with FL (National LymphCare Study, n=2,429), the median progression-free survival (PFS) was 6.62 years at first line, 1.50 years at second line, 0.83 years at third line, 0.69 years at fourth line and 0.68 years at fifth line.[9]

The aim of treatment for FL is to control symptoms and extend remission in order to improve quality of life. Many patients initially have asymptomatic, slowly progressing disease and will be on a 'watch and wait' policy until treatment becomes necessary. However, approximately 85% of patients have advanced disease at presentation.[10] Most of these patients have first-line induction with rituximab in combination with chemotherapy (R-chemo).[11] This is usually followed by rituximab maintenance therapy. Second-line treatment for FL depends on the timing of relapse following first-line treatment and the chemotherapy agents used first-line. Patients with FL who do not respond to induction treatment with R-chemo as well as those who initially respond but relapse within 6 months are considered to have uncontrolled disease and adverse prognosis.[12] These patients are considered to have disease that is refractory to rituximab, that is, “rituximab-refractory” FL. At this point, treatment options are limited for the patient.

FL that is rituximab-refractory displays characteristics of “high-risk FL” which is likely to have early progression and associated poor outcomes.[13] Therefore, it is conceivable that FL which is refractory to two previous lines of treatment, hereafter referred to as double-refractory FL, is likely to confer the worst prognosis. There is no treatment consensus or standard of care for these patients and life expectancy typically falls below 24 months.[8, 14, 15]

There are a number of classification systems for FL, including the World Health Organization (WHO)/Revised European-American Lymphoma (REAL) classification, the Cotswolds modified Ann Arbor staging system for FL (NHL) or the Follicular Lymphoma International Prognostic Index (FLIPI) score, as summarised in Table 3.[16]

In the pivotal Study 101-09 (see Section B.2) which uses the FLIPI classification system, over half of all patients (54.2%) had a score ≥3 which relates to a high-risk category, indicative of a poor prognosis (see life expectancy).

Table 3: Classification systems for follicular lymphoma

WHO/REAL	Cotswolds modified Ann Arbor	FLIPI score
Grade 1: 0–5 centroblasts **Grade 2**: 6–15 centroblasts **Grade 3**: >15 centroblasts	**Stage I:** Single lymph node **Stage II**: Multiple lymph node groups on same side of diaphragm. **Stage III**: Multiple lymph nodes on both sides of diaphragm. **Stage IV**: Multiple extranodal sites or lymph nodes and extranodal disease. **Stage X**: Bulk >10 cm **Stage E**: Extranodal extension or single isolated site of extranodal disease. **Stage A/B**: Absence or presence of symptoms – B symptoms include weight loss >10%, fever, drenching night sweats.	**Factors (1 point for each variable present):** • Age >60 years • Ann Arbor Stage III–IV • Haemoglobin level <12g/dl • LDH level >upper limit of normal • ≥4 nodal sites of disease **Risk category (factors):** • **Low** (0 or 1) • **Intermediate** (2) • **High** (>3)
Key: FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; REAL, Revised European-American Lymphoma; WHO, World Health Organization. **Source:** Hernandes-Ilizaliturri et al. 2016[16]		

Epidemiology

The Haematological Malignancy Research Network (HMRN) estimate that 1,930 people are diagnosed with FL every year in the UK.[4] Following diagnosis, 69.3% of FL patients are estimated to have symptomatic, progressing disease and thus receive active treatment for their disease; of patients receiving active treatment, 10.1% are treated at third-line or beyond; and of these, 38.2% are estimated to have disease refractory to chemotherapy and rituximab.[17] The number of people diagnosed with double-refractory FL in the UK is therefore not thought to exceed 52 patients per year (43 in England).

Life expectancy

FL has commonly been seen as a chronic, relapsing, indolent tumour with a median survival of 7–10 years in the pre-rituximab era.[5] Although life expectancy has improved with advancements in therapy (such that the median survival estimate from diagnosis is approximately 18 years[18]), prognosis worsens with increased risk categorisation, and increased aggressiveness of disease. Patients with high-risk disease according to FLIPI categorisation have a significantly higher risk of death than patients with low-risk disease (see Table 4).[19] Patients who experience disease progression within 2 years (suggesting chemoimmunotherapy resistance) have also been shown to have a significantly increased risk of death: 5-year overall survival was 50% in an early progression of disease (<2 years post-diagnosis) group of patients (n=110) in the National LymphCare Study compared to 90% in patients without early progression of disease (n=420): unadjusted hazard ratio (HR) = 7.17 (95% CI: 4.83, 10.65).[13] These prognostic factors are closely associated with a retrospective study of patients receiving R-chemo for symptomatic FL showing high-risk FLIPI score was independently and significantly predictive of chemoimmunotherapy resistance.[20]

Table 4: Outcomes and relative risk of death according to Follicular Lymphoma International Prognostic Index risk group

Risk group	Number of factors	Distribution of patients, %	5-year OS, % (SE)	10-year OS, % (SE)	RR (95% CI)[a]
Low	0–1	36	90.6 (1.2)	70.7 (2.7)	N/A
Intermediate	2	37	77.6 (1.6)	50.9 (2.7)	2.3 (1.9, 2.8)
High	≥3	27	52.5 (2.3)	35.5 (2.8)	4.3 (3.5, 5.3)

Key: CI, confidence interval; N/A, not applicable; OS, overall survival; RR, relative risk; SE, standard error.
Notes: [a], Reference = low risk group.
Source: Solal-Céligny et al. 2004[19]

Patients who have double-refractory FL, such as those enrolled in the idelalisib pivotal Study 101-09, have features that resemble that of FL with early progression with rapidly progressing disease compared with other FL patients. As we would expect, with increasing resistance to treatment, there is substantial reduction to life expectancy. In the aforementioned UK cohort study, median overall survival (OS) was shown to decrease from 9.2 years at first presentation of FL, to 2.0 years at the

third recurrence, and a median survival from response to third-line therapy of 1.2 years.[8] While it is important to note this study was conducted before the rituximab era, it is not expected that rituximab refractory patients would have improved survival outcomes today (as they would not receive rituximab). End of life considerations specific to double-refractory FL patients are presented in Section B.2.13.

Burden of disease

Alongside reduced life expectancy, FL is associated with a number of physical and psychological symptoms that affect patients' health-related quality of life (HRQL). Initially, the most common symptom of FL is a painless swelling in the lymph nodes of the neck, armpit or groin.[10] FL is also associated with 'B-symptoms' such as fatigue, weight loss, fever and night sweats.[21] Patients with FL will also have multiple sites of lymphadenopathy that can result in restricted movement, disfigurement, pain, and/or bone marrow disease that can result in anaemia, leukopenia, and thrombocytopenia.[22, 23]

In addition to physical symptoms, FL negatively affects the mental health of patients, with depression and stress commonly reported.[24-26] Being generally a chronic, incurable and progressive condition, it is emotionally unsettling. Indeed, HRQL diminishes with each treatment relapse. In a UK cross-sectional study using a variety of patient-reported outcome (PRO) instruments to assess HRQL, patients with relapsed FL were more likely to experience worse HRQL compared to FL patients who were newly diagnosed, in partial or complete remission or disease-free.[22] Patients with relapsed FL had lower mean physical, emotional, functional and social wellbeing scores and reported statistically significantly higher levels of anxiety, depression and activity impairment levels compared with disease free patients.[22] As such, the burden of illness in patients with double-refractory FL is expected to be particularly high (though data outside of the Study 101-09 trial is limited, see Section B.2)

HRQL is further affected by treatment toxicity effects, for example, chemotherapy has specifically been shown to worsen health functioning (p=0.004), depressive symptoms (p=0.005) and activity impairment (p=0.009) compared with FL patients in remission but not on treatment.[22] Patients receiving active chemotherapy for disease progression displayed considerable impairment (daily activity impairment >50%)

including in overall work productivity.[27] There is therefore an economic consideration associated with the adverse event (AE) profile of chemotherapy; not only in this indirect manner (productivity loss), but also regarding the direct costs associated with AE management, specifically the management of chemotherapy-related febrile neutropenia.[28, 29]

Alongside the burden to patients, FL also poses a substantial burden to carers. In a cross-sectional cohort of patients with iNHL, including FL, in Canada, the majority of care (74%) was unpaid assistance from a partner/spouse, relative or friend.[27] This group of unpaid caregivers provided a mean of 9.8 days of care in the 30 days prior to data collection, with a mean of 11.3 days of absenteeism.

Clinical pathway of care

Since there is no cure for advanced FL, the aim of treatment is to control symptoms and extend remission in order to improve quality of life. Double-refractory FL patients are particularly difficult to treat: the nature of the disease prompts immediate consideration of a more aggressive treatment (compared to relapsed disease) but patients are refractory to conventional treatment. In addition, patients can be old and frail, and often present with serious comorbidities such as lipometabolic disorders and chronic pulmonary disease.[14] This may help explain why there are currently no active treatments specifically licensed for double-refractory disease other than idelalisib.

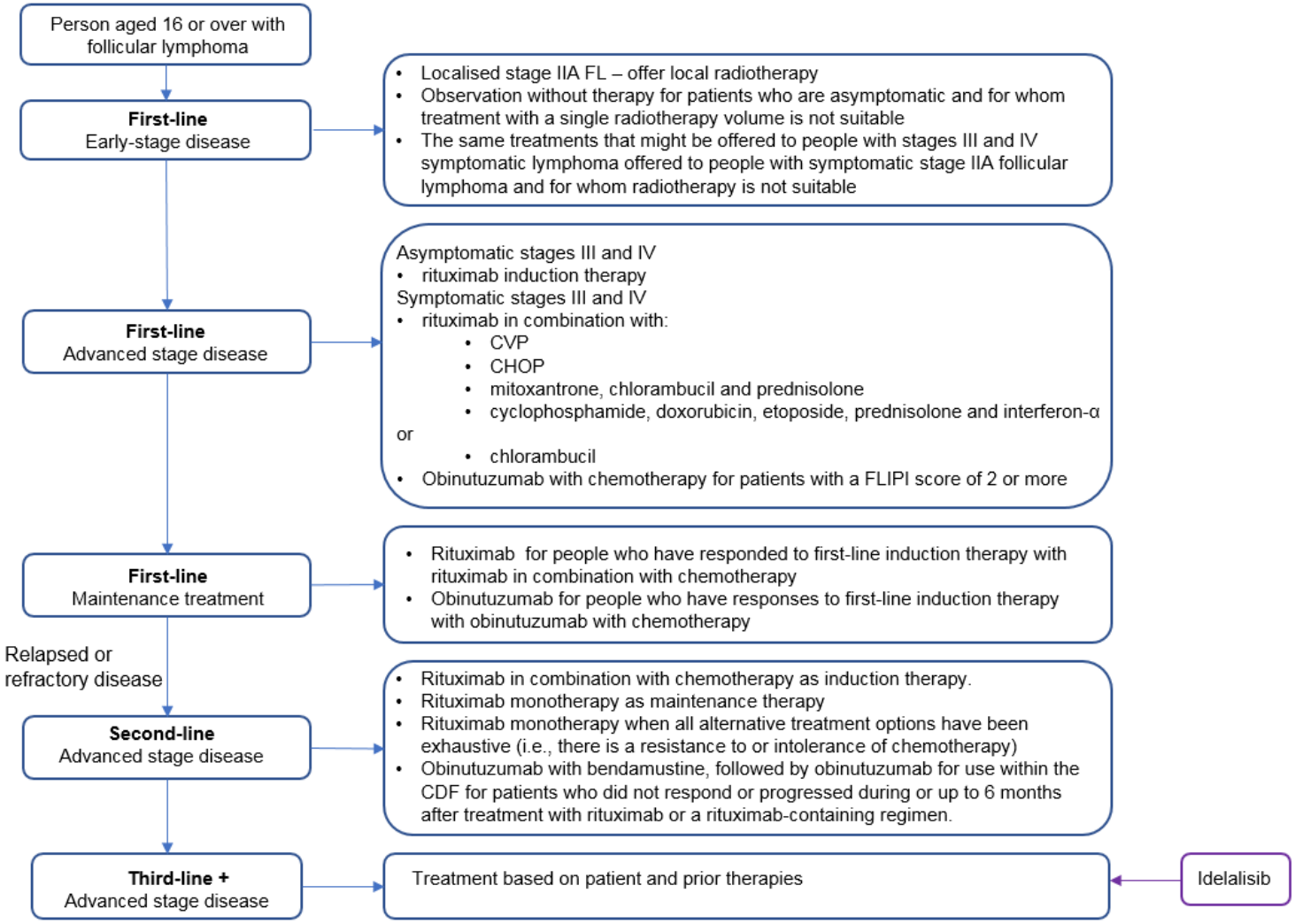
As shown in Figure 1, clinical guidelines for the management of FL make clear recommendations for first-line treatment (R-chemo followed by rituximab maintenance), whereas the approach to disease management at subsequent lines of therapy is less defined.[5, 11, 30] Second-line and subsequent treatments include retreatment with the same, or similar, regimens provided there was no evidence of refractoriness to the therapy as defined by lack of response (or progression) during treatment or progression within 6 months of treatment completion. Of note, while not captured in the treatment algorithm presented (Figure 1), consolidation with stem cell transplantation (SCT) should be considered for patients who are fit enough for transplantation and who have not already had a transplant, or for whom a suitable donor can be found and when autologous stem cell transplantation (ASCT) has not resulted in remission or is inappropriate.[11]

As patients approach third- and later-lines of therapy, their options are markedly diminished. There is no standard of care (SOC) and treatment tends to be via a 'trial and error' approach. The only regimens and agents available are those used in previous lines, and therefore treatments are either repeated or administered in a different combination according to individual clinician choice. However, there are considerable limitations with such management: reinduction with rituximab and/or chemotherapy often has a short duration of remission, reduced overall survival, limiting toxicity and a negative impact on HRQL.[22, 31] Patients who can no longer tolerate further rituximab or chemotherapy treatment have no alternatives outside of best supportive case (BSC), which involves regular follow-up with a lymphoma specialist and/or palliative care team, blood product support if required, and antibiotics to treat infection.

Idelalisib is anticipated to fit in the third-line setting, therefore providing an active treatment option for an extremely high-risk group of patients who have no proven management option in NHS England. Following registration, idelalisib was incorporated into the European Society for Medical Oncology (ESMO) clinical practice guidelines as a recommended treatment option for double refractory cases of FL.[30] Idelalisib is also routinely reimbursed in NHS Wales and NHS Scotland.[32, 33]

Due to the current lack of SOC, it is challenging to further define the relevant comparator treatments for NHS England outside of chemotherapy regimens or BSC in patients for whom chemotherapy is unsuitable (see Section B.1.1). Chemotherapy regimens considered in the economic evaluation are based on the previous line of treatment received by FL patients enrolled in Study 101-09 (see Section B.2), and treatment received by FL patients with disease refractory to rituximab and an alkylating agent registered to the HMRN (see Section B.2.9). These treatments are listed in Table 5, and can be seen as representative of the chemotherapy regimens used to treat double-refractory FL in clinical practice. The extent of this list reinforces the lack of SOC for these patients.

Figure 1: Treatment algorithm for FL patients in England



Key: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; FL, follicular lymphoma.
Source: Adapted from NICE Pathway NG52 2018[11]

Table 5: Comparators included in the economic evaluation

Comparator	Rationale for relevance
R-CHOP	Treatment regimen most commonly received by patients with FL prior to trial enrolment in Study 101-09. Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN
R-DHAP	Treatment regimen most commonly received by patients with double-refractory FL registered to the HMRN.
Rituximab	Treatment received by patients with FL prior to trial enrolment in Study 101-09. Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
R-bendamustine	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
R-CVP	Treatment received by patients with FL prior to trial enrolment in Study 101-09. Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
CHOP	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
R-prednisolone	Treatment received by patients with FL prior to trial enrolment in Study 101-09. Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
R-CHO	Treatment received by patients with FL prior to trial enrolment in Study 101-09
CVP	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
R-fludarabine	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
R-FC	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
R-ICE	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
CHPE	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
R-chlorambucil	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
CHOEP	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
CHEPi	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
GEM-P	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
DHAP	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.

Comparator	Rationale for relevance
G-CVP	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
IVE	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
FC	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
Chlorambucil plus prednisone	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
Fludarabine plus mitoxantrone	Treatment received by patients with FL prior to trial enrolment in Study 101-09.
Chlorambucil-based therapy	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
Bendamustine-based	Treatment received by patients with FL refractory to rituximab and an alkylating agent registered to the HMRN.
Key: CHEPi, cyclophosphamide, doxorubicin, etoposide, prednisone, interferon; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; CHPE, cyclophosphamide, doxorubicin, etoposide, prednisone; CVP, cyclophosphamide, vincristine, prednisone; DHAP, dexamethasone, cytarabine, cisplatin; FC, fludarabine with chlorambucil; FL, follicular lymphoma; G-CVP, gemcitabine, cyclophosphamide, vincristine, prednisone; GEM-P, gemcitabine, cisplatin, methylprednisone; HMRN, Haematological Malignancy Research Network; IVE, ifosfamide, epirubicin, etoposide; R-bendamustine, rituximab with bendamustine; R-chlorambucil, rituximab with chlorambucil; R-fludarabine, rituximab with fludarabine; R-prednisone, rituximab with prednisone; R-CHO, rituximab, cyclophosphamide, doxorubicin, vincristine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-FC, rituximab, fludarabine, chlorambucil; R-ICE, rituximab, ifosfamide, carboplatin, etoposide.	

B.1.4. Equality considerations

No equality concerns have been identified or are anticipated with the introduction of idelalisib. Idelalisib is already available to double-refractory FL patients in NHS Wales and NHS Scotland, so availability in NHS England would remove any concerns of inequality across the devolved nations of the UK.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

The pivotal trial that supported product registration, providing data on the use of idelalisib monotherapy for the treatment of double-refractory FL, is the Phase II Study 101-09. This is a multi-centre, single arm study investigating the efficacy and safety of idelalisib in patients with indolent non-Hodgkin's lymphoma (iNHL) refractory to rituximab and an alkylating agent.

Although Study 101-09 enrolled patients with different types of iNHL, marketing authorisation was granted for the FL population, as this represents the largest subpopulation of patients enrolled (72 of 125). A comparative assessment of clinical efficacy of idelalisib has been performed against the observed efficacy of previous lines of treatment in the same cohort of patients.

Further data from a Phase 1b dose-finding study (101-02), combined with extension study (101-99), support the conclusions from the pivotal study. Although conducted as two separate trials, the methodology and results have been written up within a single publication, and as such, will be described as one study throughout this submission (101-02/99).

A summary of real world evidence (RWE) from a compassionate use programme (CUP) of idelalisib for the treatment of relapsed or refractory FL, specific to the UK and Ireland setting, provides further supportive evidence. Similar to Study 101-09, an assessment of clinical efficacy associated with previous lines of treatment in the CUP cohort provides indirect comparative efficacy data for idelalisib versus current management. An early access programme (EAP) across Europe (Belgium, Greece, Spain) and Australia was also identified that was designed to look at the characteristics of refractory FL patients treated with idelalisib, and the safety of its use in a real-world setting.

Sources of clinical effectiveness evidence for idelalisib in refractory or relapsed FL are summarised in Table 6.

Study 101-2/99 was not used to populate the economic model but is included in Section B.2 for completeness of efficacy and safety evidence of idelalisib monotherapy. As a small-scale dose escalation study, the evidence was considered less relevant to the economic evaluation. The Europe and Australia EAP was also not used to populate the economic model but is included in Section B.2.10 to provide further safety data for idelalisib monotherapy. Efficacy data are not available from this non-UK programme, and data have only been presented at conferences to date, so this evidence was not considered appropriate for the economic evaluation.

Table 6: Clinical effectiveness evidence for idelalisib in refractory or relapsed FL

Study	**101-09**[34]	**101-2/99**[35]	**Compassionate use programme: UK**[36]	**Early access programme: Europe/Australia**[37]
Study design	Phase II, open label, single arm study of idelalisib	Phase Ib dose escalation and extension study	Retrospective data collection from real world patients	Retrospective data collection from real world patients
Population	Patients with relapsed iNHL refractory to rituximab and chemotherapy containing an alkylating agent. Histological subtypes included FL.	Patients with relapsed iNHL, refractory to or relapsed after at least one prior chemotherapy regimen and rituximab. Histological subtypes included FL.	Patients with refractory or relapsed FL.	Patients with refractory FL
Intervention(s)	Idelalisib 150mg (or reduced to 75/100mg) BID, taken orally	Idelalisib Doses: 50mg, 100mg, 200mg and 350mg BID. Regimens of idelalisib: 150mg BID, 150mg or 300mg QD, and 150mg BID taken 2 weeks on and 1 week off subsequently added. Dose escalation: 3+3 design in sequential cohorts.	Idelalisib 150mg BID	Idelalisib Presume 150mg BID
Comparator(s)	None	None	None	None
Indicate if trial used in the marketing authorisation	Yes	Yes	No	No
Indicate if trial used in the	Yes	No	Yes	No

Study	101-09[34]	101-2/99[35]	Compassionate use programme: UK[36]	Early access programme: Europe/Australia[37]
economic model				
Rationale for use/non-use in the model	Pivotal trial	Small scale, dose escalation study	Provides additional data from real world evidence with relevant endpoints	Safety data limited, no efficacy data
Reported outcomes specified in the decision problem: those marked in bold are incorporated in the economic model	• **Overall survival** • **Progression-free survival** • Response rates • Duration of response/remission • **Adverse effects of treatment** • **Health-related quality of life**	• Adverse effects of treatment • Response rate • Progression-free survival	• Overall response rate • **Progression-free survival** • **Overall survival** • Adverse effects of treatment	• Adverse effects of treatment
All other reported outcomes	• **Time to progression** • **Post-progression survival** • **Time on treatment** • Laboratory abnormalities	• Pharmacokinetics		• Patient characteristics
Key: BID, twice a day; CR, complete response; iNHL, indolent non-Hodgkin lymphoma; PD, progressive disease; PR, partial response.				

HMRN

Data collected via the disease registry for the HMRN has also been included in Section B.2.9 to provide RWE for chemotherapy regimens currently used to treat double-refractory FL in UK practice.

These data are subsequently used to perform a matching-adjusted indirect comparison (MAIC), providing an estimate of comparative effectiveness for chemotherapy regimens (HMRN data) versus idelalisib (Study 101-09 data) (see Section B.2.9).

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

A methodology summary of the pivotal and key supporting trials for idelalisib in refractory or relapsed FL is presented in Table 7.

Study 101-09

The pivotal Study 101-09 is a multi-centre, single arm, open label, Phase II study that enrolled iNHL patients to receive 150mg idelalisib twice daily. Patients had received at least two prior treatments for iNHL and were refractory to both rituximab and an alkylating agent; all patients with FL had double-refractory disease.

The primary outcome of Study 101-09 was overall response rate (ORR), assessed by an independent review committee (IRC) using standard criteria for lymphoma[38] and Waldenström's macroglobulinaemia[39], as defined in Appendix L. This primary outcome was assessed in the intention-to-treat (ITT) population and FL population of interest to this submission (see Section B.2.4).

Study 101-02/99

The supportive Study 101-02/99 is a Phase Ib dose escalation study and its extension that enrolled iNHL patients to receive various doses of idelalisib. Patients had received at least 1 prior chemotherapy and prior rituximab, to which they were refractory to or had relapsed after.

The primary outcome of Study 101-02 was to determine dose-limiting toxicity (DLT) for patients with haematological malignancies. Patients permitted to enter the

extension study were identified as benefiting from continued idelalisib treatment. The primary outcome of Study 101-99 was ORR.

UK & Ireland CUP

The supportive CUP was initiated following the marketing authorisation of idelalisib for the treatment of FL that is refractory to two prior lines of therapy.

Patients with refractory or relapsed FL were treated with 150mg idelalisib twice daily until progressive disease, toxicity or death as per license terms. Data were retrospectively collected and analysed to determine ORR, PFS and OS. Information on adverse events (AEs) was also collected but grading of AEs was not routine.

Table 7: Summary of methodology of relevant clinical effectiveness evidence

Study	101-09	101-02/99	Compassionate use programme
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	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	• 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

Study	101-09	101-02/99	Compassionate use programme
	diffuse large B cell lymphoma • History of a non-lymphoma malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, superficial bladder cancer, localised prostate cancer, other adequately treated Stage I or II cancer currently in complete remission, or any other cancer that had been in complete remission for ≥5 years • Evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment	• Prior stem cell transplantation with active graft-versus-host disease	
Settings and locations where data were collected	Investigators and their research teams collected all data, and sponsors confirmed the accuracy of the data and compiled the data for summation and analysis		
Trial drugs	Idelalisib 150mg BID	Dose escalation trial Idelalisib x 28 days: 50, 75, 100, 150, 200, 350mg BID; 150, 300mg daily Idelalisib x 21 days, 7 days off: 150mg BID	Idelalisib 150mg BID
Permitted and disallowed concomitant medication	No restriction on concomitant medication		
Primary outcomes (including	ORR, defined as the proportion of patients who achieved CR or PR during treatment with idelalisib	Study 101-02: Safety and dose-limiting toxicity	ORR, including CR/unconfirmed CR and PR

Study	101-09	101-02/99	Compassionate use programme
scoring methods and timings of assessments)	Response rates were assessed by an independent review committee (IRC) Patients were evaluated at 2 week intervals during the first 12 weeks of treatment, at 4 week intervals from Week 12 to Week 24 of treatment, at 6 week intervals from Week 24 to Week 48 of treatment, and at 12 week intervals thereafter	Study 101-99: ORR (defined as proportion of patients who achieve CR, PR or minor response (for WM only) Safety, as assessed by incidence of Grade ≥3 AEs	
Other outcomes used in the economic model/specified in the scope	• ORR assessed by an investigator • PFS, defined as the interval from the start of treatment to the earlier of the first documentation of PD or death from any cause • OS, defined as the interval from the date of first treatment to death from any cause • TTP, defined as the interval from the start of treatment until objective tumour progression, but does not include deaths • ToT, time on treatment • Change in HRQL as assessed through the FACT-Lym questionnaire • AEs, defined as any untoward medical occurrence in a patient who began or worsened in the period from administration of the first dose of the study drug to 30 days after administration of the last dose	Study 101-02: • Clinical response rate Study 101-99: • DOR (from onset of response to disease progression) • PFS (from enrolment to disease progression or death) • OS (from start of treatment to death) • TTR (from first dose to first documentation of CR or PR)	• PFS • OS • AE
Pre-planned subgroups	• Age (<65 or 65+ years) • Sex • Lymphoma subtype		

Study	101-09	101-02/99	Compassionate use programme
	• Presence/absence of bulky disease • Number of previous therapies (<4 or 4+) • Previous bendamustine use (yes/no) • Refractoriness to bendamustine (yes/no) • Refractoriness to last therapy (yes/no)		

Key: AE, adverse event; BID, twice daily; CR, complete response; DOR, duration of response; FL, follicular lymphoma; HRQL, health-related quality of life; iNHL, indolent non-Hodgkin's lymphoma; LPL, lymphoplasmacytic lymphoma; N/A, not applicable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; TTP, time to progression; TTR, time to response; WM, Waldenström's macroglobulinaemia.
Source: Gopal et al. 2014[34]**;** Study 101-99 CSR[40]; Flinn et al. 2014[35]: Eyre et al. 2017[36]

B.2.3.2 Baseline characteristics

Study 101-09

Baseline demographics and clinical characteristics of patients enrolled in Study 101-09 are presented in Table 8 for the ITT population and FL population.

Among patients enrolled to Study 101-09, all were refractory to rituximab and 99% had disease that was refractory to an alkylating agent; 86% of patients had disease that was refractory to rituximab plus alkylating agent combination therapy.[34] Among patients who had received prior regimens consisting of R-bendamustine, R-CHOP, or R-CVP 78%, 71%, and 81%, respectively, had disease that was refractory to those therapies. The majority of patients (90%) were refractory to the last therapy they had received prior to trial enrolment. Of the 72 patients in the study with double-refractory FL, more than half (37/72) also had early progression of the disease after receiving first-line chemoimmunotherapy, indicating additional high-risk features.

As previously discussed (see Section B.1.3), in the absence of other options, patients with double-refractory FL are most commonly retreated with chemotherapy regimens. Repetition of first line therapy agents despite relapse was readily observed in Study 101-09. In the total population, 47 unique therapies were used as the last treatment regimen prior to study entry, including a broad cross section of combinations of monoclonal antibodies, alkylating agents, anthracyclines, purine analogues and investigational agents[40]; reflecting the lack of a clearly defined therapeutic approach or standard of care (SOC) in this setting. Patients had received a median of four prior regimens (range 2–12), with 73 patients (58%) having received four or more prior regimens. A total of 25 patients (20%) had received six or more prior therapies. The most common prior regimens included R-bendamustine (48%), R-CHOP (45%), rituximab monotherapy (40%) and R-CVP (29%).

Reflecting the rapidly progressing nature of their double-refractory disease, patients enrolled in Study 101-09 had features of high-risk FL at baseline.[34] Most patients (89%) had Stage III or IV disease and over half (54%) of patients in the FL population had a high (≥3) FLIPI score at baseline.[31, 34] Furthermore, as a result of their considerable treatment history, a number of patients enrolled in Study 101-09 were exhibiting common side effects of chemotherapy at baseline. In the FL

population, neutropenia, anaemia and thrombocytopenia were observed in 13%, 11% and 7% of patients at baseline, respectively.[31]

Table 8: Baseline characteristics of patients in Study 101-09

Baseline characteristic	Overall population (n=125)	FL population (n=72)
Median age, years (range)	64 (33–87)	62 (33–84)
Sex, male, n (%)	80 (64)	39 (54.2)
Performance status, 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)
Median time since diagnosis, years (range)	5.3 (0.4–18.4)	4.7 (0.8–18.4)
Disease subtype, n (%)		
Follicular lymphoma	72 (57.6)	72 (100)
Small lymphocytic lymphoma	28 (22.4)	Not applicable
Marginal zone lymphoma	15 (12.0)	Not applicable
Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinaemia	10 (8.0)	Not applicable
Health assessment, n (%)		
Disease Stage III or IV	111 (88.8)	60 (83.3)
Elevated LDH	38 (30.4)	21 (29.2)
Bulky disease (one or more nodes with at least one dimension of 7cm or more)	33 (26.4)	16 (22.2)
Baseline neutropenia (ANC <1,500 per mm^3)	17 (13.6)	9 (12.5)
Baseline anaemia (haemoglobin <10 g/dL)	19 (15.2)	8 (11.1)
Baseline thrombocytopenia (platelet count <75,000 per mm^3)	10 (8.0)	5 (6.9)
High FLIPI risk score at baseline	Not applicable	39 (54.2)
FL grade	Not applicable	1: 21 (29.2) 2: 39 (54.2) 3A: 12 (16.7)
Treatment history		
Median prior regimens (range)	4 (2–12)	4 (2–12)
Median time since completion of last treatment, months (range)	3.9 (0.7–41.4)	4.3 (0.7–39.1)

Baseline characteristic	Overall population (n=125)	FL population (n=72)
Prior therapy, n (%)		
Rituximab	125 (100)	72 (100)
Alkylating agent	125 (100)	72 (100)
Bendamustine	81 (64.8)	50 (69.4)
Anthracycline	79 (63.2)	51 (72.2)
Purine analogue	42 (33.6)	17 (23.6)
Stem cell transplantation	14 (11.2)	12 (16.7)
Prior therapy to which the disease was refractory, n/total n (%)		
Rituximab	125/125 (100)	72/72 (100)
Alkylating agent	124/125 (99)[a]	72/72 (100)
R-bendamustine	47/60 (78.3)	23/36 (72.2)
R-CHOP	40/56 (71.4)	23/35 (65.7)
R-CVP	29/36 (80.6)	15/20 (75.0)
Bendamustine	61/81 (75.3)	32/50 (64.0)
Refractory to ≥2 regimens	99/125 (79.2)	57/72 (79.2)
Refractory to most recent regimen	112/125 (89.6)	62/72 (86.1)

Key: ANC, absolute neutrophil count; ECOG, European Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; NR, not reported; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisone.
Notes: [a], Refractoriness to two cycles was required to meet the criteria for alkylator-refractory disease. One patient received only one cycle, with no response after this cycle. Refractory defined as lack of response or progression within 6 months from completion of prior therapy; [b], All patients refractory to rituximab and 99% refractory to an alkylating agent; [c], Missing data for four patients.
Source: Gilead 2013[40]; Gopal et al. 2014[34]; Salles et al. 2015[31]

Study 101-02/99

Full details of baseline demographics and clinical characteristics of the 64 patients enrolled in Study 101-02/99 are presented in Appendix M.

As was observed in Study 101-09, patients enrolled to Study 101-02/99 were extensively pre-treated with a median number of four prior therapies (range 1–10).[35] Most patients had received rituximab (97%) or an alkylating agent (91%); more than half of the patients (52%) had previously received an anthracycline, 27 patients (42%) had been treated with a purine analogue, and 17 patients (27%) had prior bendamustine.

Thirty-seven patients (58%) were refractory to their last prior regimen.[35] Although the FLIPI was not reported for the FL cohort of patients enrolled in this study, the high prognostic risk of these patients is shown by the levels of bulky disease presented by these patients. Of 64 patients, 28 (44%) presented with bulky lymphadenopathy, defined as having ≥1 lymph node ≥5cm in diameter. In addition, 24 (38%) patients presented with elevated lactate dehydrogenase (LDH), another important prognostic factor.

Again reflecting the extensive nature of their treatment history, a high proportion of patients enrolled in Study 101-02/99 presented with anaemia (64%) and/or thrombocytopenia (56%) at baseline.[35]

UK & Ireland CUP

Baseline demographic and clinical characteristics of patients included in the CUP are presented in Table 9.

Generally, baseline characteristics of the CUP cohort were similar to patients enrolled in Study 101-09, with the following exceptions: a larger proportion of patients were categorised as high-risk (FLIPI score 3–5) (75% versus 54%); a larger proportion of patients had a performance status (ECOG) score >1 (25% versus 8%); a larger proportion of patients had received previous stem cell transplantation (27% versus 17%); a smaller proportion of patients had disease refractory to the most recent regimen (54% vs 86%).[36]

Table 9: Baseline characteristics of patients in the CUP cohort

Characteristic	**CUP cohort (n=79)**
Median age, years (range)	64 (29–86)
>60 years, n (%)	51 (65)
Gender, n (%)	
Male	40 (51)
Female	39 (49)
ECOG performance score, n (%)	
0–1	59 (75)
2–4	20 (25)
Median NHL duration, years (range)	4.5 (0.4–24.6)
Baseline tumour assessment, n/N (%)	
Refractory	41/76 (54)

Characteristic	CUP cohort (n=79)
Relapsed	35/76 (46)
Ann Arbor staging, n (%)	
1–2	12 (15)
3–4	67 (85)
FLIPI score, n/N (%)	
0–2	19/78 (25)
3–5	59/78 (75)
Response to most recent chemotherapy, n/N (%)	
CR/CRu	19/77 (25)
PR	29/77 (38)
SD	16/77 (21)
PD	13/77 (17)
Median time from last chemotherapy to idelalisib, months (range)	8.6 (0.9–99.2)
Median number of previous chemotherapy regimens (range)	3 (1–13)
Prior rituximab, n (%)	78 (99)
Prior rituximab maintenance, n (%)	51 (65)
Prior alkylator, n (%)	78 (99)
Previous SCT, n (%)	21 (27)

Key: CR, complete response; CRu, unconfirmed complete response; CUP, compassionate use programme; ECOG, Eastern Cooperative Oncology Group; FLIPI, follicular lymphoma international prognostic index; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SCT, stem cell transplantation; SD, stable disease.
Source: Eyre et al. 2017[36]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Study 101-09

The hypothesis and associated statistical methods in Study 101-09 are presented in Table 10.

The primary analyses were conducted on the ITT population. Additional *post-hoc* analyses were conducted for the population of patients with FL. These analyses were carried out at the request of the Committee for Medicinal Products for Human Use (CHMP) and included analyses of demographics, response rates, duration of

response (DOR), PFS, OS and safety data for patients with FL, as per the target population of interest to this submission.[41]

The data presented in this submission are taken from the latest database lock (DBL), of 30th June 2015, which provide a minimum of 31.5 months follow-up in the majority. Data for the FL population from the published DBL of 11th June 2014 (20 months minimum follow-up), which were utilised in the MAIC presented in Section B.2.9, are provided in Appendix N. Health-related quality of life (HRQL) data were not updated in the latest DBL and therefore are presented from June 2014 analyses.

Participant flow data for the ITT population and the FL population, in Study 101-09, are presented in Appendix D. At the latest DBL (30th June 2015), four FL patients (5.6%) were continuing to receive idelalisib. Of those no longer on treatment, the most common reason for discontinuation was progressive disease (55.6%). Of note, three patients discontinued at the request of the investigator as they were referred to undergo SCT.

Study 101-02/99

The primary analysis was conducted on the ITT population. Response rates, exact binomial 95% confidence intervals, and p-values were calculated for the primary efficacy outcome of ORR. Time to response (TTR) and DOR were summarised using the Kaplan–Meier (KM) method.

Participant flow data for Study 101-02/99 is detailed in Appendix D, showing 19 patients completed the planned 48 week duration of Study 101-02 and were enrolled in Study 101-99. Of the 45 patients who discontinued before 48 weeks, the majority was due to progressive disease (51.1%), and half of all patients enrolled in Study 101-99 (n=19) also discontinued treatment for this reason.

UK & Ireland CUP

Data were collected between January 2015 and August 2016 from 46 of 51 approached centres in the UK and Ireland. The median follow-up at the time of analysis was 6.1 months (0.1–18.8 months).

PFS and OS were calculated in standard fashion with follow-up censored at most recent visit or death. Cox regression determined univariate predictors of PFS.

Participant flow data are not fully reported but 24 patients received treatment post-idelalisib. Of the remaining 55 patients, 18 died without further therapy because of progressive disease (n=17) or toxicity (n=1), 35 remained on idelalisib without progression, and two stopped treatment due to toxicity without progression.

Table 10: Summary of statistical analysis for Study 101-09

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study objective: to characterise the clinical activity and safety of idelalisib Hypothesis: that the ORR would be 39% or higher Null hypothesis: that the ORR would be 20% or lower ORR, defined as the proportion of patients who achieved complete response or partial response during treatment with idelalisib	Response rates, exact binomial 95% confidence intervals and p-values (based on the exact binomial test) were calculated for the primary outcome measure. Secondary outcome measures of time to response, duration of response, progression-free survival and overall survival were summarised using the Kaplan–Meier method. If there was a significant degree of non-normality for a continuous endpoint, analysis was performed on log-transformed data or using nonparametric methods, as appropriate. Repeated measures mixed-effects models used to assess mean change from baseline in FACT-Lym score.	Using Simon's two-stage design, a sample size of at least 100 patients provided a power of at least 90% to test the hypothesis against the null hypothesis at a one sided significance level of 0.005.	A missing data point could be due to a number of reasons: a visit occurred but data were not collected or were unusable; a visit did not occur; or a patient permanently discontinued from the study before reaching the window for a visit. In general, values for missing data were not imputed. Patients with inadequate data for an assessment of response were considered to be a non-responder. Standard censoring methods were applied to time to event analyses. Data from patients with non-progressing disease or ≥ 2 consecutive missing tumour assessments before PD or death were censored on the date of the last tumour assessment. Data from surviving patients were censored at the last time the patient was known to be alive. In the FACT-Lym assessment, if ≤50% of item scores were missing, the subscale score was calculated by multiplying the sum of the item scores by the number of items in the subscale, then dividing by the number of non-missing item scores.

Key: FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; ORR, overall response rate; PD, progressive disease.
Source: Gilead 2013[40]; Gopal et al. 2014[34]; Salles et al. 2014[42]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

Studies 101-09 and 101-02/99 were conducted according to principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The accuracy and reliability of the clinical trial data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the Sponsor.

For the pivotal Study 101-09, response endpoints were assessed by both the investigator and an IRC. The IRC included four primary independent board-certified radiologists who evaluated the radiographic images in two reader pairs, a board-certified adjudicating radiologist who resolved any differences between readers, and two independent board-certified oncologists. The radiologists' findings, along with prospectively defined clinical data for each subject (including bone marrow examinations and lymph node or other tissue biopsies), were then reviewed by a board-certified oncologist. A final assessment was based on the combined input of the radiology and clinical review. All reads were performed retrospectively and had no impact on subject management.

All endpoints used in the pivotal study were relevant for the population and are widely used in the haematology clinical trials. While direct comparative efficacy data are not available from the relevant clinical effectiveness evidence, assessment of clinical efficacy associated with previous lines of treatment are available from Study 101-09 and the CUP. These data allow a crude estimate of indirect comparative efficacy (in the absence of trial data for comparator treatments), but do not reflect true PFS (as patients could not have died prior to study enrolment) and are at high risk of selection bias; in the case of Study 101-09, these data are also primarily based on clinician recall. In the case of the CUP, analyses are based on subjective, non-uniform assessment of disease progression. Both analyses should therefore be treated with the necessary caution.

A quality assessment based on a standard checklist for non-randomised controlled trials is presented in Appendix D.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 Study 101-09

Clinical response

The ORR was generally similar for patients whether analysed for the total population (iNHL) or the FL population.

In the total population, the ORR as assessed by the IRC was 57.6% (95% CI: 48.4–66.4), comprising 11 complete responses (CRs) (8.8%) and 60 partial responses (PRs) (48.0%).[43] In the FL population, the ORR (95% CI) was 55.6% (43.4, 67.3) as assessed by the IRC, comprising 10 CRs (13.9%) and 30 PRs (41.7%).[43]

The median DOR (IRC assessed) was 14.7 months in the total population and 11.8 months in the FL population.[43] The median TTR (IRC assessed) was 1.9 months in the total population and 2.6 months in the FL population[31, 34]; time to first CR in the FL population ranged from 1.9 to 19.2 months and median time to PR was 3.3 months (range: 1.6–11.0).[31]

Clinical response outcomes are summarised in Table 11, and the KM plot for DOR in the FL population is provided in Figure 2.

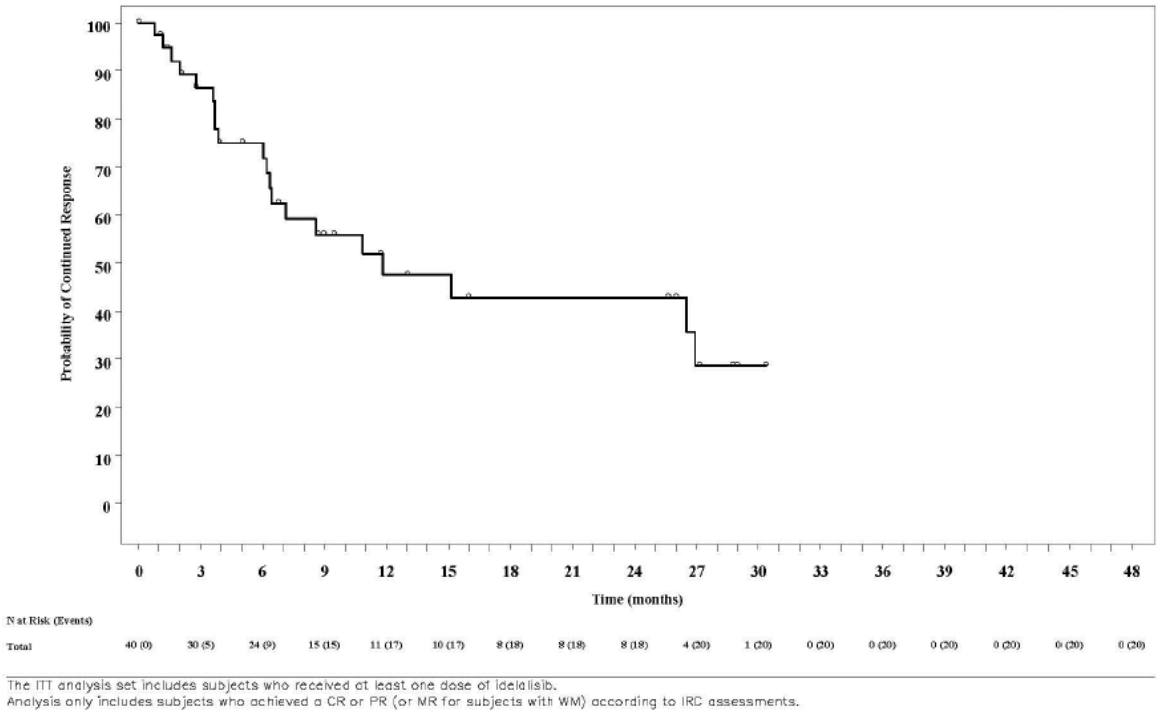
Table 11: Summary of clinical response outcomes, Study 101-09, June 2015 data-cut

	Total population (N=125)		FL population (N=72)	
	IRC assessment	**Investigator assessment**	**IRC assessment**	**Investigator assessment**
Overall response rate				
n (%)	72 (57.6)	75 (60.0)	40 (55.6)	44 (61.1)
95% CI	48.4, 66.4	50.9, 68.7	43.4, 67.3	48.9, 72.4
Best overall response, rate (%)				
CR	11 (8.8)	8 (6.4)	10 (13.9)	6 (8.3)
PR	60 (48.0)	66 (52.8)	30 (41.7)	38 (52.8)
MR	1 (0.8)[a]	1 (0.8)	0	0
SD	41 (32.8)	38 (30.4)	23 (31.9)	19 (26.4)
PD	10 (8.0)	11 (8.8)	8 (11.1)	8 (11.1)

	Total population (N=125)		FL population (N=72)	
	IRC assessment	**Investigator assessment**	**IRC assessment**	**Investigator assessment**
Duration of response				
Events, n (%)	37 (51.3)	44 (58.7)	20 (50.0)	29 (65.9)
PD	34 (47.2)	42 (56.0)	17 (42.5)	27 (61.4)
Death	3 (4.2)	2 (2.7)	3 (7.5)	2 (4.5)
Median DOR, months (95% CI)	14.7 (7.4, 22.2)	13.6 (9.2, 16.7)	11.8 (6.4, 26.9)	9.2 (5.9, 14.9)

Key: CI, confidence interval; CR, complete response; DOR, duration of response; FL, follicular lymphoma; IRC, independent review committee; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.
Notes: [a], Patient with Waldenström's macroglobulinemia.
Source: Gilead 2015.[43]

Figure 2: KM plot for DOR by IRC assessment, Study 101-09, FL population, June 2015 data-cut



Key: DOR, duration of response; FL, follicular lymphoma; IRC, independent review committee; KM, Kaplan–Meier.
Source: Gilead 2015.[43]

Progression-free and overall survival

A summary of PFS and OS for the total population and FL population is presented in Table 12. Both outcomes were very similar across these populations.

Median PFS was 11 months in both populations (11.1 months in the total population; 11.0 months in the FL population) and approximately half of all patients were progression-free at 48 weeks.[43] The KM plot for PFS in the FL population is provided in Figure 3.

Median OS was 38.1 months in both populations and over 80% of all patients were still alive at 48 weeks: 82.5% of patients in the total population and 88.4% of patients in the FL population.[43] This is a clear extension to standard life expectancy for patients with double-refractory FL (currently estimated to be less than 24 months, see Section B.2.13). The KM plot for OS in the FL population is provided in Figure 4.

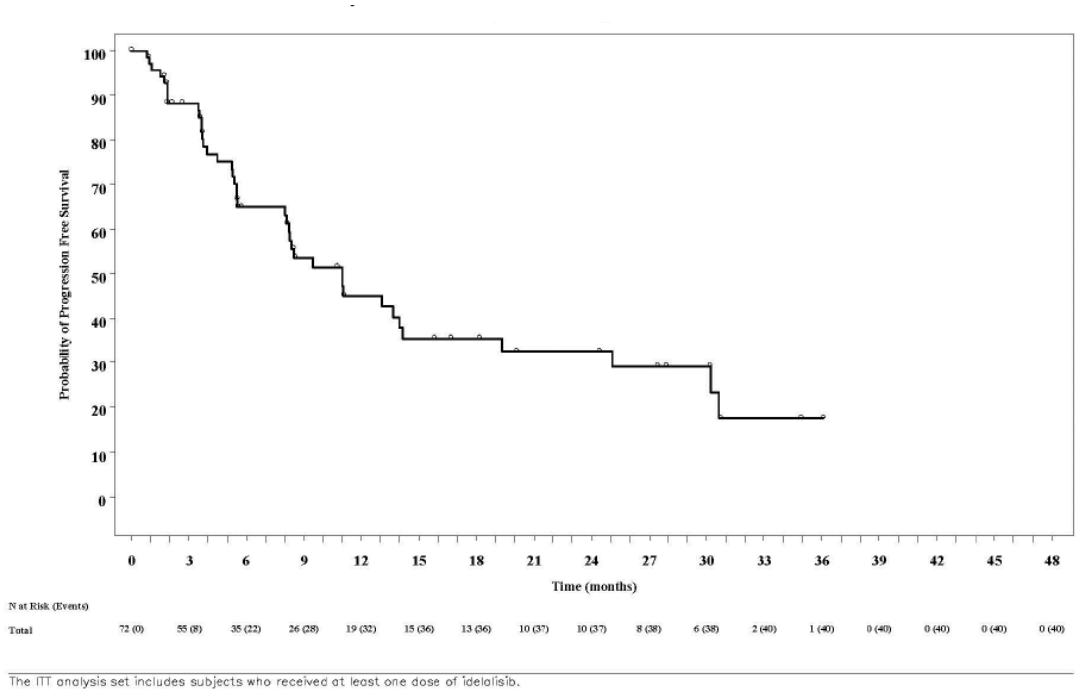
Table 12: Summary of PFS and OS, Study 101-09, June 2015 data-cut

	Total population (N=125)		**FL population (N=72)**	
	IRC assessment	**Investigator assessment**	**IRC assessment**	**Investigator assessment**
Progression-free survival				
Patients with event, n (%)	72 (57.6)	78 (62.4)	40 (55.6)	47 (65.3)
PD	64 (51.2)	70 (56.0)	36 (50.0)	43 (59.7)
Death	8 (6.4)	8 (6.4)	4 (5.6)	4 (5.6)
Median PFS (95% CI)	11.1 (8.3, 14.0)	11.0 (8.3, 16.6)	11.0 (8.0, 14.2)	10.8 (5.7, 14.2)
KM estimate of proportion progression-free, % (95% CI)				
24 weeks	69.5 (60.8, 78.3)	72.7 (64.2, 81.1)	66.8 (55.1, 78.5)	68.5 (57.0, 80.0)
36 weeks	60.6 (51.1, 70.2)	60.0 (50.4, 69.5)	57.5 (44.9, 70.1)	56.1 (43.6, 68.7)
48 weeks	51.1 (41.0, 61.2)	49.8 (39.9, 59.8)	47.2 (34.1, 60.4)	44.7 (31.8, 57.6)
Overall survival				
Died, n (%)	49 (39.2)		24 (33.3)	
Median OS (95% CI)	38.1 (31.5, not reached)		38.1 (37.8, not reached)	

	Total population (N=125)		FL population (N=72)	
	IRC assessment	Investigator assessment	IRC assessment	Investigator assessment
KM estimate of proportion of survival, % (95% CI)				
24 weeks	93.4 (89.0, 97.8)		95.7 (91.0, 100.5)	
36 weeks	85.9 (79.7, 92.1)		89.9 (82.8, 97.0)	
48 weeks	82.5 (75.7, 89.3)		88.4 (80.9, 96.0)	

Key: CI, confidence interval; FL, follicular lymphoma; IRC, independent review committee; KM, Kaplan–Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
Source: Gilead 2015[43]

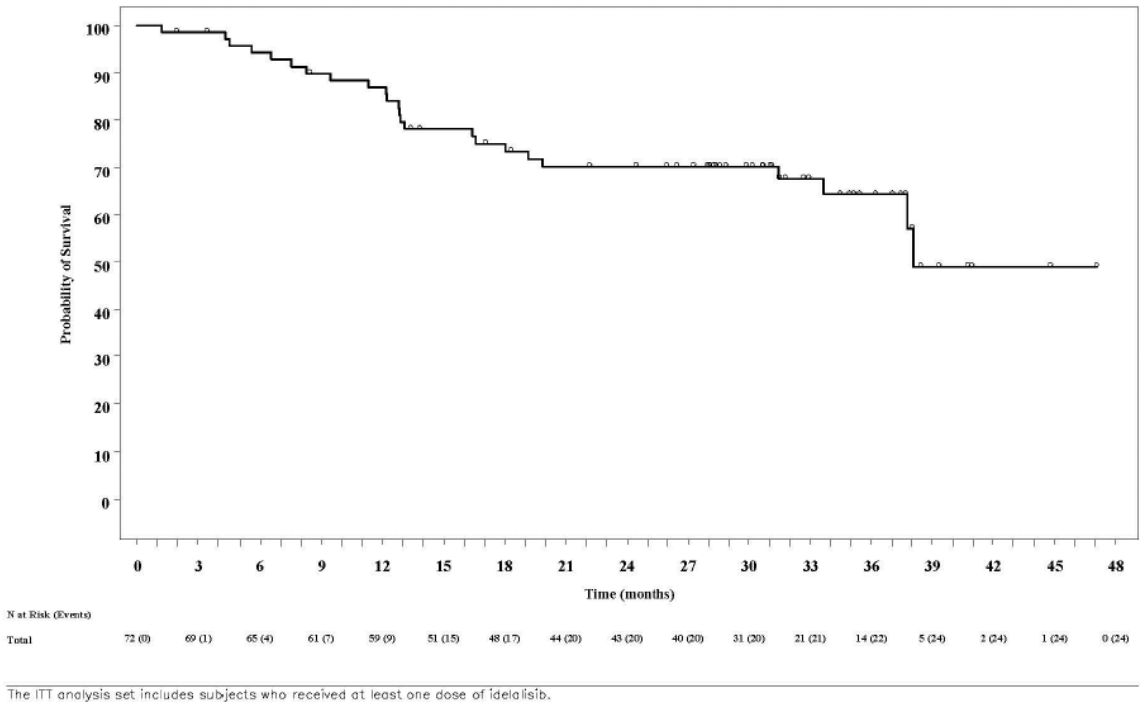
Figure 3: KM plot of PFS by IRC assessment, Study 101-09, FL population, June 2015 data-cut



Key: FL, follicular lymphoma; IRC, independent review committee; KM, Kaplan–Meier; PFS, progression-free survival.

Source: Gilead et al. 2015[43]

Figure 4: KM plot of OS, Study 101-09, FL population, June 2015 data-cut



Key: FL, follicular lymphoma; KM, Kaplan–Meier; OS, overall survival.
Source: Gilead et al. 2015[43]

Efficacy comparison to previous line of therapy

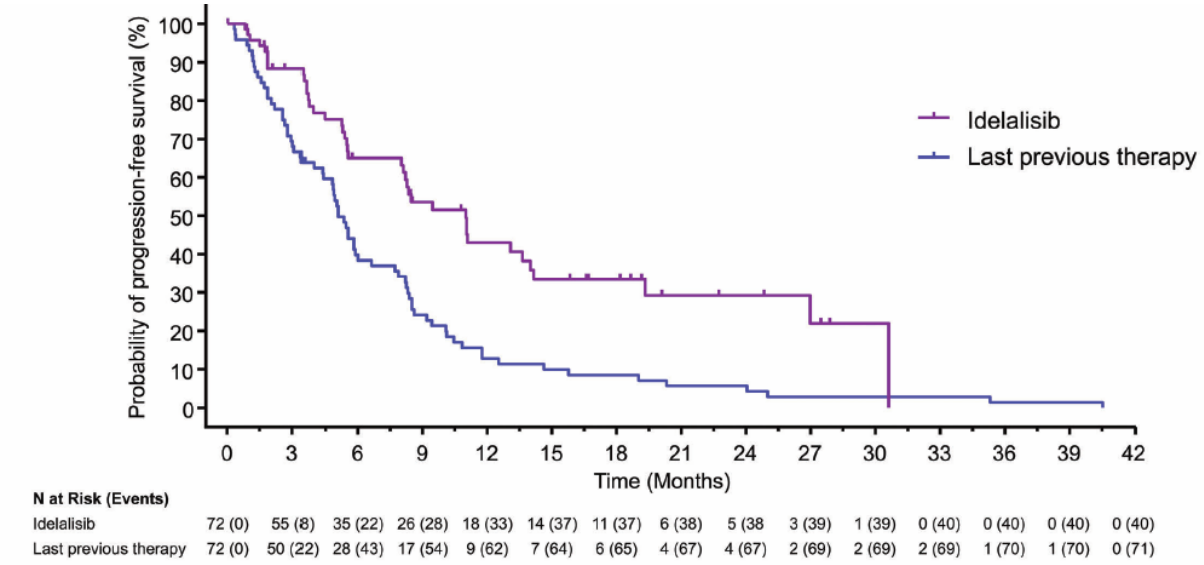
Compared to previous line of therapy, idelalisib demonstrated a clear benefit in the treatment of double-refractory FL.

The ORRs associated with idelalisib in the FL population, (55.6%) and the total population (57.6%), were markedly higher than the ORR associated with previous line of therapy in the total population (23.2%).[40, 43] The median DOR was also considerably increased from 5.9 months to 11.8 months in the FL population and 14.8 months in the total population.[40, 43]

There was a corresponding improvement in PFS with idelalisib treatment, extending median PFS by approximately 6 months in the FL population: 11.0 months versus 5.1 months.[31, 43] Similar results were observed in the total population with idelalisib treatment extending PFS from 4.6 months, with previous line of therapy, to 11.1 months.[35, 43] Although not available for the most recent DBL, overlay of the PFS KM curves for idelalisib (June 2014 DBL) and previous line of therapy for patients

enrolled in Study 101-09 clearly shows the improved clinical benefit of idelalisib monotherapy.

Figure 5: PFS for on study idelalisib versus last prior therapy, FL population, June 2014 data-cut



Key: FL, follicular lymphoma; PFS, progression-free survival.
Source: Salles et al. 2017[44]

When reviewing these data, it is important to acknowledge that patients could not have died on prior treatment if they were enrolled in Study 101-09; therefore, PFS data for previous line of treatment are more reflective of time to progression (TTP) data. Median TTP for idelalisib in Study 101-09 was slightly higher than the median PFS at 11.1 months (KM data provided in Section B.3.3.1).

It is also important to acknowledge that these data are a conservative estimate of the treatment effect that may be expected with chemotherapy regimens at the next line of therapy (where the idelalisib arm is being assessed), given that with each relapse in FL, the disease becomes more resistant and/or refractory to treatment (see Section B.1.3).

HRQL

Overall HRQL was stable or improved for patients treated with idelalisib in study 101-09 (up to 20 months minimum follow-up), and over 90% of all patients reported

an improvement in their assessment of lymphoma-related symptoms at some point in the study.[40]

Among the FL population, the median Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) Total score was 126.8 at baseline and 126.0 at Week 72. Median best change from baseline in FACT-Lym score showed clinically meaningful improvement (based on minimally important difference thresholds) at least once during follow-up for the following subscales: emotional wellbeing, functional wellbeing, additional concerns, trial outcome index score, and FACT: General (FACT-G) total score, as summarised in Table 13.

Table 13: FACT-Lym scores, Study 101-09, FL population, June 2014 data-cut

Median FACT-Lym score	Patients with FL treated with idelalisib 150mg BID, orally (N=72)		
	Best change from baseline	Median time to improvement, months	Minimally important difference
Physical well-being	1.0 (-12.0 to 11.0)	NR (0.0 to 30.6)	2–3
Social/family wellbeing	1.0 (-4.7 to 11.0)	NR (0.0 to 30.6)	2–3
Emotional wellbeing	3.0 (-9.0 to 12.0)	NR (0.0 to 30.6)	2–3
Functional wellbeing	2.0 (-10.0 to 14.0)	NR (0.0 to 30.6)	2–3
Additional concerns	5.0 (-17.0 to 19.0)	4.2 (0.0 to 27.9)	3–5
Total Outcome Index	6.0 (-34.0 to 35.0)	2.8 (0.0 to 30.6)	7–8
FACT-G total score	4.0 (-29.7 to 31.0)	6.9 (0.0 to 30.6)	3–7
FACT-Lym total score	7.5 (-39.0 to 47.0)	1.9 (0.0 to 30.6)	10–11

Key: BID, twice daily; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; FL, follicular lymphoma; NR, not reported.
Source: Salles et al. 2015[31]

B.2.6.2 Study 101-02/99

Clinical response

Clinical response outcomes are summarised in Table 14.

In the total population, the ORR in Study 101-02/99 was 47%, with one complete response and 25 partial responses to idelalisib therapy observed.[35] In the FL population, idelalisib demonstrated a similar ORR of 45%.

The median TTR in the total population was 1.3 months (range 0.7–14 months) from the start of idelalisib treatment, and the median DOR was 18.4 months (range 0.03–34 months). This DOR is longer than that associated with previous line of treatment in Study 101-09 by over 1 year.

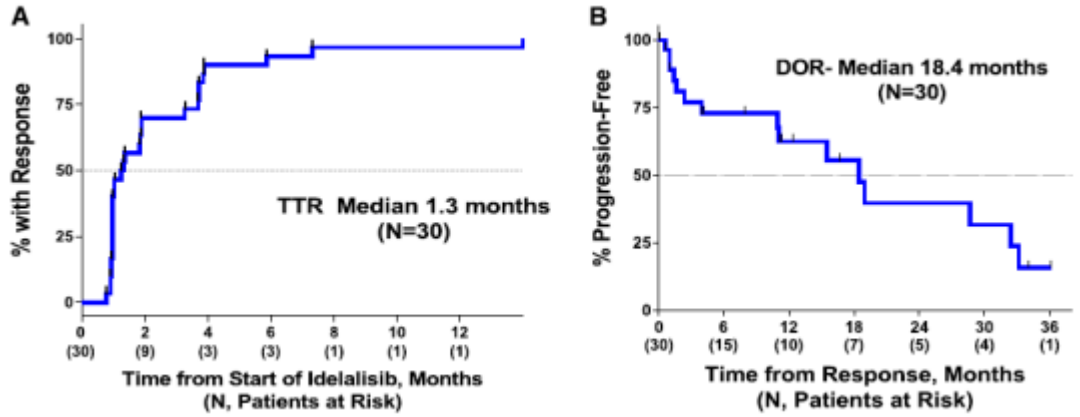
The KM curves for TTR and DOR in all patients responding to idelalisib treatment are presented Figure 6.

Table 14: Summary of clinical response outcomes, Study 101-02/99

	Total population (N=64)	FL population (N=38)
Overall response rate, n (%)	30 (47.0)	17 (45)
CR, n (%)	1 (1.6)	NR
PR, n (%)	25 (39)	NR
SD, n (%)	25 (39)	NR
PD, n (%)	4 (6)	NR
Median TTR (range)	1.3 (0.7–14)	NR
Median DOR (range)	18.4 (0.03–34)	NR

Key: CR, complete response; DOR, duration of response; FL, follicular lymphoma; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.
Source: Flinn 2014[35]

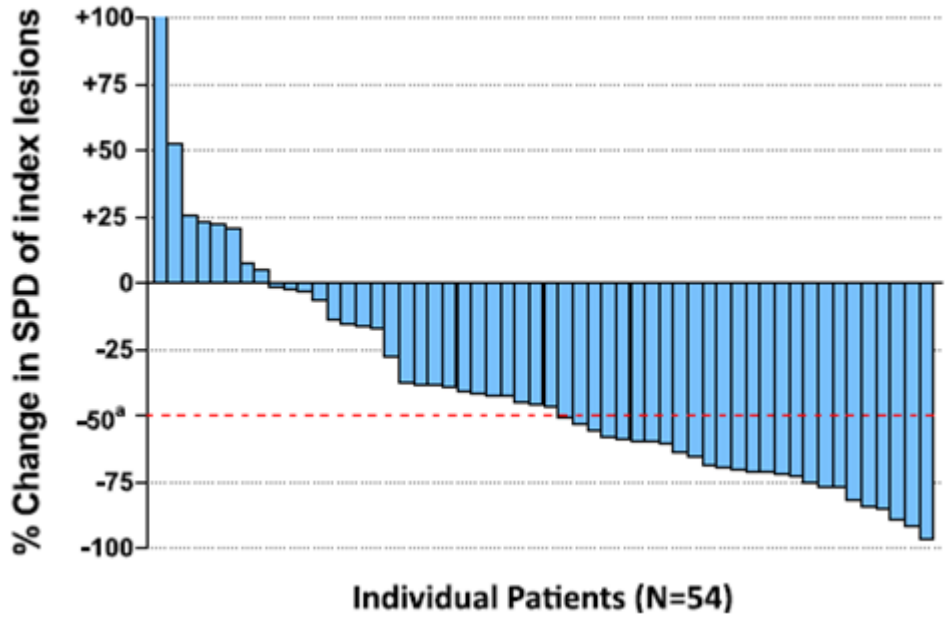
Figure 6: KM plots for (A) TTR and (B) DOR in patients who responded to treatment, Study 101-02/99, total population



Key: DOR, duration of response; KM, Kaplan–Meier; TTR, time to response.
Source: Flinn et al. 2014[35]

Of the 54 patients included in the response evaluable population, 46 (85%) had a reduction from baseline in lymph node size. A waterfall plot of the best overall response with respect to tumour size is presented in Figure 7.

Figure 7: Best overall response during idelalisib treatment in individual patients included in the response evaluable population, Study 101-02/99, total population



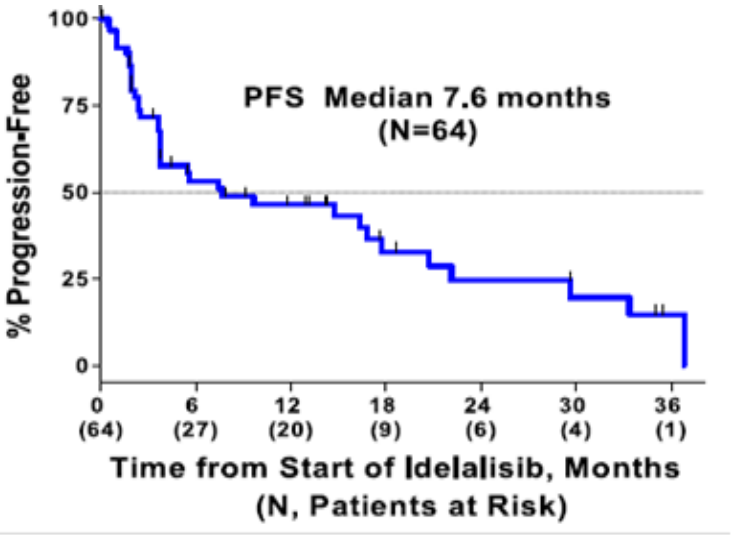
Key: SPD, sum of the products of the perpendicular dimensions.
Notes: The horizontal dashed line (red) indicates the percentage change that represents the criterion for response.
Source: Flinn et al. 2014[35]

Progression-free survival

Median PFS in the total population was 7.6 months (range 0.03–37 months), as presented in Figure 8.

The shorter duration of PFS observed in this trial, compared with that observed in Study 101-09, is likely reflective of differences in the patient populations (higher rates of bulky disease and elevated LDH are observed in the Study 101-02/99 population) enrolled (see Section B.2.3), and the shorter duration of idelalisib treatment (see Section B.2.10).

Figure 8: KM plot of PFS, Study 101-02/99, total population



Key: KM, Kaplan–Meier; PFS, progression-free survival.
Source: Flinn et al. 2014[35]

B.2.6.3 UK & Ireland CUP

Reported response rates for the CUP retrospective cohort are similar to Study 101-09, as summarised in Table 15, supporting the effectiveness of idelalisib in clinical practice.

Median OS was not reached, which is to be expected since median follow-up for the CUP was only 6.1 months (range 0.1–18.8 months)[36] and patients in Study 101-09 achieved a median OS of 38.1 months (Table 15).[43] Of note, eight patients received autologous or allogenic SCT following idelalisib treatment in the CUP, two of which were planned.[36]

Median PFS was 7.1 months (95% CI 5.0, 9.1 months) in the total population, 9.3 months (95% CI 6.0 months, not reached) in patients with FLIPI low- or intermediate-risk disease, 6.6 months (95% CI 3.5, 8.4 months) in patients with FLIPI high-risk disease, and 14.1 months (95% CI 8.1 months, not reached) in patients responding to idelalisib treatment.[36]

The median PFS for the total population was lower than that observed in Study 101-09 (Table 15). This may reflect the differences in the quality of study designs and rigour of progression assessment methods across trials. In standard clinical practice

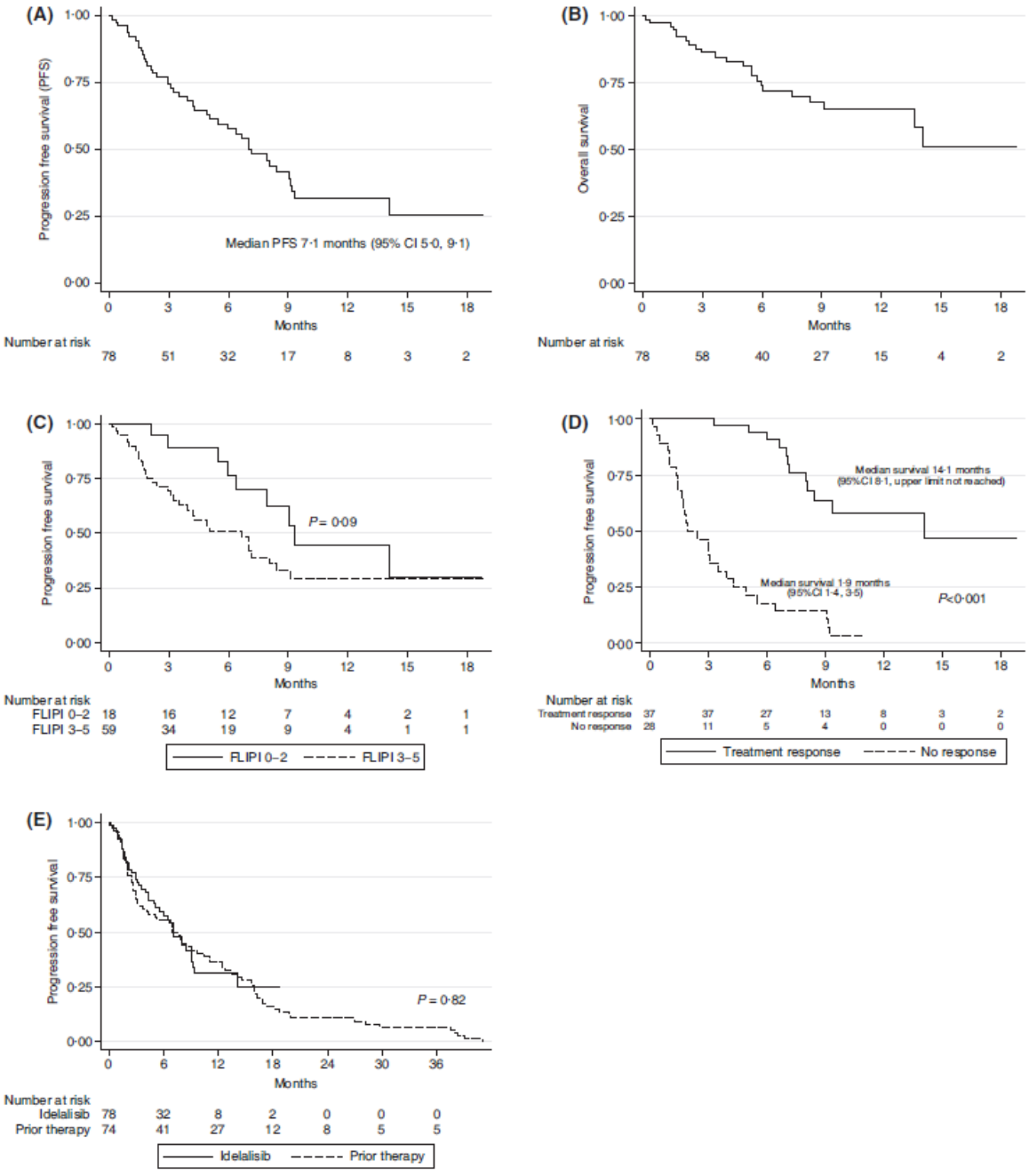
there is no objective, uniform approach to disease progression assessment, and thus, there are inherent errors when assessing PFS in a real-world, retrospective setting. More definitive endpoints such as OS and ORR are more reliable but due to an immaturity of follow-up in the CUP and a relatively short average duration of treatment (see Section B.2.10.3), OS data also have to be interpreted with caution. The higher proportion of patients who had high-risk FLIPI score, and an ECOG performance status score of 2 or more is also a factor, suggesting some patients may have been treated through the CUP as a 'last resort' but with little expectation of long-term benefit. If routinely available, it is expected that patients with double-refractory FL would be immediately treated and therefore would have a better chance of longer-term benefit on receipt of idelalisib in clinical practice.

When compared with PFS of the prior treatment, no difference in PFS was observed (Figure 9E; p=0.82).[36] However, as is the case for Study 101-09, data for the prior treatment line should be considered more reflective as TTP, given patients in the study could not have died on prior treatment. For economic modelling purposesB.3, TTP is estimated from PFS and OS data presented (see Section B.3.3.3) and shows approximately a 1 month estimated extension in TTP with idelalisib: 8.1 months versus 6.9 months.

Table 15: Summary of results, CUP compared to Study 101-09

	Study 101-09 FL population (N=72)	**CUP retrospective cohort (N=65)**
Overall response rate, n (%)	40 (55.6)	37 (57)
CR/CRu, n (%)	10 (13.9)	10 (15)
PR	30 (41.7)	27 (42)
Median PFS, months (95% CI)	11.0 (8.0, 14.2)	7.1 (5.0, 9.1)
Median OS, months (95% CI)	38.1 (37.8, not reached)	Not reached (13.7, not reached)
Key: CR, complete response; CRu, unconfirmed complete response; CUP, compassionate use programme; PR, partial response. **Source:** Gilead 2015[43]; Eyre et al. 2017[36]		

Figure 9: KM plots for (A) PFS, (B) OS, (C) PFS according to FLIPI, (D) PFS according to response and (E) PFS comparison to prior line of therapy, CUP cohort



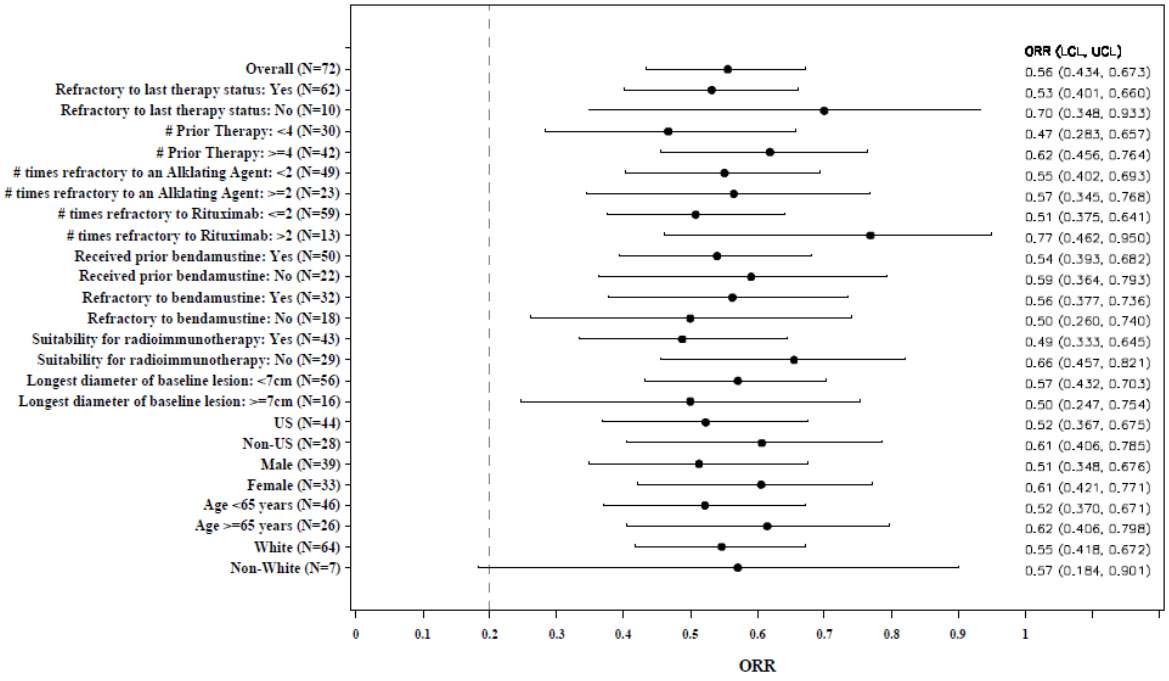
Key: CI, confidence interval; CUP, compassionate use programme; FLIPI, follicular lymphoma international prognostic index; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.
Source: Eyre et al. 2017[36]

B.2.7. Subgroup analysis

In general, results across pre-defined subgroups in Study 101-09 were consistent with those of the total population and favoured idelalisib treatment.[43] The primary endpoint, ORR, was robust with responses observed regardless of number or type of prior regimens, refractoriness, bulky disease, age, race, or gender. A summary of these results is provided in Appendix E.

Similar consistency was observed across subgroups within the FL population. As depicted in Figure 10, for all subgroups (with the exception of the non-white group, which only included seven patients) the ORR was above the 20% threshold defined by the null hypothesis.[43] Interestingly, there was no relationship between response and the degree of prior therapy or the frequency of refractoriness.

Figure 10: Forest plot of ORR by IRC assessment, Study 101-09, FL population, June 2015 data-cut



Key: IRC, independent review committee; FL, follicular lymphoma; LCL, lower control limit; ORR, overall response rate; UCL, upper control limit.
Notes: The dashed vertical line shows the null hypothesis response rate of 20%.
Source: Gilead 2015[43]

Further retrospective analyses that investigated response and survival in FL patients enrolled to Study 101-09, who had also experienced early progression of disease

(defined as starting second-line treatment within 24 months of initial first-line treatment), demonstrated clinical activity of idelalisib in this high-risk and difficult-to-treat group. A summary of these results is provided in Appendix E.

B.2.8. Meta-analysis

As no randomised controlled trials (RCTs) on idelalisib in FL were identified in the searches, a meta-analysis was not performed.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1 Methodology

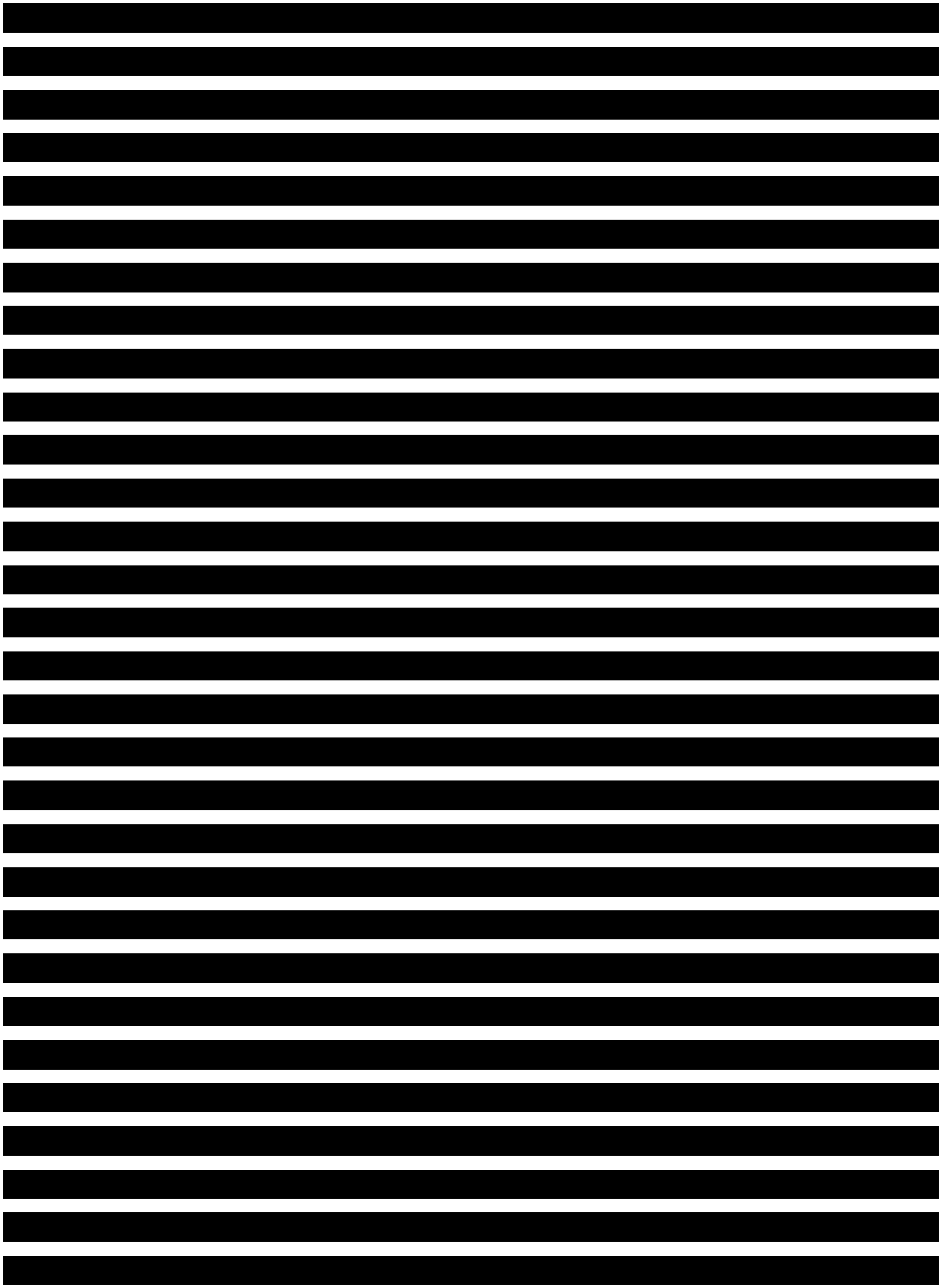
In the absence of an RCT providing an active comparison of idelalisib versus alternative chemotherapy, a further indirect treatment comparison (ITC) (to the comparisons with previous line of treatment presented in Section B.2.6) was conducted utilising UK-specific RWE for the comparator arm.

These analyses were commissioned through the HMRN: a population-based cohort comprising a total population of 3.8 million people covering the former adjacent UK Cancer Networks of Yorkshire and the Humber & Yorkshire Coast. The HMRN was set up in 2004 to provide robust, generalisable data to inform clinical practice and research and collects detailed information about all haematological malignancies in the region. The full HMRN report is provided in Appendix D.

The HMRN identified patients within their cohort who had received ≥2 prior lines of chemotherapy/immuno-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent; or had a relapse within 6 months after receipt of those therapies, and who were subsequently treated. Following identification of these patients, a MAIC was conducted to match to the characteristics reported in the Study 101-09 trial population, using the methodology as described in Signorovitch et al.[45] and referenced in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[46] Summary data, as reported in the primary publication of the FL population of Study 101-09 (June 2014 database lock)[44], was compared with individual patient data (IPD) from HMRN. Outcomes of interest were OS, PFS in patients with a response to treatment, time to next treatment (TTNT), and relative

survival (RS), defined as the interval from the data of the first dose of treatment to death from FL.

B.2.9.2 Results: population data and treatment patterns



[redacted]

Figure 11:

[redacted]

[redacted]

Key: DHAP, dexamethasone, cytarabine, cisplatin; HMRN, Haematological Malignancy Research Network; OS, overall survival; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; RS, relative survival.

B.2.9.3 Results: patients with disease refractory to rituximab and an alkylating agent

[redacted]

Table 16:

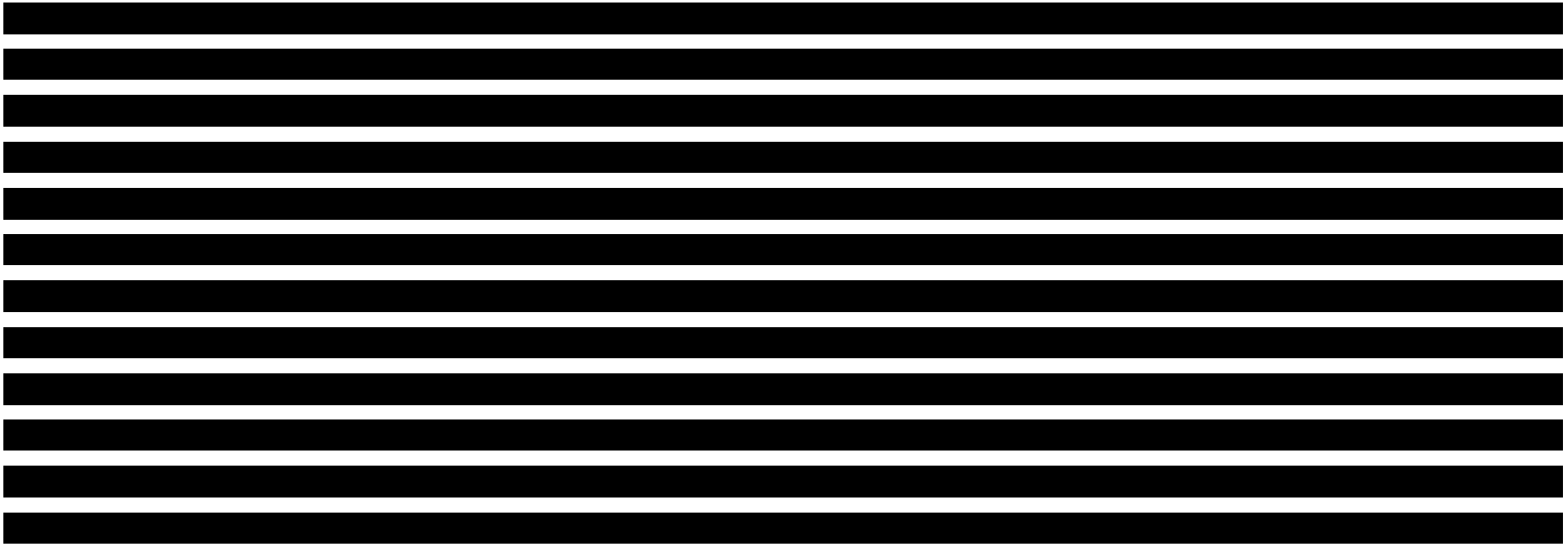
[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: ASCT, autologous stem cell transplantation; HMRN, Haematological Malignancy Research Network; FL, follicular lymphoma.

[redacted]

Figure 12: [redacted]



Key: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CMD, cladribine, mitoxantrone, dexamethasone; DHAP, dexamethasone, cytarabine, cisplatin; ESHAP, etoposide, methylprednisone, cytarabine, cisplatin; FC, fludarabine with chlorambucil; FL, follicular lymphoma; G-CVP, gemcitabine, cyclophosphamide, vincristine, prednisone; GEM-P, gemcitabine, cisplatin, methylprednisone; HMRN, Haematological Malignancy Research Network; ICE, ifosfamide, carboplatin, etoposide; IVE, ifosfamide, epirubicin, etoposide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

B.2.9.4 Results: matching-adjusted indirect comparison

All variables which were common to both datasets were considered for inclusion in the MAIC, namely those presented in Table 16.

[redacted]

Table 17:

[redacted]

[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: HMRN, Haematological Malignancy Research Network; FL, follicular lymphoma.

[redacted]

The respective 2-year OS rate of FL patients treated with idelalisib in the Study 101-09 trial was 69.8% and the 1-year PFS rate was 43.0%, in the data-cut used for MAIC (11th June 2014 DBL).[44] KM plots that show PFS and OS pre- and post-matching are provided in Figure 13.

Figure 13:

[redacted]

Key: HMRN, Haematological Malignancy Research Network; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

B.2.9.5 Limitations and conclusions

There is uncertainty associated with these analyses, primarily stemming from the small sample of FL patients with disease refractory to rituximab and an alkylating agent identified in the HMRN cohort. This is an unavoidable reflection of the rare (equivalent to ultra-orphan status) nature of this disease.

[redacted]

Despite these limitations, the HMRN analyses provides further support for the current lack of SOC and poor survival benefit associated with those treatments that are currently available in clinical practice.

[redacted]

, idelalisib could provide a SOC with proven survival benefit to the high-risk and difficult to treat group of double-refractory FL patients.

B.2.10. Adverse reactions

B.2.10.1 Study 101-09

Study drug exposure

A summary of study drug exposure data from Study 101-09 is presented in Table 18.

Idelalisib is the first PI3K inhibitor to be approved which demonstrated impressive activity and a generally well tolerated safety profile. While idelalisib has proven to be efficacious for patients with CLL and FL, unexpected autoimmune and infectious toxicities have demonstrated the need for careful monitoring of these novel agents which reveal autoimmune type toxicities such as pneumonitis, hepatitis and noninfectious colitis.

In the total population, the median duration on treatment was 6.6 months with 54.4% of patients receiving treatment for at least 6 months and 34.4% of patients receiving treatment for at least 12 months.[43] Similarly, in the FL population, the median duration on treatment was 6.5 months with 51.4% of patients receiving treatment for at least 6 months and 29.2% of patients receiving treatment for at least 12 months.

Table 18: Study drug exposure, Study 101-09, June 2015 data-cut

	Total population (N=125)	FL Population (N=72)
Number of patients exposed, n (%)		
≥1 day	125 (100)	72 (100)
≥2 months	108 (86.4)	61 (84.7)
≥4 months	86 (68.8)	50 (69.4)
≥6 months	68 (54.4)	37 (51.4)
≥12 months	43 (34.4)	21 (29.2)
≥18 months	31 (24.8)	15 (20.8)
≥24 months	21 (16.8)	10 (13.9)
≥30 months	14 (11.2)	6 (8.3)
≥36 months	5 (4.0)	1 (1.4)
≥42 months	2 (1.6)	0
≥48 months	1 (0.8)	0
≥54 months	0	0
Duration on treatment (months)		
Median (range)	6.6 (0.6–48.1)	6.5 (0.6–38.7)

Key: FL, follicular lymphoma; Sd, standard deviation.
Source: Gilead 2015.[43]

Safety profile

An overall summary of safety is presented in Table 19.

The majority of patients enrolled in Study 101-09 experienced at least one AE, many of which were deemed to be treatment-related (Table 19).[43] However, the rate of discontinuation was relatively low (25% of FL patients discontinued treatment due to an AE despite 85% of them experiencing a treatment-related AE), suggesting most were medically manageable. Importantly, cumulative exposure was not shown to markedly increase AE rates, with very few additional AEs observed in the June 2015 data-cut compared with earlier data-cuts, a summary of which is provided in Appendix F. This supports the long-term safety of idelalisib.

Table 19: Overall summary of safety, Study 101-09, June 2015 data-cut

Adverse event	Total population (N=125)	FL population (N=72)
Any AE, n (%)	123 (98.4)	71 (98.6)
Grade ≥3 AE, n (%)	94 (75.2)	48 (66.7)
Treatment-related AE	107 (85.6)	61 (84.7)
Treatment-related Grade ≥3 AE, n (%)	74 (59.2)	41 (56.9)
Any SAE, n (%)	72 (57.6)	36 (50.0)
Treatment-related SAE, n (%)	45 (36.0)	24 (33.3)
AE leading to dose reduction, n (%)	40 (32.0)	22 (30.6)
AE leading to study drug discontinuation, n (%)	36 (28.8)	18 (25.0)
AE leading to death, n (%)	13 (10.4)	6 (8.3)
Death on study drug or within 30 days of last study drug dose, n (%)	13 (10.4)	7 (9.7)
All deaths, n (%)	49 (39.2)	24 (33.3)

Key: AE, adverse events; FL, follicular lymphoma; SAE, serious adverse event.
Source: Gilead 2015[43]

Adverse events

In the total population, the most common AE reported in at least 20% of patients was diarrhoea, which was reported in 60 (48%) patients.[43] Other common AEs included cough and pyrexia, both reported in 40 (32%) patients; fatigue and nausea, both reported in 39 (31.2%) patients; and neutropenia, reported in 36 (28.8%) patients. In the FL population, diarrhoea was also the most common AE, reported in 37 (51.4%) patients. As in the total population, other common AEs included cough, reported in 23 (31.9%) patients; pyrexia, reported in 22 (30.6%) patients; fatigue and nausea, reported in 20 (27.8%) patients; and neutropenia, reported in 17 (23.6%) patients.

The most frequently reported AEs of Grade ≥3 are reported in Table 20.

In both the total population and the FL population, the most common Grade ≥3 AE was neutropenia, occurring in 27 (21.6%) and 16 (22.2%) patients, respectively.[43] Other common Grade ≥3 AEs included diarrhoea and pneumonia, both reported by more than 10% of patients (Table 20).

Table 20: Grade ≥3 AEs reported for ≥2% of patients, Study 101-09, June 2015 data-cut

Adverse event	Total population (N=125)	FL population (N=72)
Patients with any Grade ≥3 AE	94 (75.2)	60 (83.3)
Neutropenia	27 (21.6)	16 (22.2)
Diarrhoea	21 (16.8)	14 (19.4)
Pneumonia	15 (12.0)	8 (11.1)
Alanine aminotransferase increase	11 (8.8)	9 (12.5)
Aspartate aminotransferase increased	8 (6.4)	7(9.7)
Hypokalaemia	9 (7.2)	5 (6.9)
Thrombocytopenia	8 (6.4)	7 (9.7)
Anaemia	7 (5.6)	5 (6.9)
Dehydration	6 (4.8)	6 (8.3)
Dyspnoea	6 (4.8)	3 (4.2)
Colitis	4 (3.2)	1 (1.4)
Febrile neutropenia	5 (4.0)	2 (2.8)
Asthenia	4 (3.2)	4 (5.6)
Hypotension	4 (3.2)	3 (4.2)
Pyrexia	4 (3.2)	1 (1.4)
Renal failure acute	4 (3.2)	2 (2.8)
Abdominal pain	3 (2.4)	1 (1.4)
Confusional state	3 (2.4)	2 (2.8)
Deep vein thrombosis	3 (2.4)	1 (1.4)
Hepatic enzyme increased	3 (2.4)	2 (2.8)
Hypercalcaemia	3 (2.4)	2 (2.8)
Hyponatraemia	3 (2.4)	2 (2.8)
Pleural effusion	3 (2.4)	3(4.2)
Pneumonitis	3 (2.4)	2 (2.8)
Sepsis	3 (2.4)	2 (2.8)
Vomiting	3 (2.4)	3 (4.2)

Key: AE, adverse event; FL, follicular lymphoma.
Source: Gilead 2015[43]

Serious adverse events

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.[43] This rate of SAEs was expected *a priori* in consideration of the Study 101-09 population, which was heavily pre-treated.

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).

Deaths

In total, 13 (10.4%) patients had an AE that resulted in death.[43] The most common of these was pneumonia, three (2.4%) patients and multi-organ failure in two (1.6%) patients. In the FL population, six (8.3%) patients had an AE that resulted in death; fatal AEs were multi-organ failure, acute abdomen, cardiac arrest, cardiac failure, pneumonitis and splenic infarction.

Laboratory abnormalities

Decreased absolute neutrophil count (ANC) was the most frequent haematological laboratory abnormality of Grade ≥3 observed in ≥15% of patients.[43] This was reported in 35 (28.0%) patients, but most of these decreases were transient, isolated events with no specific time of onset. Additionally, decreased lymphocyte count was reported in 20 (16.0%) patients. In the FL population, 16 (22.2%) patients experienced decreased ANC, 15 (20.8%) patients experienced decreased lymphocyte count, and 11 (15.3%) patients experienced decreased leukocyte count.

Grade 1–4 alanine aminotransferase (ALT) was reported in a total of 62 (49.6%) patients, with 16 (12.8%) reporting Grade ≥3 ALT.[43] Patients with Grade 1–2 ALT could continue idelalisib treatment, and patients with Grade ≥3 elevations were managed with drug interruption. Grade 1–4 aspartate aminotransferase (AST) was reported in a total of 47 (37.6%) patients, with 11 (8.8%) patients reporting Grade ≥3 AST. In the FL population, eight (11.1%) patients reported Grade ≥3 ALT, and the same number of patients (n=8) reported Grade ≥3 AST.

Of note, in patients with baseline anaemia and thrombocytopenia, clinically favourable changes in haemoglobin level and platelet count were observed during idelalisib treatment, respectively; ANC also increased slightly in patients with baseline neutropenia.[40]

B.2.10.2 Study 101-02/99

Safety profile

In Study 101-02/99, the median duration of idelalisib treatment was 3.8 months (range 0.3–41 months).[35]

AEs leading to idelalisib discontinuation included serum AST/ALT elevations in four (6.3%) patients, pneumonia in three (4.7%) patients, and diarrhoea, acute renal failure and thrombocytopenia in two (3%) patients each.

Adverse events

AEs in ≥10% of patients are presented in Table 21. AEs and laboratory abnormalities were graded as in Study 101-09. Most AEs were Grade 1 to 2 in severity, and all were expected *a priori*, reflecting the underlying disease and treatment history, as well as the known risks associated with idelalisib treatment.

Table 21: AEs and laboratory abnormalities (at any grade) during idelalisib treatment in ≥10% of patients in the Phase I dose-ranging and extension study

Event of abnormality	Patients treated with Idelalisib (N=64)	
	Any grade, n (%)	Grade ≥3, n (%)
Diarrhoea	23 (35.9)	6 (9.4)
Fatigue	23 (35.9)	2 (3.1)
Nausea	16 (25.0)	1 (1.6)
Rash	16 (25.0)	2 (3.1)
Chills	13 (20.3)	0
Pyrexia	13 (20.3)	2 (3.1)
Cough	12 (18.8)	1 (1.6)
Pneumonia	12 (18.8)	11 (17.2)
Upper respiratory tract infection	11 (17.2)	0
Peripheral oedema	9 (14.1)	2 (3.1)
Constipation	8 (12.5)	0
Insomnia	8 (12.5)	0
Night sweats	8 (12.5)	0
Vomiting	8 (12.5)	0
Haematological laboratory abnormalities		
Decreased neutrophils	28 (43.8)	15 (23.4)
Decreased haemoglobin	20 (31.3)	3 (4.7)
Decreased platelets	16 (25.0)	7 (10.9)

Event of abnormality	Patients treated with Idelalisib (N=64)	
	Any grade, n (%)	Grade ≥3, n (%)
Chemical laboratory abnormalities		
Increased AST	34 (53.1)	13 (20.3)
Increased ALT	31 (48.4)	15 (23.4)
Increased alkaline phosphatase	25 (39.1)	3 (4.7)
Increased bilirubin	12 (18.8)	2 (3.1)
Increased glucose	25 (39.1)	1 (1.6)
Decreased glucose	13 (20.3)	1 (1.6)

Key: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Source: Flinn et al. 2014[35]

The most frequent AEs or laboratory abnormalities at Grade ≥3 were pneumonia (17.2%), diarrhoea (9.4%), decreased neutrophils (23.4%), decreased platelets (10.9%), increased ALT (23.4%) and increased AST (20.3%).[35] There was no clear relationship between the idelalisib dose regimen and AEs or laboratory abnormalities.

Serious adverse events

The most common SAEs included pneumonia in 11 (17.2%) patients and acute renal failure, diarrhoea, febrile neutropenia and pulmonary embolism in four (6%) patients each.

Deaths

There were two deaths in the primary study, both patients had previously discontinued due to pneumonia. There was an additional death in the extension study in a patient who developed bowel obstruction, sepsis and acute renal insufficiency.[35]

Laboratory abnormalities

In the initial dose escalation, one patient had Grade 3 elevation in hepatic transaminases while receiving 350mg twice daily (BID), leading to the suspension of enrolment at that dose. A further four patients had Grade ≥3 AST/ALT elevations occurring with three different dosing regimens: 150mg BID (n=1), 200mg BID (n=2) and 300mg QD (n=1).[35] All of these serum transaminase abnormalities were dose

limiting toxicities because they occurred within the first 28 days of the start of idelalisib therapy.

Asymptomatic transaminase elevations occurred in 31 (48%) patients, 16 (25%) of which were Grade ≥3 in severity.[35] Grade 1 and 2 elevations were transient and reverted to normal despite continued idelalisib dosing. Of the 16 patients with Grade ≥3 elevations, eight were re-challenged with idelalisib, and six (75%) had no recurrence. The Grade ≥3 elevations occurred with a median onset of 5.3 weeks (range 2–9 weeks), were managed with temporary interruption of idelalisib and resolved to Grade ≤1 in a median of 3.7 weeks.

Increases in patients with absolute lymphocyte count were occasionally noted, particularly in patients with small lymphocytic lymphoma (SLL). A threefold or greater increase in absolute lymphocyte count was found in 15 patients overall and seven out of 38 (18%) patients with FL.

Consistent with the results from Study 101-09, trends to improvements in baseline cytopenia's were observed in the Phase Ib study, especially for anaemia.[35]

B.2.10.3 UK & Ireland CUP

The median duration on treatment was 4.3 months (range 0.1–18.8 months); this is 2.2 months less that the median duration on treatment in the FL population of Study 101-09 (6.5 months [range 0.6–31.0]).[36]

Idelalisib was well tolerated, with no AEs reported in 66% of patients (although this could be reflective of a lack of recording of mild events). In accordance with Study 101-09, common AEs were non-neutropenic infection and bronchial infection.

Grade 3 to 4 diarrhoea/colitis was noted in five patients and Grade 3 to 4 pneumonitis in four patients after two cycles (n=3) and six cycles (n=1); one was associated with cytomegalovirus (CMV) reactivation. Of the 79 patients under observation, idelalisib was stopped permanently in seven due to toxicity, two of whom had not progressed. The majority of Grade 3 to 4 AEs were managed with supportive care, temporarily withholding idelalisib and dose reduction.

B.2.10.4 Early access programme

In patients with refractory FL treated with idelalisib within the EAP in Austria, Belgium, Greece and Spain (n=66), idelalisib monotherapy was well tolerated.[37] Only six patients (9.1%) reported an SAE, regardless of causality. These included one each of febrile neutropenia, neutropenia, diarrhoea, gastrointestinal inflammatory disorder, pancytopenia, progressive disease, liver enzyme elevation, hypotension and colon adenocarcinoma.

B.2.10.5 Additional evidence on safety

In addition to the trial data presented, the idelalisib summary of product characteristics (SmPC) describes AEs recorded across a number of different studies (two Phase III and six Phase I or II studies across chronic lymphocytic leukaemia [CLL] and iNHL). The full SmPC is provided in Appendix C, and a summary of the 'Undesirable effects' section of the SmPC is provided in Appendix F.

It should be acknowledged that three Phase III clinical trials investigating the use of idelalisib, in combination with chemotherapy for the treatment of first-line CLL, and other indications were stopped in 2016 following reports of an increased risk of death and higher incidence of SAEs with this combination. Following a comprehensive review by the Pharmacovigilance Risk Assessment Committee (PRAC), the CHMP confirmed that the existing marketing authorisations for idelalisib (Table 2) should be maintained as the benefit was seen to outweigh the risk of side effects in the current indications.[47]

B.2.10.6 Safety overview

Study 101-09 provides the principal safety data supporting the use of idelalisib monotherapy for the treatment of patients with double-refractory FL. Idelalisib has been shown to have an acceptable safety and tolerability profile in this population in consideration of its clinical benefit:

- AEs were manageable and reversible in the majority of cases, requiring minimal medical intervention and supportive care.
- The most frequently reported Grade ≥3 AEs, such as neutropenia, diarrhoea, pneumonia and elevated aminotransferase, were anticipated *a priori* in light of

common risks associated with idelalisib and in the context of an extensively pre-treated population.
- Clinically favourable changes were observed in patients with baseline myelosuppression (anaemia, thrombocytopenia and neutropenia).
- A safety profile consistent over long-term treatment with similar rates of common AEs in all patients and those receiving idelalisib for at least 1 year.

These findings were supported across the supportive studies (Study 101-02/99 and the CUP). Although a safety signal was flagged to the European Medicines Agency (EMA) in 2016, this was based on findings from trials of idelalisib in combination therapy for the treatment of non-FL indications at earlier lines of therapy. [47] The indication of interest to this submission (Zydelig as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment) did not change at any point during the EMA review process and remains unchanged, that is, maintained positive benefit-risk profile.

B.2.10.7 Relevance of the safety findings to clinical practice

Safety findings from clinical trials are consistent with one another and with clinician feedback from current idelalisib monotherapy use in clinical practice. In the CUP study, idelalisib was shown to be well tolerated when used in clinical practice across the UK and Ireland.

As with other cancer therapies, treatment with idelalisib should be prescribed by a physician experienced in the use of anticancer therapies, and patients should be regularly monitored for signs or symptoms of common AEs. Appropriate precautions to be followed by healthcare professionals and patients, in light of the potential risks associated with idelalisib treatment, are clearly outlined in its SmPC and a risk management plan for the safe use of idelalisib, detailed in Appendix F.

B.2.11. Ongoing studies

A dose optimisation study of idelalisib monotherapy in adult patients with previously treated FL is ongoing with a primary objective of evaluating efficacy and tolerability of idelalisib 150mg BID versus 100mg BID (NCT02536300).

However, with a primary completion date of August 2021 and an estimated study completion date of May 2023, data are not anticipated to be available within the next 12 months.

B.2.12. Innovation

Idelalisib is the first PI3Kδ inhibitor to be authorised globally. It produces clinically meaningful response even in patients with high-risk FL that is refractory to rituximab and alkylating agents. Idelalisib is thus the first agent to be specifically licensed for use in double-refractory FL and can provide a SOC treatment for these patients, representing a paradigm change in the management of this difficult to treat disease as it offers a different mode of action for treatment of patients who have disease that has demonstrated a lack of good response to immunochemotherapy. The side effect profile and oral administration also contrasts with the usual chemotherapy administered for FL.

While the clinical and HRQL benefit of idelalisib will mostly be captured in the quality-adjusted life years (QALY) calculation, the convenience of an oral treatment (compared to regular IV chemotherapy) may not be fully captured but should be considered a further benefit of idelalisib to patients, carers and health services alike. Furthermore, the extended DOR may allow patients to return to normal living for a period of time, markedly improving their quality of life, and the lives of their families and carers. HMRN data show 35% of all patients diagnosed with FL in the UK are under 60 years of age[4], so this symptom-free period may even include a return to work for some. The hope that an effective therapy gives patients with no proven treatment option (and their family and friends) should also not be overlooked.

B.2.13. Interpretation of clinical effectiveness and safety evidence

The double-refractory FL population represents a small (equivalent to orphan status in England) but extremely high-risk patient group, with significant clinical unmet need. These patients have rapidly-progressing disease, characterised by short-term response to treatment which currently only consists of repeat cycles of chemotherapy-based treatment, upon which they have already relapsed or become refractory to (see Section B.1.3).

Idelalisib provides a solution to this clinical unmet need, being the first agent to demonstrate a clinical benefit including durable disease control in patients with double-refractory FL within a clinical trial setting. Idelalisib could profoundly change the life of patients in England with highly refractory FL, and align care with that available to Scottish and Welsh patients with FL.

Principal findings from the clinical evidence base

Key evidence supporting the use of idelalisib is taken from the pivotal Phase II Study 101-09, within which 72 FL patients with disease refractory to rituximab and an alkylating agent were treated with idelalisib. Despite the poor prognosis of double-refractory patients, 55.6% responded to treatment and the median DOR was 11.8 months. This represented approximately a 20% increase in the ORR and a 6-month extension in DOR compared to previous line of treatment. This is a noteworthy increase that goes against the commonly observed reduction in response and remission periods with each progressive line of treatment, and can even be considered a conservative estimate as generally the disease becomes more aggressive and less responsive to treatment with each progression.[7, 8] A survival benefit was also observed with idelalisib treatment. In the FL population, the median PFS was 11.0 months. This was greater than double and, in absolute terms, almost 6 months longer than that observed with previous line of treatment (5.1 months). Again, this observation is a conservative estimate as a reduction in PFS periods with each line of treatment is typically observed.[9] The median OS was 38.1 months and the proportion of patients alive at 2 years was 69.8%; this is a marked extension to the current life expectancy (Table 22) of these difficult to treat patients. Importantly, idelalisib treatment was also associated with stable and potentially improved patient HRQL, demonstrating that contrary to chemotherapy treatment[27], daily activity is not significantly impaired with idelalisib.

Supportive evidence of the clinical effectiveness of idelalisib and its comparative effectiveness to current treatment is available from several data sources. In the supportive Phase 1b Study 101-02/99, 45% of relapsed refractory FL patients (n=38) responded to idelalisib treatment and the median DOR across all patients enrolled (iNHL, n=64) was 18.4 months. In a CUP of real world use of idelalisib to treat relapsed or refractory FL in the UK and Ireland, 57% of patients (n=65) responded to

idelalisib treatment, and the median PFS in responding patients was 14.1 months. Eight patients also went onto receive SCT following idelalisib treatment, two of which were planned. While evidence is not sufficient for consideration of a formal subgroup of patients suitable to receive SCT and for whom idelalisib could be used to induce remission before transplantation, these observations (along with the three patients referred to undergo SCT post-idelalisib in Study 101-09) suggest this is a possibility.

Although comparison to previous line of treatment within the CUP cohort showed no difference in median PFS across all patients (i.e. irrespective of response), these data should be treated with caution (see Section B.2.5 and Internal validity in this section). Further comparative effectiveness data are available from a MAIC using Study 101-09 data and HMRN data of FL patients with disease refractory to rituximab and an alkylating agent, who received further chemotherapy treatment in UK clinical practice. The estimated improvement in the proportion of patients alive at 2 years (based on these analyses) was a remarkable 50%; an 18.3% estimated improvement in the proportion of patients alive at 1 year was also observed.

Internal validity

The primary clinical evidence for idelalisib in the double-refractory FL setting is derived from a single arm study (Study 101-09). The lack of randomisation to a control arm in this study can be explained by the absence of SOC for these patients; a placebo arm would not have been suitable due to ethical concerns. Indirect estimates of comparative efficacy are available through comparison with preceding line of treatment. However, clinical effect of previous line of treatment was primarily based on clinician recall and thus should be interpreted with the relevant caution. It should also be acknowledged that PFS associated with previous line of treatment is better aligned to the standard definition of TTP in both Study 101-09 and CUP analyses, and is at high risk of selection bias. It is also an estimate of treatment effect at an earlier position in the treatment pathway than the idelalisib comparison. In the HMRN analyses, some variables had to be excluded from the MAIC.

Further evidence to corroborate the Study 101-09 findings is available from Study 101-02/99, the CUP and the HMRN dataset and subsequent analyses. Generally consistent effects are observed across datasets; any differences that are observed in absolute estimates of effect are explained by differences in study methodologies and

duration, and patient populations. Study 101-09 provides the most robust evidence base to support treatment decision making in the double-refractory FL arena to date.

The small sample sizes of individual trials should also be acknowledged, but this is an unavoidable consequence of the rare nature of this disease. Even when patients were retrospectively identified at diagnosis of disease refractory to rituximab and an alkylating agent, as was the case in the HMRN analyses, only 26 patients were found over a period of 9 years in the large Yorkshire and Humber region of the UK. This represented 2.6% of all newly diagnosed FL patients (n=1,007) within the same region and period. Budget impact assessment estimates that 385 people will be living with double-refractory FL by the end of 2018 (see separate document); double-refractory FL is thus equivalent to ultra-orphan status (<1 per 50,000 people).

External validity

Study 101-09 and the Study 101-09/HMRN comparison provide evidence to support the use of idelalisib in double-refractory FL, the target population for reimbursement in NHS England. The CUP study provides RWE to support the use of idelalisib in a UK-specific setting. The HMRN analyses also provides estimates of comparative effectiveness to current treatments used to treat double-refractory FL patients in NHS England. Clinical consultation confirms these data provide a generally applicable evidence base on which to make treatment decisions for double-refractory FL patients in clinical practice.[9]

Assessments of clinical benefit across studies were generally conducted in line with established methodologies and are directly applicable to routine clinical practice. They are also reflective of the health benefits idelalisib is expected to offer patients; that is, a good chance of durable response and improved survival benefit with minimal harm.

In summary, despite some limitations, the breadth and general consistency of data from the clinical evidence base of idelalisib for the treatment of double-refractory FL supports the validity of the overall conclusions. Indeed, the conclusions of the CHMP that the benefits of idelalisib monotherapy outweigh the risks in this area of unmet medical need are reinforced by the data that have become available since market authorisation; all of which are used to support the clinical- and cost-effectiveness case presented in this submission.

End of life considerations

As described in Section B.1.3, patients have substantially reduced life expectancy with increasing resistance to treatment.[8] FL patients with double-refractory disease have a life expectancy that typically falls below 24 months with current treatment options. In the HMRN dataset, the 2-year OS rate in FL patients with disease refractory to rituximab and an alkylating agent and treated with chemotherapy at third-line in NHS England was [redacted] when patient characteristics were adjusted to match those of the study 101-09 FL population, the 2-year OS rate was [redacted]

The clinical evidence base presented in this submission demonstrates that idelalisib is likely to offer a significant extension to life compared with current NHS treatment with study 101-09 and HMRN-data based MAIC showing a [redacted] in 2-year OS rates with idelalisib versus chemotherapy (see Section B.2.9).

Idelalisib for the treatment of double-refractory FL is therefore thought to meet NICE end of life criteria, as summarised in Table 22.

Table 22: End of life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months.	UK HMRN data: 2-year OS rate in FL patients with disease refractory to rituximab and an alkylating agent and treated with chemotherapy at third-line was [redacted] 2-year OS rate in FL patients with disease refractory to rituximab and an alkylating agent and further characteristics matched to the Study 101-09 population was [redacted]	Section B.2.9.3 Page 59 Section B.2.9.4 Page 61
	Median OS in FL patients with disease refractory to rituximab and an alkylating agent and treated with chemotherapy at third-line was [redacted] months.	Section B.2.9.3 Page 59
	Median OS in FL patients with disease refractory to rituximab and an alkylating agent and further characteristics matched to the Study 101-09 population was [redacted] months.	Section B.2.9.4 Page 61
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	Study 101-09: 2-year OS rate in FL patients with disease refractory to rituximab and an alkylating agent was 69.8% (June 2014). Median OS in FL patients with disease refractory to rituximab and an alkylating agent was 38.1 months (June 2015).	Section B.2.9.4 Page 60 Section B.2.6.1 Page 44
	Study 101-09/HMRN MAIC: 2-year OS rate in FL patients with disease refractory to rituximab and an alkylating agent was [redacted] with idelalisib versus chemotherapy: 69.8% vs [redacted]	Section B.2.9.4 Page 61
	Estimated life years gained with idelalisib range from 0.70 to 3.04 years in economic modelling.	Section B.3.7.1 Page 143 Section B.3.8.3 Pages 149-150
Key: HMRN, Haematological Malignancy Research Network.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search for economic evaluations of treatments for refractory FL, first conducted in February 2014, was updated to inform this submission in February 2018. The methods and results from both the original systematic review and its update are documented in Appendix G. No economic evaluations of idelalisib for double-refractory FL were identified by either search.

Not identified by the systematic search of published literature, but known to the company, are the economic evaluations underpinning dossier submissions to the Scottish Medicines Consortium (SMC), the National Centre for Pharmacoeconomics (NCPE) in Ireland and the All Wales Medicines Strategy Group (AWMSG) for idelalisib monotherapy to treat FL patients. Idelalisib monotherapy has been recommended within its licensed indication for FL patients in each of these jurisdictions.[32, 33, 48] In each case, economic analysis to inform HTA-centred decision making was based on a clinical effectiveness comparison to prior treatment as a proxy for current care for chemotherapy-eligible patients, and to Study 101-09 post-progression survival only as a proxy for current care for those patients unable to tolerate chemotherapy.

As described throughout Section B.3, the base case economic analysis we present is designed to be consistent with submissions that have led to recommendations for idelalisib to treat double-refractory FL patients in Scotland, Ireland and Wales in recent years[32, 33, 48], while also improving upon them by harnessing results from an updated Study 101-09 dataset. In addition, this submission has the benefit of additional economic scenarios driven by clinical comparisons to (i) the latest available data on outcomes for patients in this indication from the HMRN database, and (ii) published real-world NHS England evidence from the UK and Ireland compassionate use programme (CUP) to make idelalisib available to eligible FL patients.

B.3.2. Economic analysis

B.3.2.1 Patient population

Idelalisib monotherapy is licenced by the EMA to treat adults with FL that is refractory to two prior lines of treatment.[49-51] Throughout B.3, we use the term "double-refractory" as shorthand for this treatment history. In line with the Final Scope for this appraisal and the patient group in Study 101-09, the pivotal trial supporting regulatory approval[34], the economic analysis submission focuses on these patients, with consideration of the different treatment options and likely clinical outcomes for patients for whom chemotherapy (i) is and (ii) is not suitable.

In the absence of RCT or other comparative data, the approach to cost-effectiveness analysis harnesses available data from 177 patients across three key clinical data sources identified in Section B.2 to address the decision problem:

- The 72 double-refractory FL patients who received idelalisib monotherapy in Study 101-09
- The 26 double-refractory FL patients who had received further treatment in the latest available HMRN database[17]
- The 79 double-refractory FL patients who received idelalisib monotherapy in the 2015–16 CUP for idelalisib for UK and Ireland patients, reported by Eyre et al.[36]

The use of patient outcomes from each of these sources across different comparative analyses enables confidence in the estimated cost-effectiveness of idelalisib for double-refractory FL patients to be built, mitigating some of the decision uncertainty associated with cost-effectiveness estimates based on single-arm clinical data.

The core clinical effectiveness comparisons informing cost-effectiveness results in this submission can be summarised with reference to the treatment options of patients and clinical data sources informing comparative analysis.

To compare idelalisib versus chemotherapy, in people for whom chemotherapy is suitable:

Comparison A (Base case): 101-09 / 101-09

"Comparison A" compares clinical outcomes for Study 101-09 idelalisib patients with clinical outcomes on the previous line of therapy for the same patient group. Table 23 summarises clinical outcomes data informing this comparison. Comparison A is consistent with that used to inform cost-effectiveness analyses for chemotherapy-suitable patients in submissions to the SMC, the NCPE and the AWMSG that have led to access to idelalisib for double refractory FL patients in Scotland, Ireland and Wales in recent years[32, 33, 48]; yet it is also an improvement, as it is based on the more recent 30 June 2015 Study 101-09 database lock.

Data on both time on treatment (ToT) and TTP on previous treatment are available from Study 101-09. Comparison of these clinical outcomes across treatment lines may be viewed as the most robust proxy available for comparison to standard care for chemotherapy-suitable patients. As described in Section B.1.3, the regimens and agents available for use in subsequent lines of therapy are similar to those available in previous lines of therapy. With no standard of care and variation in clinical practice, it is nearly impossible to select one appropriate comparator; the selection of treatments received in the previous line of therapy by Study 101-09 patients may represent the most appropriate comparator for idelalisib for chemotherapy-eligible double-refractory FL patients. In addition, unobserved individual heterogeneity across intervention and comparator groups can be considered minimal, as data for each treatment arm are from the same patient sample. Of course, this approach is inherently conservative. At previous therapy, patients are less pre-treated, closer to time of diagnosis, with disease that is likely to be less severe. Using outcomes data from these patients as proxy for a contemporaneous comparator implicitly biases against the intervention. To address this, following submissions to the SMC, the NCPE and the AWMSG, we apply a hazard ratio (HR) to prior therapy clinical data where they are treated as current comparator data, as set out in Sections B.3.3.1 and B.3.3.2.

Patients in Study 101-09 had, by definition, survived any previous therapy; this has implications for survival comparisons both pre-and post-disease progression.

Furthermore, pre-progression mortality is estimated from the few pre-progression death events in Study 101-09 (4 in 30 June 2015 dataset), as reported in Sections B.3.3.1 and B.3.3.2.

Post-progression survival (PPS) is assumed equal across model arms. Equivalence in PPS across model arms implies no benefit for idelalisib beyond delaying disease progression. This likely underestimates the relative survival benefit of idelalisib, and the base case cost-effectiveness results presented in Section B.3.7.1 can therefore be viewed as conservative.

Table 23: (Base case) Comparison A; patient dataset and key clinical outcomes summary

Comparison	Idelalisib	Chemotherapy regimens
101-09 / 101-09 Base Case	Dataset: Study 101-09 • idelalisib TTP • idelalisib ToT • idelalisib PPS • idelalisib PrePS	Dataset: Study 101-09 • prior treatment TTP • prior treatment ToT • idelalisib PPS • idelalisib PrePS
Key: PPS, post-progression survival; PrePS, pre-progression survival; ToT, time on treatment; TTP, time to progression.		

Comparison B: 101-09 / HMRN

"Comparison B" compares clinical outcomes for Study 101-09 patients with outcomes for 26 FL patients in the HMRN database. As reported in Section B.2.9, these 26 patients were those in the HMRN database who met the pre-treatment entry criteria for Study 101-09; patients who: had received ≥2 prior lines of chemotherapy/immune-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent, or had a relapse within 6 months after receipt of those therapies; and were subsequently treated with chemotherapy.[17]

Table 24 summarises clinical outcomes data informing this comparison. As evidence for chemotherapy outcomes are from a separate dataset, PFS and OS are directly compared. These endpoints were predefined Study 101-09 secondary endpoints and are typical HTA endpoints in cancer technology appraisals, and the need to estimate progression and death events separately encountered in Comparison A does not apply to this comparison. HMRN data are available only at the aggregate level, and

the approach to analyse these aggregate data is described across Sections B.2.9 and B.3.3. Treatment duration data are not available from HMRN, and Study 101-09 prior therapy ToT assumptions are used to inform this comparison.

The key limitations of this comparison include the small number of patients informing HMRN chemotherapy outcomes and the comparability of these patients with Study 101-09 idelalisib patients, as documented in Section B.2.9. Importantly, the median number of prior therapies among the 72 Study 101-09 FL patients at baseline was 4 (range 2–12), compared to only [redacted] (range [redacted]) among the 26 included HMRN FL patients, while baseline median time since diagnosis was 4.7 years for Study 101-09 FL patients versus [redacted] years for HMRN patients.[17] As shown in Table 24, Comparison B uses MAIC-adjusted outcomes for HMRN patients to try to account for this bias. However, MAIC-adjustment means that outcomes are based on an effective sample size of 6.9 patients and that adjustment was only subject to available variables and patient overlap across samples, as reported in Section B.2.9 and explored further in Section B.3.3.

Table 24: Comparison B; patient dataset and key clinical outcomes summary

Comparison	Idelalisib	Chemotherapy regimens
101-09 / HMRN	Dataset: Study 101-09 • idelalisib OS • idelalisib PFS • idelalisib ToT	Dataset: HMRN • MAIC-adjusted "chemotherapy" OS • MAIC-adjusted "chemotherapy" PFS Dataset: Study 101-09 • prior treatment ToT
Key: HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.		

Comparison C: CUP / CUP

Similar to Comparison A, "Comparison C" compares clinical outcomes for double-refractory FL patients treated with idelalisib with clinical outcomes from their previous line of therapy, except using the data available from the 2017 publication by Eyre et al. where possible.[36] Table 25 summarises clinical outcomes data informing this comparison. Comparison C makes use of the available real-world evidence from UK and Ireland for idelalisib in double-refractory patients to provide an alternative clinical

data approach to Comparison A, to explore uncertainty around the cost-effectiveness of idelalisib based solely on Study 101-09 results.

While Study 101-09 IPD are available to Gilead, the data available from the CUP are limited to those reported by Eyre et al.[36] Comparison C relies therefore on pseudo-IPD estimated from reported KM curves for pre-progression clinical outcomes and Comparator A assumptions for pre-progression survival, PPS and ToT, as shown in Table 25.

Comparison C shares key characteristics, strengths and a conservative nature with Comparison A. Again, patients essentially act as their own controls, meaning unobserved heterogeneity across intervention and comparator patient samples can be safely assumed to be low. Again, prior therapy outcomes are used as a proxy for comparator outcomes, and a consistent attempt is made to adjust for the use of last therapy results as representative of current care. In addition, PPS is again assumed equivalent across treatment groups, which underestimates the relative survival benefit of idelalisib if it offers a post-progression survival benefit for FL patients.

However, there are key limitations to Comparison C that do not apply to Comparison A. The CUP data collection and management may be different to that in a registered clinical trial such as Study 101-09, and the information available is limited to that in a six-page correspondence publication in the British Journal of Haematology, its supplementary materials, and brief but helpful email clarifications with the corresponding author, Dr Toby Eyre. Importantly, the summary baseline characteristics reported by Eyre at al indicate a higher proportion of ECOG 2–4 and FLIPI 3–5 patients in the CUP versus Study 101-09 (25% versus 8% and 75% versus 54%), that may both (i) predispose CUP patients to worse outcomes than in Study 101-09 and (ii) indicate that the CUP patient group has worse predisposition than the FL patient group, who are likely to benefit from idelalisib in practice. These factors were previously discussed in Section B.2.6.3, and warrant consideration when considering Comparison C results in Section B.3.8.3.

Table 25: Comparison C; patient dataset and key clinical outcomes summary

Comparison	Idelalisib	Chemotherapy regimens
UK&I CUP / UK&I CUP	Dataset: Eyre et al. (CUP) • idelalisib TTP (estimated from Kaplan–Meier PFS and OS figures reported as Fig.1(A) and Fig.1(B) by Eyre et al.) Dataset: Study 101-09 • idelalisib ToT • idelalisib PPS • idelalisib PrePS	Dataset: Eyre et al. (CUP) • prior treatment TTP (presented as prior therapy PFS in Fig. 1(E) of Eyre et al.) Dataset: Study 101-09 • prior treatment ToT • idelalisib PPS • idelalisib PrePS
Key: CUP, compassionate use programme; ONS, Office for National Statistics; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival; ToT, time on treatment; TTP, time to progression.		

To compare idelalisib versus best supportive case (BSC), in people for whom chemotherapy is unsuitable:

Comparison D: 101-09 / 101-09

This approach assumes that the only survival without idelalisib is that observed post-progression in Study 101-09 FL patients, and that if patients were not treated, they would have simply experienced post-progression survival. To capture outcomes for chemotherapy-ineligible patients treated with idelalisib, the approach follows that for idelalisib patients in Comparison A.

A similar approach was taken to inform adoption decisions for idelalisib for the few double-refractory FL patients unsuitable for chemotherapy in Scotland, Wales and Ireland.

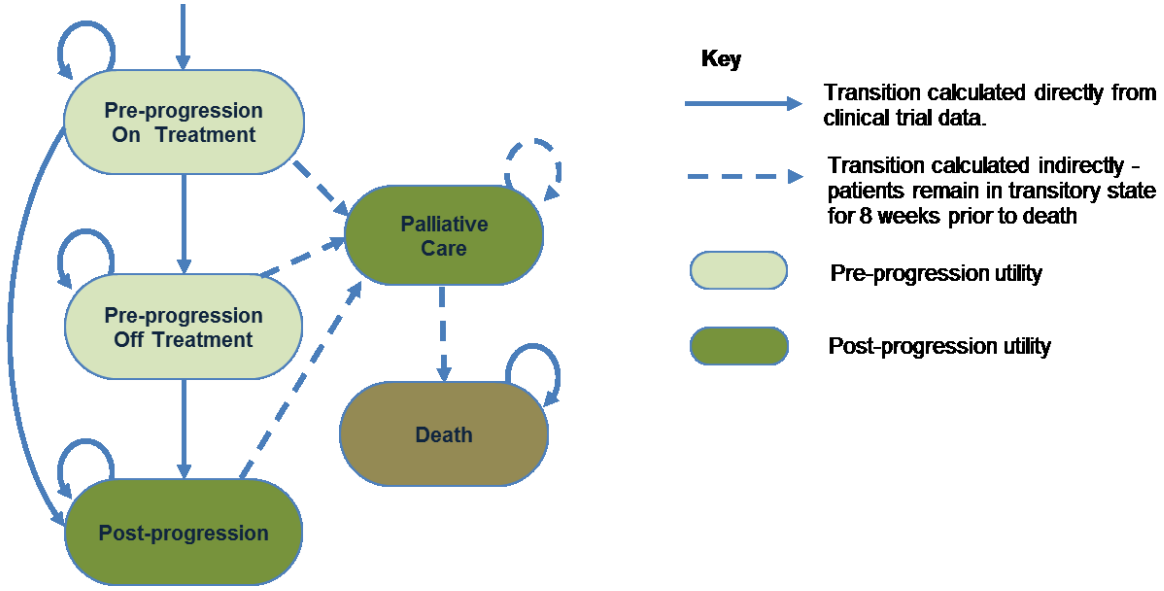
Table 26: Comparison D; patient dataset and key clinical outcomes summary

Comparison	Idelalisib	Best supportive care
101-09 / 101-09 Base Case	Dataset: Study 101-09 • idelalisib TTP • idelalisib ToT • idelalisib PPS • idelalisib PrePS	No treatment costs and instant disease progression assumed. Dataset: Study 101-09 • idelalisib PPS
Key: ONS, Office for National Statistics; PPS, post-progression survival; PrePS, pre-progression survival; ToT, time on treatment; TTP, time to progression.		

B.3.2.2 Model structure

A cohort-level decision-analytic model is used to capture each comparative cost-effectiveness analysis; Figure 14 illustrates the health states and possible transitions in each model treatment arm.

Figure 14: Economic model health states and structure, one treatment arm



The model is an updated version of that used to inform cost-effectiveness submissions to the SMC, the NCPE and the AWMSG, which have led to access to idelalisib for double refractory FL patients in Scotland, Ireland and Wales, respectively, in recent years.

As shown in Figure 14, the cohort enters the model in the “Pre-progression, On Treatment” health state, and thereafter, health states are used to distinguish between pre-and post-progressive disease. In Study 101-09, as in clinical practice, patients could withdraw from active treatment before disease progression; therefore, model states distinguish between those patients with pre-progressive disease receiving active treatment and those not receiving active treatment. It is possible to transition to death from any of the disease-related health states, via the transitory palliative care health state, which captures the heightened cost of palliative care for cancer patients in the weeks immediately preceding death.

Table 27 summarises and justifies some key features of the economic analysis, 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), illustrating how the approach has been designed for consistency with (i) previous relevant TAs, (ii) the *Guide to the Methods* Reference Case[52], and (iii) methodological guidance from the Institute.

A 1-week cycle length is considered sufficiently short to accurately capture key clinical outcomes and dosing regimens. In line with the Reference Case, cost and QALY outcomes are discounted at a rate of 3.5% per annum, to reflect expected time preferences. Given the short cycle length, a half-cycle correction is not applied to any cost or health outcomes.

Table 27: Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**TA472[a]**	**Chosen values**	**Justification**
Time horizon	25 years. Assumed to be sufficient to capture lifetime outcomes.[53]	38 years	After 38 years, the cohort are 100 years old, and >99% of patients in either arm of the model are dead, across scenarios.
Treatment waning effect?	Without specific reference to "waning" in key documentation, the survival modelling approach was central to the ERG critique of the CS. The ERG preferred to use partitioned survival approach to estimate OS, as opposed to capturing it implicitly as a function of (1) time in pre-progression and (2) time in post-progression survival.[53]	The multifaceted nature of the approach to cost-effectiveness analyses means different survival assumptions and structural approaches to survival analyses are considered, within the context of the clinical data limitations at hand. Parametric survival analysis of clinical endpoints is central to each approach	Consistency with the NICE Reference Case and DSU Technical Support Documentation. See Section B.3.3 for further explanation and justification.
Source of utilities	PFS and PPS utility values were sourced from Wild et al.[54], sourced from a systematic review of the published literature.[53]	PFS and PPS utility values from Pettengell et al.[22], who report the same data as Wild et al.[54]	Consistency with (i) the NICE Reference Case and (ii) the only recent previous NICE appraisal in refractory FL. See Section B.3.4 for further explanation and

	Previous appraisal	Current appraisal	
Factor	**TA472[a]**	**Chosen values**	**Justification**
			justification.
Source of costs	ESMO-guideline-informed frequencies for disease management costs consisting of haematological visits, and diagnostic tests / examinations including CT scan, decreasing in frequency with time in PFS state, or upon progression. No CT scan assumed after 30 months in PFS states or at any point in PPS state.[55]	ESMO-guideline-informed frequencies for disease management costs, validated by a practicing Consultant Haematologist, with >30 years ongoing experience practising in England. Resource use costs associated with the precautionary requirements for serious infections specific to idelalisib patients are considered in all analyses.	Consistency with (i) the NICE Reference Case, (ii) the only recent previous NICE appraisal in refractory FL and (iii) relevant clinical guidelines. See Section B.3.5 for further explanation and justification.

Key: CS, company submission; CT, computerised tomography; ERG, Evidence Review Group; ESMO, European Society for Medical Oncology; FL, follicular lymphoma; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TA, Technology Appraisal.
Note: [a], In the absence of appraisal history in double-refractory FL, TA472 is considered as the only TA in refractory FL since the terminated appraisal of bendamustine in 2010 (TA206).

B.3.2.3 Intervention technology and comparators

In all cost-effectiveness analyses, idelalisib is implemented in the model as per its marketing authorisation: as a monotherapy, 150mg orally, twice daily.

In the base case economic analysis (Comparison A), patient outcomes on previous therapy in Study 101-09 are used as the best available comparator data. Study 101-09 prior therapies were summarised in Section B.2.3; they and their dosing regimens, as applied in the cost-effectiveness analysis, are described in detail in Section B.3.5.1.

As described in Section B.3.2.1, economic comparisons using key clinical effectiveness data outside of Study 101-09 (Comparisons B and C) rely on base case assumptions and data for comparator treatment cost, dosing and duration inputs.

B.3.3. Clinical parameters and variables

As set out in Section B.3.2.1, cost-effectiveness comparisons A to D draw on TTP, ToT, PPS, pre-progression survival, PFS and OS data across multiple databases, in order to inform cost-effectiveness results with relative effectiveness estimates in the context of single-arm regulatory trial evidence. The data for most of these outcomes

are incomplete, and where longer-term evidence is available for some outcomes in some datasets, it is based on very few patients. Given this, and the need to take a lifetime perspective to address the decision problem, parametric survival analysis was undertaken to inform key clinical parameters in the cost-effectiveness analysis. In the case of Comparison B, matched-adjusted clinical comparison was also required.

Following methods guidance in NICE DSU TSDs 14 and 18[46, 56], the remainder of this section sets out the clinical variables and parameters sourced from each dataset used and describes how they are implemental in the cost-effectiveness model.

B.3.3.1 Study 101-09

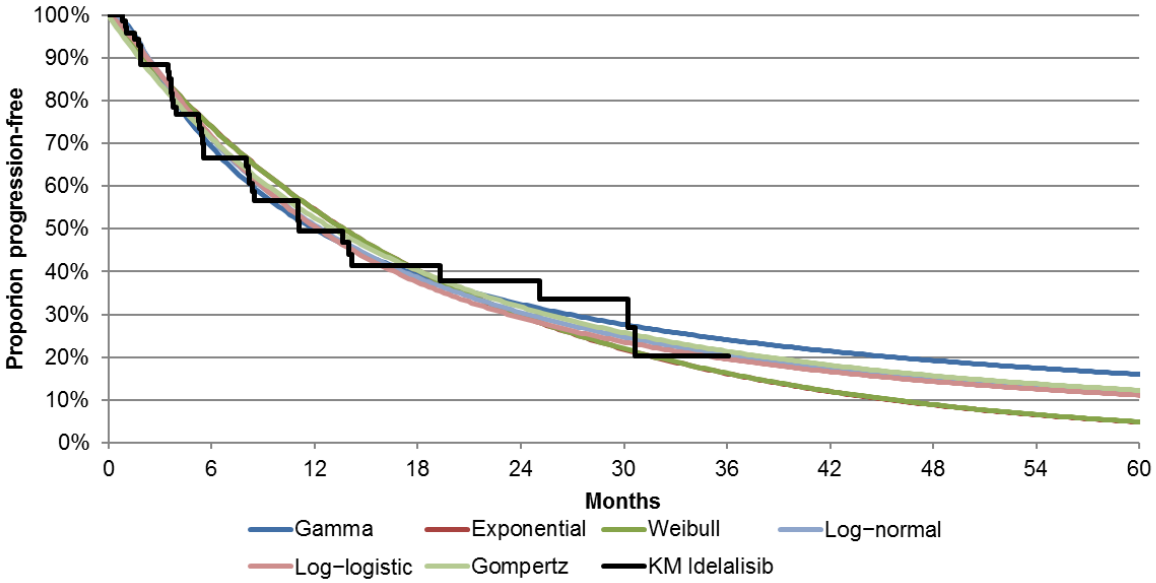
Patient-level data from the latest dataset from Study 101-09 (30 June 2015) were used to generate KM data for TTP, ToT, PPS, OS and PFS for idelalisib and, where appropriate, previous therapy. Parametric curves were then fitted to the data following NICE DSU TSD 14.[56]

Six standard parametric model forms were estimated (exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma), and the fit of each parametric model was compared with the observed data. The most appropriate functional form was assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics. These measures provide an indication of the statistical fit between the observed KM data and the parametric model estimates throughout the trial period. The appropriateness of curve fits was further assessed during a 8 May 2018 meeting with Dr Robert Marcus, described in Section B.3.10 and documented in a meeting report included as a reference in this submission[15], to ensure the predicted extrapolations were credible.

Time to progression (TTP)

TTP KM data for Study 101-09 FL patients treated with idelalisib, and parametric survival model fits to these data, are shown in Figure 15. AIC and BIC statistics for these model fits are shown in Table 28.

Figure 15: KM and fitted parametric curves, Study 101-09 idelalisib TTP, June 2015 database



Key: KM, Kaplan–Meier; TTP, time to progression.

Table 28: Goodness of fit statistics, fitted parametric curves, Study 101-09 idelalisib TTP, June 2015 database

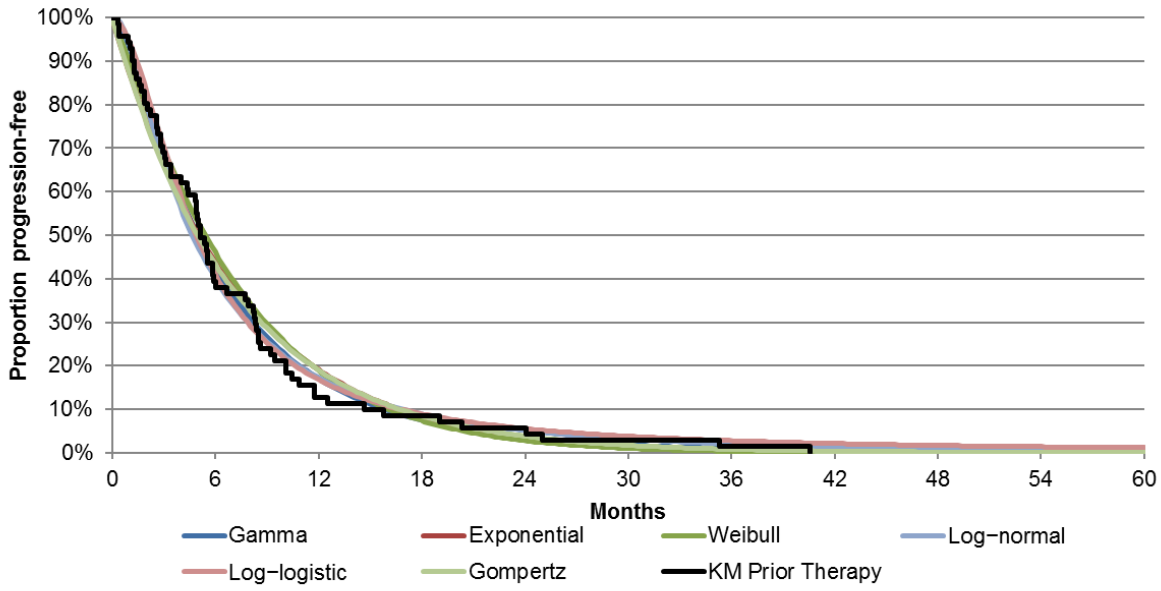
Model	AIC	BIC
Exponential	288.81	291.09
Generalised gamma	287.01	293.84
Gompertz	289.92	294.48
Log-logistic	287.65	292.20
Lognormal	**285.81**	**290.36**
Weibull	290.81	295.36

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan–Meier; TTP, time to progression.
Notes: Best fitting model in bold.

The 101-09 idelalisib TTP KM data are almost 80% complete, and goodness-of-fit statistics suggest lognormal and generalised gamma models provide the best fit to the KM data. As the survival projections beyond the KM data are more favourable for the generalised gamma fit versus the lognormal model fit, the lognormal model was conservatively used to capture Study 101-09 idelalisib TTP in the economic base case (Comparison A) analysis.

TTP KM data for prior therapy for Study 101-09 FL patients, and parametric survival model fits to these data, are shown in Figure 16. AIC and BIC statistics for these model fits are shown in Table 29.

Figure 16: KM and fitted parametric curves, Study 101-09 prior therapy TTP, June 2014 database [data complete]



Key: KM, Kaplan–Meier; TTP, time to progression.

Table 29: Goodness of fit statistics, fitted parametric curves, Study 101-09 prior therapy TTP, June 2014 database [data complete]

Model	AIC	BIC
Exponential	912.27	916.79
Generalised gamma	**909.12**	**915.91**
Gompertz	912.23	916.76
Log-logistic	911.15	917.93
Lognormal	911.30	918.09
Weibull	913.16	919.95

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTP, time to progression.
Notes: Best fitting model in bold.

The Study 101-09 prior therapy TTP KM data are complete, and goodness-of-fit statistics show generalised gamma and log-logistic models provide the best fit to the KM data, with the lognormal model providing the third best AIC fit to the data of the

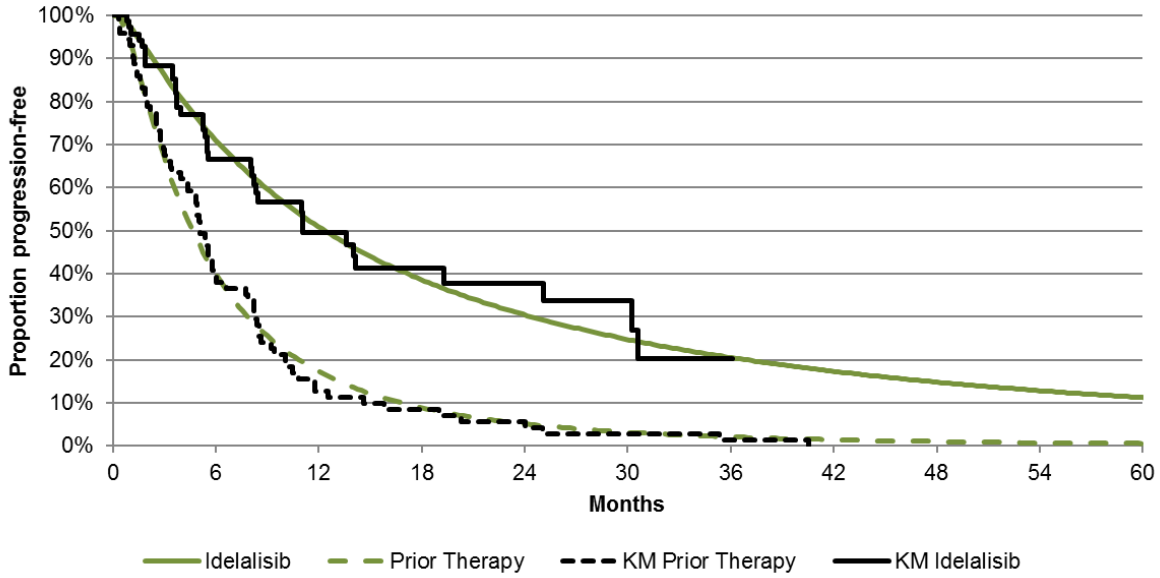
six models tested. Nevertheless, as the data are complete, the differences in lifetime TTP projections are far less important than if extrapolation were required.

With respect to model selection, where parametric models are fitted separately to individual treatment arms, NICE DSU TSD 14 (pages 39–40) states:

"*…it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two-dimensional treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions. If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis.*"[56]

Although the prior therapy TTP data are being used as proxy comparator data, rather than being comparator data within an RCT, it seems sensible, given this advice, to choose the same parametric model to capture both idelalisib and prior therapy TTP from Study 101-09. Given the primacy of idelalisib TTP extrapolation assumptions, and visual similarity of prior therapy TTP model fits, lognormal models were used to capture all Study 101-09 TTP in the base case. Figure 17 shows Study 101-09 idelalisib and prior therapy TTP KM data, alongside base case lognormal model fits.

Figure 17: KM data and base case (lognormal) parametric model fits, Study 101-09 TTP



Key: KM, Kaplan–Meier; TTP, time to progression.

During the meeting with Dr Marcus, the approach to address the intrinsic bias in using prior therapy data as proxy for current therapy was discussed.[15] As outlined in Section B.3.2.1, unless there is a step change in treatment, patient outcomes are expected to worsen with every line of therapy. Accordingly, time to disease progression is expected to fall with each consecutive line of similar therapy. Expectation from Dr Marcus is that the reduction in remission is compounded with every treatment line (a HR further from 1 with each treatment line). For patients who are refractory to two prior treatments, a HR of 0.75 may be appropriate when using last prior therapy as proxy for current therapy.[15]

[redacted]

Elsewhere, one cohort study of 212 FL patients treated at a single UK centre reported median duration of response to treatment of 31 months at 1st remission, 13 months at 2nd and 3rd remission, and 6 months at 4th remission,[8] another retrospective study of 349 patients treated across two institutions in Spain reported

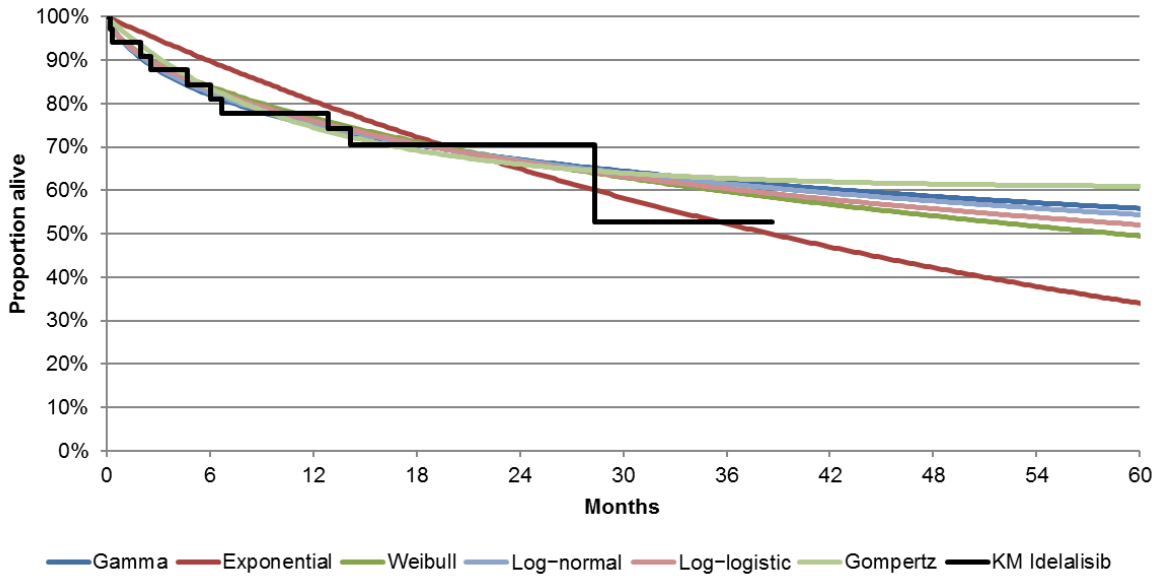
median PFS times of 10.1 years at 1st line, 2.4 years at 2nd line and 1.8 years at 3rd line,[57] and a US study of 2,728 FL patients reported median PFS times ranging from 6.62 years at 1st line, 1.50 years at 2nd line, 0.83 years at 3rd line, 0.69 years at 4th line and 0.68 years at 5th line.[9]

The 0.75 HR is applied in the economic model wherever prior therapy outcomes data are used as proxy for current therapy data and affects Comparisons A and C (but not B or D). The distribution around this uncertain input is assumed to follow a uniform distribution (0.5, 1) in sensitivity analysis and extreme-value scenario analyses in Section B.3.8.3.

Post-progression survival (PPS)

PPS KM data for the 36 Study 101-09 FL patients treated with idelalisib who progressed before a death event, and parametric survival model fits to these data, are shown in Figure 18. AIC and BIC statistics for these model fits are shown in Table 30.

Figure 18: KM and fitted parametric curves, Study 101-09 idelalisib PPS, June 2015 database



Key: KM, Kaplan–Meier; PPS, post-progression survival.

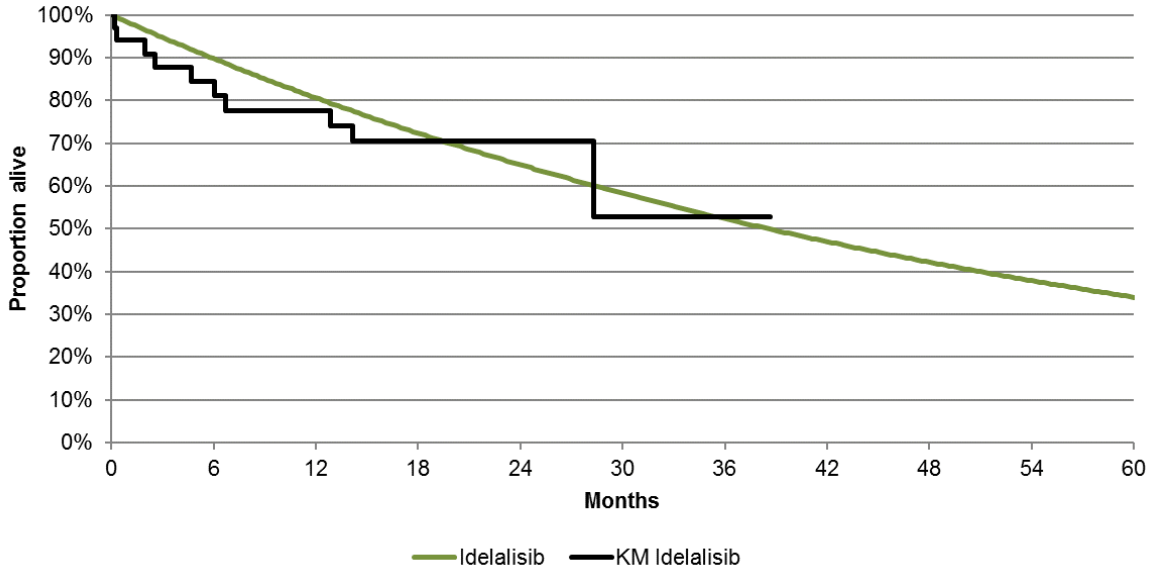
Table 30: Goodness of fit statistics, fitted parametric curves, Study 101-09 idelalisib PPS, June 2015 database

Model	AIC	BIC
Exponential	102.36	103.95
Generalised gamma	102.07	106.82
Gompertz	101.44	104.61
Log-logistic	100.42	103.59
Lognormal	**100.10**	**103.27**
Weibull	100.56	103.73

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PPS, post-progression survival.
Notes: Best fitting model in bold.

The PPS data remain less than 50% complete, even in the updated dataset, locked over 4 years and 3 months after the first patient was enrolled, and parametric model selection is clearly important for the total area under the curve. The key property of the exponential model (constant hazard) means it is a poor visual fit to the data, but provides by far the most pessimistic long-term PPS predictions. In line with clinical expert advice received for the AWMSG submission for an earlier database (locked 11 June 2014), and echoed by insight from Dr Marcus[15], the exponential model is used for Study 101-09 PPS in the base case, as illustrated in Figure 19. In all cost-effectiveness analyses where Study 101-09 PPS data are required, the same PPS assumptions are used across model arms, as set out in Section B.3.2.1.

Figure 19: KM data and base case (exponential) parametric model fit, Study 101-09 PPS, June 2015 database



Key: KM, Kaplan–Meier; PPS, post-progression survival.

Time on treatment (ToT)

ToT KM data for Study 101-09 FL patients treated with idelalisib, and parametric survival model fits to these data, are shown in Figure 20. AIC and BIC statistics for these model fits are shown in Table 31. ToT KM data for prior therapy for Study 101-09 FL patients, and parametric survival model fits to these data, are shown in Figure 21. AIC and BIC statistics for these model fits are shown in Table 32.

Figure 20:

[redacted]

Key: KM, Kaplan–Meier; ToT, time on treatment.

Table 31: Goodness of fit statistics, fitted parametric curves, Study 101-09 idelalisib ToT, June 2015 database

Model	AIC	BIC
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.
Notes: Best fitting model in bold.

Figure 21:

[redacted]

Key: KM, Kaplan–Meier; ToT, time on treatment.

Table 32: Goodness of fit statistics, fitted parametric curves, Study 101-09 prior therapy ToT, June 2014 database [data complete]

Model	AIC	BIC
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.
Notes: Best fitting model in bold.

Study 101-09 ToT KM data are complete for idelalisib, and by definition, for prior therapy. Goodness-of-fit statistics suggest an exponential model provides the best fit to the idelalisib ToT KM data, and second-best fit to prior therapy data. Given the importance of the expected treatment cost of idelalisib for its cost-effectiveness, model selection is driven by the goodness and plausibility of fit to idelalisib ToT data, and the exponential model is used. Assuming the same functional form for prior therapy ToT, in line with inference from NICE TSD 14 set out earlier in this section, the exponential model is also used to capture Study 101-09 prior therapy ToT in cost-effectiveness analyses. Figure 22 shows Study 101-09 idelalisib and prior therapy ToT KM data, alongside base case exponential model fits.

Figure 22:

[redacted]

[redacted]

Key: KM, Kaplan–Meier; ToT, time on treatment.

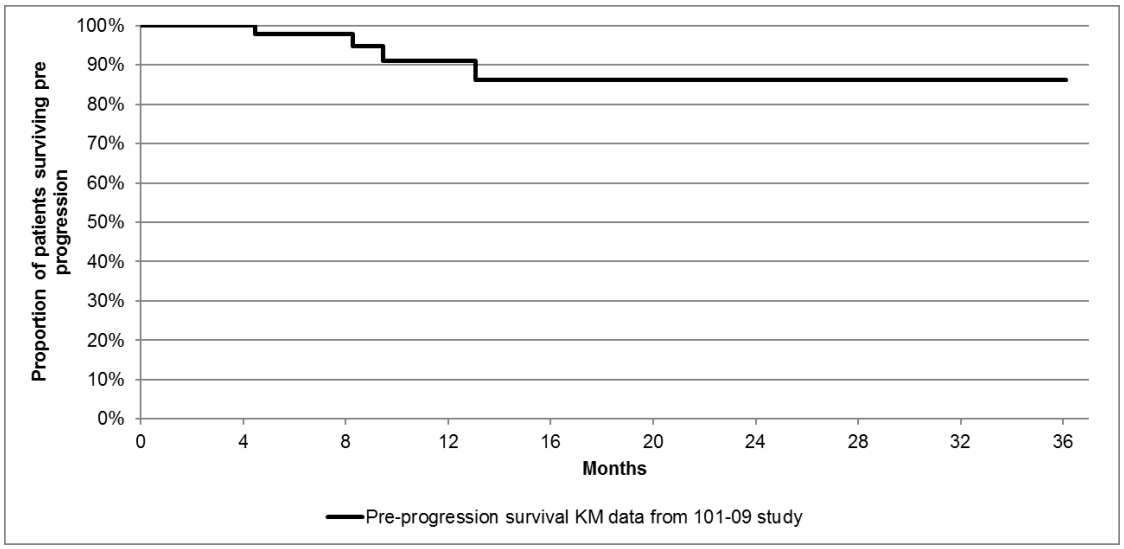
The clinically informed 0.75 HR applied to the TTP curve for prior therapy, to address an intrinsic bias against idelalisib in the approach to an extent as time to disease progression is expected to fall with each consecutive line of therapy, is also applied to the ToT curve for prior therapy. As well as less effective, treatment at subsequent lines is likely to be less costly, with a reduction in treatment exposure at each subsequent line.

ToT assumptions are used solely to inform estimated treatment cost in the model. Other inputs and assumptions affecting treatment cost are reported in Section B.3.5.1, including the different treatment regimens received as prior therapy, the proportions of 101-09 FL patients receiving each prior therapy, and the maximum treatment duration for each regimen, where these applied. In all economic analyses, where comparator treatment costs are informed by Study 101-09 prior therapies, time on treatment is set equal to the minimum of (i) the base case parametric fit to the observed KM data, and (ii) the maximum treatment duration given the distribution and recommended treatment lengths of the Study 101-09 prior therapies received.

Pre-progression survival

In the latest dataset, in which over 82% of Study 101-09 patients have experienced at least one progression or death event, only four pre-progression deaths were recorded.[43] Pre-progression survival data treats death as an event and censors for progression; Study 101-09 pre-progression survival data are shown in Figure 23.

Figure 23: KM curve, Study 101-09 idelalisib pre-progression survival, June 2015 database



Key: KM, Kaplan–Meier.

While survival estimates based on only 4 events are subject to great uncertainty, evidence from Study 101-09 clearly indicates that the vast majority of patients progress before dying, these data are used to inform pre-progression death risks in the economic model base case (Comparison A) and other economic scenarios in which TTP rather than PFS data are used, in combination with general population mortality data from the latest Office for National Statistics (ONS) Life Tables for England.[58] As for PPS, pre-progression survival, when required for analysis, is assumed equal across idelalisib and chemotherapy patients. As for PPS, this is very likely conservative.

A HR of 5.71 for double-refractory FL pre-progression survival versus age- and gender-equivalent general population survival was estimated, as the natural logarithm of the proportion of Study 101-09 FL patients surviving pre-progression at the end of the KM data (Figure 23) divided by the natural logarithm of age- and gender-equivalent general population KM survival at the same timepoint. This approach was chosen to allow the data in Figure 23 to be used while incorporating the shape of age- and gender-matched general population mortality data.

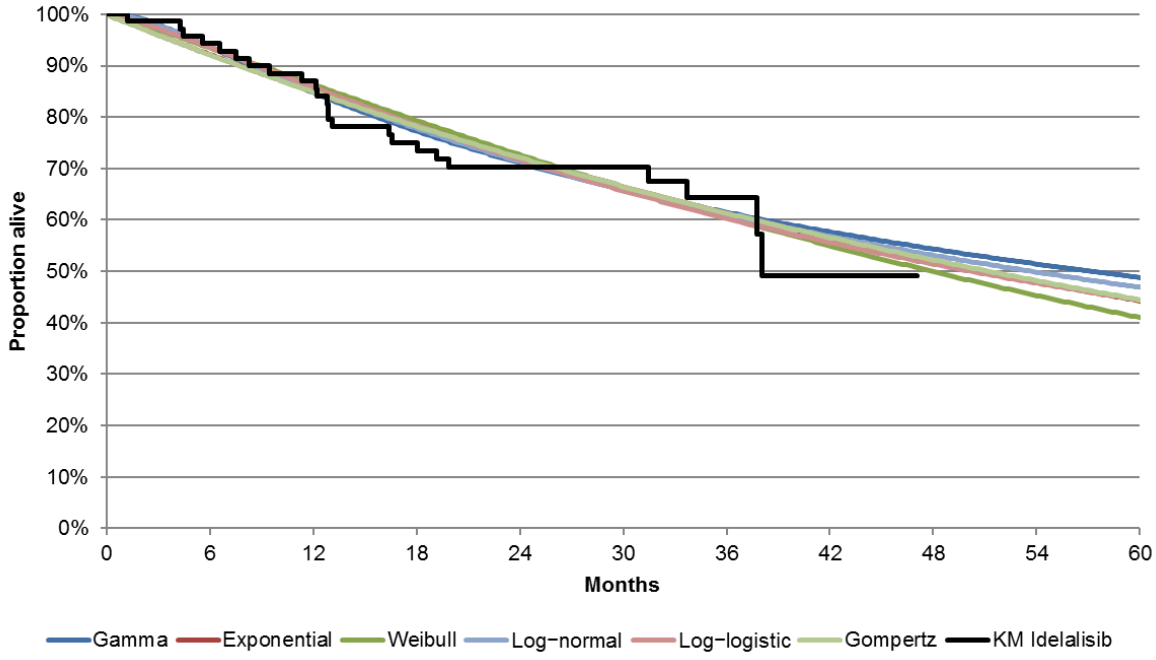
At clinical review, Dr Marcus felt the use of Study 101-09 FL pre-progression data, though limited, was likely representative, with around 5% of patients (4/72, 5.6%) dying pre-progression.[15] An exploratory search of published literature revealed only one relevant study; a longitudinal study of 90 patients with relapsed FL at a single institution in Spain reporting (3.3%) 3 patients to have died from non-lymphoma related causes.[59] Similar to Study 101-09 FL evidence, this estimate is supported by very few datapoints, but is broadly supportive of the approach taken, and suggestive that the approach selected is conservative.

Overall Survival (OS)

Although not used in the economic base case, OS (and PFS) KM data from Study 101-09 are useful both for validation purposes and to directly inform comparison to real-world chemotherapy evidence from HMRN (Comparison B).

OS KM data for Study 101-09 FL patients, and parametric survival model fits to these data, are shown in Figure 24. AIC and BIC statistics for these model fits are shown in Table 33.

Figure 24: KM and fitted parametric curves, Study 101-09 idelalisib OS, June 2015 database



Key: KM, Kaplan–Meier; OS, overall survival.

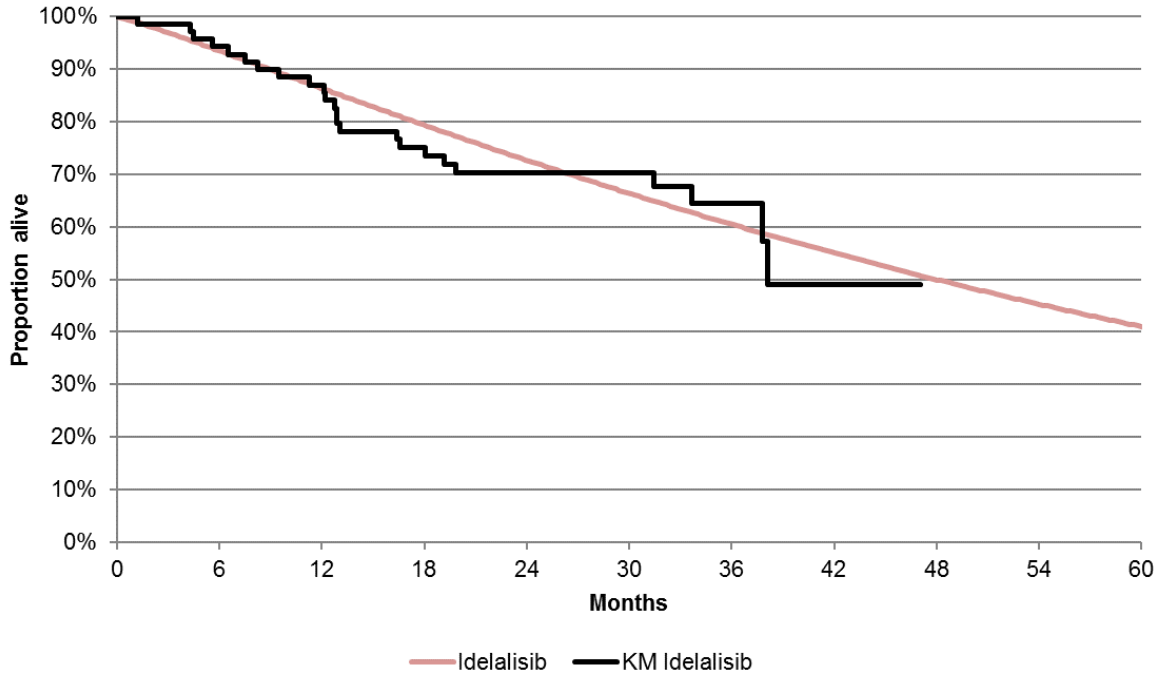
Table 33: Goodness of fit statistics, fitted parametric curves, Study 101-09 idelalisib OS, June 2015 database

Model	AIC	BIC
Exponential	256.31	**258.59**
Generalised gamma	258.07	264.90
Gompertz	258.31	262.87
Log-logistic	257.21	261.77
Log-normal	**256.20**	260.75
Weibull	257.95	262.51

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
Notes: best fitting model in bold

The OS data remain just over half complete in the most recent dataset, and as for PPS, parametric model selection is clearly important for total area under the curve. Despite providing a worse statistical fit to the KM data than three other models, the Weibull model fit provides the most pessimistic extrapolation of the six models tested and is the only fit to predict less than 5% survival after 15 years. As such, the Weibull model was deemed the most plausible at clinical validation and is used to inform OS assumptions in Comparison B. Figure 25 shows Study 101-09 OS KM data alongside the Weibull model fit used in Comparison B.

Figure 25: KM data and Comparison B parametric model fit (Weibull), Study 101-09 OS, June 2015 database

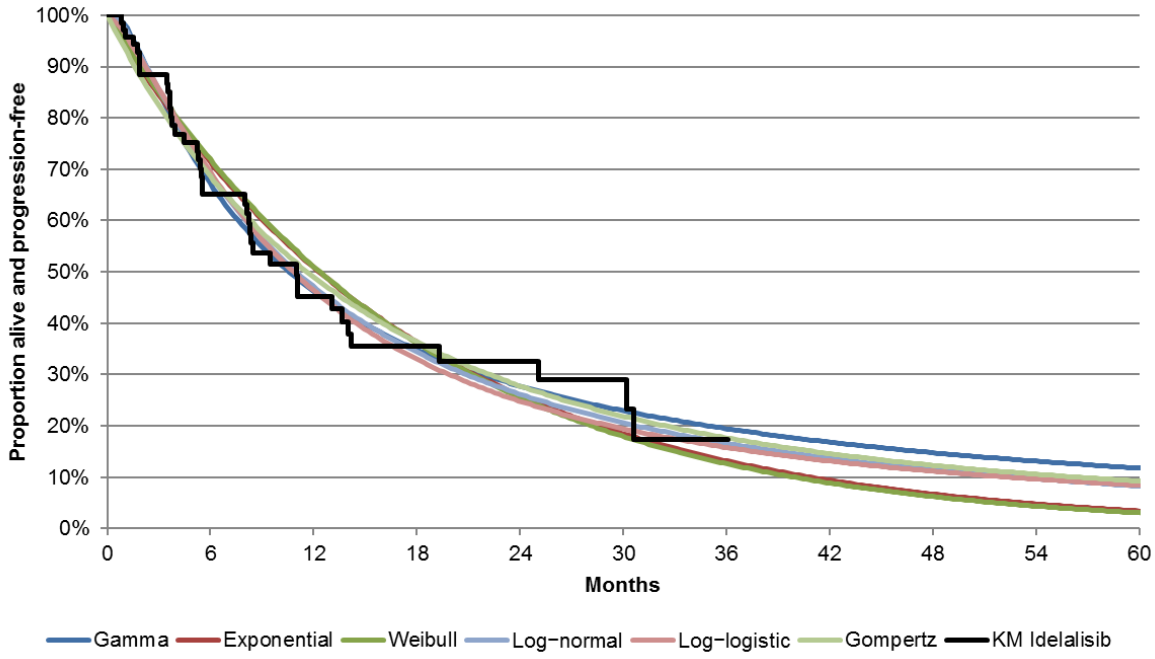


Key: KM, Kaplan–Meier; OS, overall survival.

Progression-free survival (PFS)

PFS KM data for Study 101-09 FL patients, and parametric survival model fits to these data, are shown in Figure 26. AIC and BIC statistics for these model fits are shown in Table 34.

Figure 26: KM and fitted parametric curves, Study 101-09 idelalisib PFS, June 2015 database



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Table 34: Goodness of fit statistics, fitted parametric curves, Study 101-09 idelalisib PFS, June 2015 database

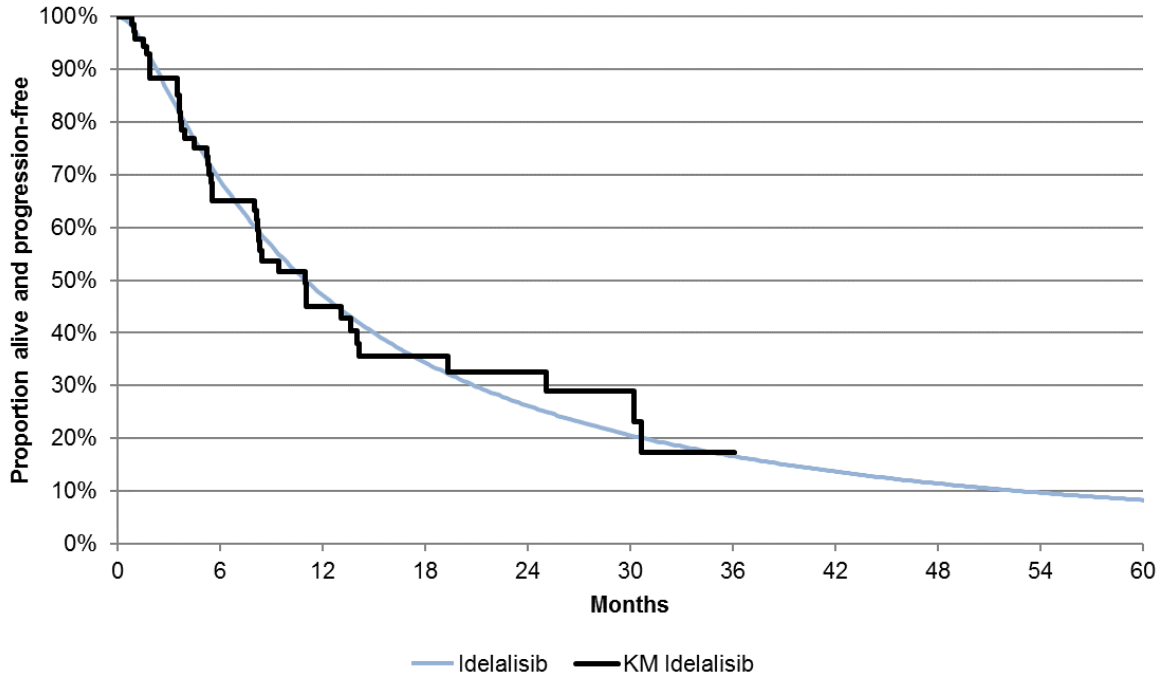
Model	AIC	BIC
Exponential	312.25	314.53
Generalised gamma	309.68	316.51
Gompertz	313.38	317.93
Log-logistic	309.90	314.45
Lognormal	**308.36**	**312.91**
Weibull	314.21	318.77

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Notes: Best fitting model in bold.

As described above, where PFS is discussed and illustrated by Figure 26, the Study 101-09 PFS data are over 82% complete in the latest available dataset. Figure 27 shows Study 101-09 PFS KM data alongside the Weibull model fit used in Comparison B. The lognormal model provides the best statistical fit to these data, by both AIC and BIC statistics, and as such is used as the most appropriate model to

capture Study 101-09 PFS in the Comparison B scenario. Figure 27 shows Study 101-09 PFS KM data alongside the lognormal model fit used to capture PFS in Comparison B.

Figure 27: KM data and Comparison B parametric model fit (lognormal), Study 101-09 PFS



Key: KM, Kaplan–Meier; PFS, progression-free survival.

B.3.3.2 HMRN

Section B.2.9 documents an ITC to RWE data from the HMRN database, including an MAIC of OS and PFS between Study 101-09 FL patients and double-refractory patients who received further treatment in the HMRN database. Comparison B, as described in Section B.3.2.1, harnesses this comparative evidence to provide a further clinical comparison for cost-effectiveness analysis.

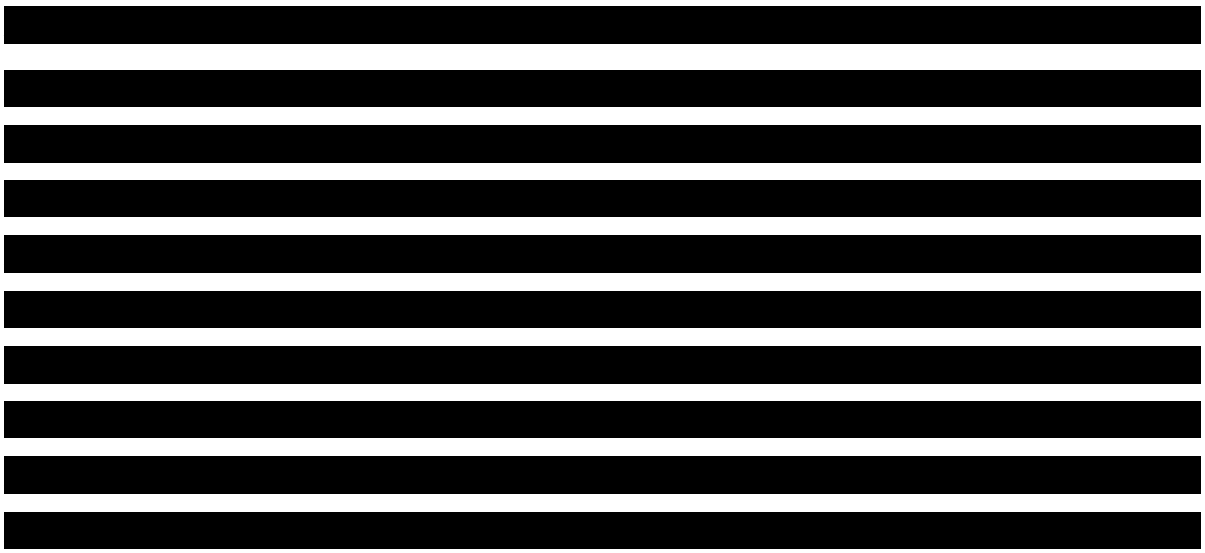
Figure 13 (Section B.2.9) shows KM diagrams for OS and PFS for HMRN patients with double-refractory FL, both pre- and post-MAIC adjustment. To harness these incomplete KM data for lifetime economic analysis, a parametric survival model following NICE DSU TSD 14 was again used. In the absence of raw time-to-event data or propensity weights produced by the MAIC, the first necessary step here was

digitisation of the data in Figure 13, using *GetData Graph Digitizer* software[60], following the method to recreate CUP data described in Section B.3.3.3.

From the digitised MAIC-adjusted KM data, the algorithm proposed by Guyot et al. to map digitised curves back to KM data was used to create pseudo-IPD.[61] The Guyot et al. algorithm requires the analyst to input number-at-risk at time zero as an input; as a starting point, the effective sample size of [redacted] patients post-MAIC was rounded up to [redacted] patients. However, this led to recreated KM data that were a very poor representation of the original KM data, which was inevitable given there were more than [redacted] events for each outcome. To use the Guyot et al. algorithm to recreate IPD that better reflected the KM curves shown in Figure 13, analyst judgement was used to increase the number-at-risk at time zero iteratively until the recreated KM curves provided a visually good fit to the original KM curves. This iterative process stopped at n=90 for OS n=80 for PFS. As a consequence of this sample-inflation approach, the variance and hence confidence intervals around parameters of parametric survival models fitted to these data will be artificially small. However, as these data inform only Comparison B, presented as a deterministic scenario, this is not of consequence for any results presented in this document.

MAIC-adjusted inflated-sample OS KM data for double-refractory FL patients in the HMRN database, and parametric survival model fits to these data, are shown in Figure 28. AIC and BIC statistics for these model fits are shown in Table 35.

Figure 28:



[redacted]

Key: FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.

Table 35: Goodness of fit statistics, fitted parametric curves, MAIC-adjusted OS, HMRN double-refractory FL patients

Model	AIC	BIC
Exponential	582.32	584.82
Generalised gamma	Did not converge	Did not converge
Gompertz	520.16	525.16
Log-logistic	479.31	484.31
Lognormal	**474.61**	**479.61**
Weibull	490.51	495.51

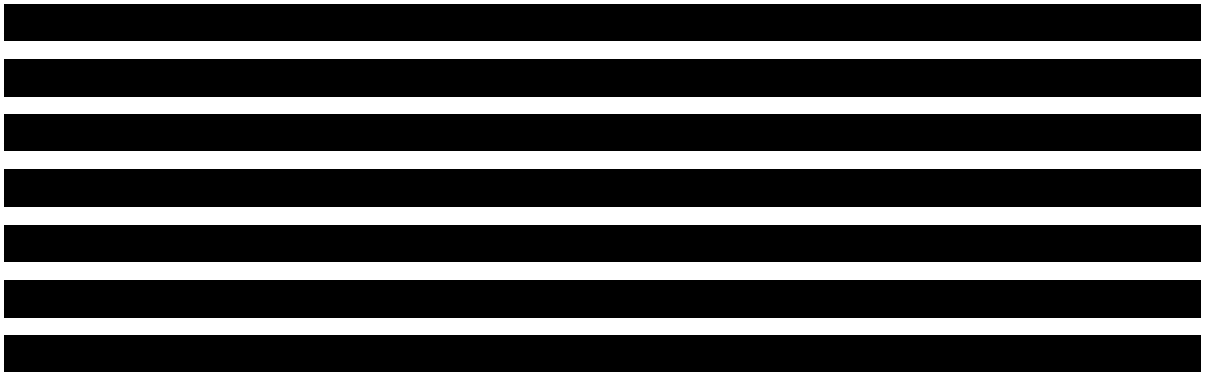
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; OS, overall survival.
Notes: Best fitting model in bold.

Of those parametric survival models that were successfully fitted to the data, the exponential model clearly provides the poorest fit, while the Gompertz model also provides a visually and statistically poor fit. Assuming chemotherapy OS does not follow a drastically different distribution to idelalisib OS, which was determined to be best captured by a Weibull distribution in Section B.3.3.1, the Weibull model fit shown in Figure 28 is used to capture MAIC-adjusted OS for HMRN FL patients in the Comparison B cost-effectiveness analysis scenario.

MAIC-adjusted inflated-sample PFS KM data for double-refractory FL patients in the HMRN database, and the parametric survival model fits to these data, are shown in Figure 29. AIC and BIC statistics for these model fits are shown in Table 36.

Figure 29:

[redacted]



Key: FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Table 36: Goodness of fit statistics, fitted parametric curves, MAIC-adjusted PFS, HMRN double-refractory FL patients

Model	AIC	BIC
Exponential	501.34	503.72
Generalised gamma	**333.39**	**340.54**
Gompertz	425.85	430.62
Log-logistic	393.00	397.76
Lognormal	389.74	394.51
Weibull	408.36	413.12

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.
Notes: Best fitting model in bold.

Although unlike the HMRN OS data, these data were sufficient to be estimated by the only three-parameter parametric survival model, the generalised gamma model, and like the HMRN OS data, the exponential model again provides a poor visual and statistical fit. Again, assuming chemotherapy PFS does not follow a drastically different distribution to idelalisib PFS in Comparison B, the lognormal model fit shown in Figure 29 is used for cost-effectiveness analysis.

As set out in Section B.3.2.1, harnessing relevant data from the HMRN database to inform a further alternative cost-effectiveness approach allows reassurance and greater evidence on the expected benefits of idelalisib for double-refractory FL patients in England. The approach is different to that in Comparisons A and C: most importantly, it directly assesses OS and PFS, outcomes familiar to regulatory bodies

and HTA assessors such as NICE for their clinical and patient experience relevance; also, data external to the 101-09 study are used for comparative effectiveness evidence.

While it has clear strengths, the approach is subject to limitations and key uncertainties. First, there are few relevant patients available from the HMRN dataset, and there is an even smaller effective sample size following MAIC to adjust for prognostic differences between the HMRN sample and the Study 101-09 sample. Second, the prognostic information collected by the HMRN is limited. Third, there is a need to digitise to recreate pseudo-IPD from HMRN-reported KM diagrams, which, as for the recreation of CUP data, is subject to error. In short, the HMRN database provides rare and useful RWE for analytical comparative purposes, but it also highlights the small number of high-need FL patients for whom idelalisib could provide a benefit, and how poor OS and PFS outcomes for these patients with currently available care likely are.

B.3.3.3 UK & Ireland CUP

As documented in Sections B.2.3 to B.2.6, a supportive CUP was initiated following EMA marketing authorisation, and data from this CUP were collected by Eyre et al. between January 2015 and August 2016 from 46 of 51 approached centres in the UK and Ireland.[36]

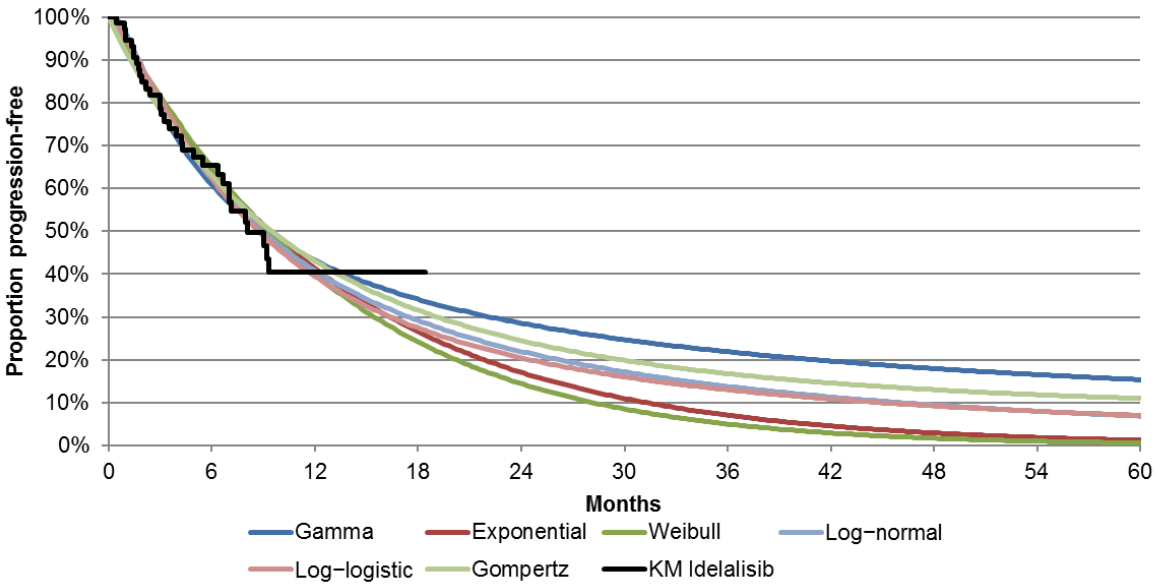
The study methodology, statistical analysis plan and results from the CUP, as reported by Eyre et al.[36], are shown in Sections B.2.3 to B.2.6. The results published include several OS and PFS KM diagrams (reported as Figure 1(E) in Eyre et al. and reproduced as Figure 10 in Section B.2.6)[36], including idelalisib PFS (shown in 1(A) and 1(E)), idelalisib OS (shown in 1(B) and prior therapy PFS (shown in 1(E)).[36] As noted in Section B.2.6 and consistent with the approach to Comparison A, PFS data on prior therapy should be considered more reflective of TTP data, given that prior therapy PFS definitively only contains progression (and not death) events.

To compare the CUP idelalisib TTP with the CUP prior therapy TTP in the absence of IPD, the idelalisib OS and PFS data for CUP patients and prior therapy PFS/TTP data for these patients were first digitised from Eyre et al., Figures 1(A), (B) and (E), using *GetData Graph Digitizer* software.[60] Next, the algorithm proposed by Guyot et

al. to map digitised curves back to KM data was used to create pseudo-IPD.[61] By comparing idelalisib OS and PFS events across (A) and (B), one analyst categorised idelalisib PFS events into death and progression events, and estimated CUP idelalisib TTP pseudo-KM data, treating digitised progression events as KM events and censoring for digitised death events. The six parametric models fitted to Study 101-09 data were then fitted to these TTP data. CUP idelalisib TTP pseudo-KM data and parametric model fits to these data are shown in Figure 30. AIC and BIC statistics for these model fits are shown in Table 37.

Parametric models were also fitted to the reproduced KM data for CUP prior therapy PFS/TTP and are shown in Figure 31. AIC and BIC statistics for these model fits are shown in Table 38.

Figure 30: KM and fitted parametric curves, CUP idelalisib TTP



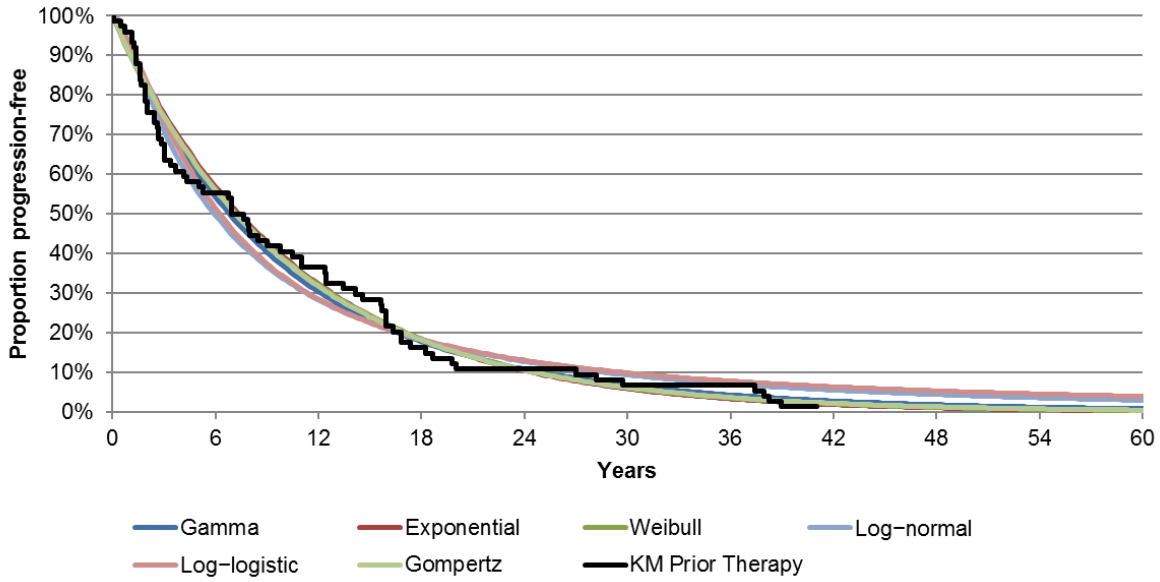
Key: CUP, compassionate use programme; KM, Kaplan–Meier; TTP, time to progression.

Table 37: Goodness of fit statistics, fitted parametric curves, CUP idelalisib TTP

Model	AIC	BIC
Exponential	240.05	242.41
Generalised gamma	237.98	245.05
Gompertz	241.58	246.29
Log-logistic	238.93	243.65
Lognormal	**237.13**	**241.84**
Weibull	241.77	246.49

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CUP, compassionate use programme; TTP, time to progression.
Notes: Best fitting model in bold.

Figure 31: KM and fitted parametric curves, CUP prior therapy TTP



Key: CUP, compassionate use programme; KM, Kaplan–Meier; TTP, time to progression.

Table 38: Goodness of fit statistics, fitted parametric curves, CUP prior therapy TTP

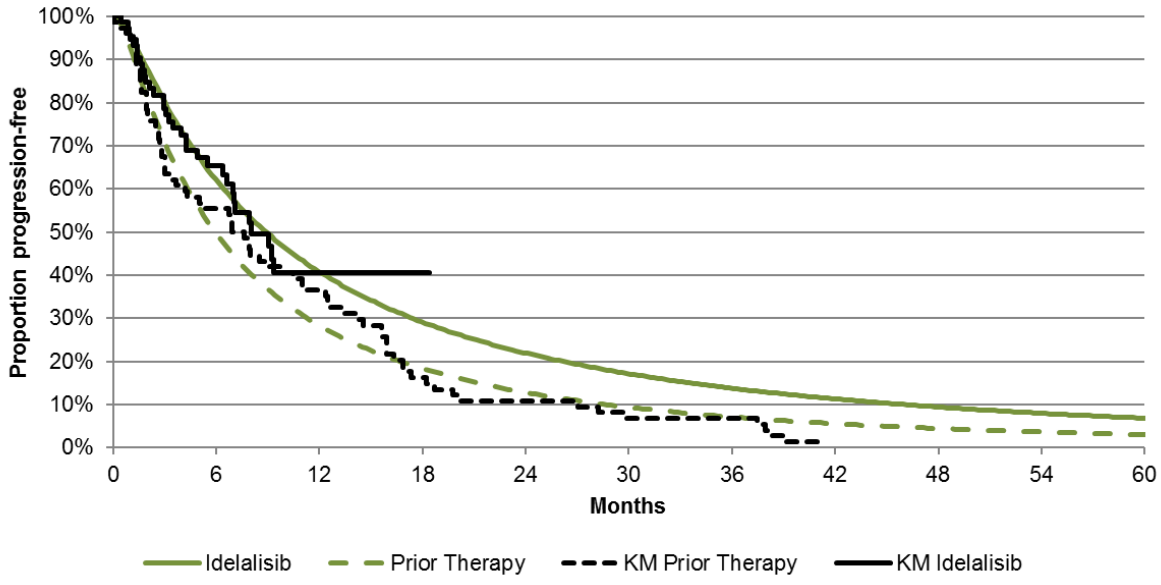
Model	AIC	BIC

Exponential	**493.04**	**495.35**
Generalised gamma	496.24	503.15
Gompertz	494.96	499.57
Log-logistic	499.87	504.48
Lognormal	498.93	503.54
Weibull	494.97	499.58

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CUP, compassionate use programme; TTP, time to progression.
Notes: Best fitting model in bold.

The lognormal model provides the best statistical fit to the reproduced CUP idelalisib TTP data, and while this is not the case for the lognormal CUP prior therapy, the complete nature of these prior therapy data mean model selection choice is less consequential for cost-effectiveness results. Further, in the base case (Comparison A) cost-effectiveness analysis, Study 101-09 TTP is assumed to follow a lognormal distribution, and distributional consistency across these datasets, for similar treatments and outcomes, is rational. As such, for Comparison C, described in Section B.3.2.1, the lognormal model is used to capture CUP idelalisib and prior therapy TTP. Figure 32 shows CUP idelalisib and prior therapy TTP KM data, alongside the Comparison C lognormal model fits.

Figure 32: KM data and Comparison C (lognormal) parametric model fits, CUP idelalisib and prior therapy TTP



Key: CUP, compassionate use programme; KM, Kaplan–Meier; TTP, time to progression.

As set out in Section B.3.2.1, harnessing available idelalisib CUP data to inform an alternative cost-effectiveness approach allows reassurance and greater evidence on the expected benefits of idelalisib for double-refractory FL patients in England, on top of the evidence from Study 101-09 and further NHS England evidence collected in HMRN. However, in addition to the intrinsic and conservative limitations in assuming the clinical benefit of idelalisib is measured by the difference in TTP in comparison to prior therapy, there are additional limitations associated with the use of the Eyre et al. data that warrant emphasis.

First, as noted in Section B.3.2.1, the summary baseline characteristics reported by Eyre at al indicate a higher proportion of ECOG 2–4 and FLIPI 3–5 patients in the CUP versus Study 101-09 (25% versus 8% and 75% versus 54%), that may both (i) predispose CUP patients to worse outcomes than in Study 101-09 and (ii) indicate the CUP patient group have worse predisposition than the FL patient group who are likely to benefit from idelalisib in practice. This should be considered when interpreting the data in Figure 32, particularly in relation to the KM data in Section B.3.3.1.

Second, the need to digitise to recreate pseudo-IPD from published KM diagrams is subject to natural error, particularly when there was a need to derive TTP KM data from OS and PFS KM curves. The company project team contacted Dr Toby Eyre by email to clarify a few points from the publication and to enquire about the possibility of IPD access. Dr Eyre was extremely helpful and communicative, answering initial clarification points, but communicated that it would not be possible to share the IPD, or to reanalyse the IPD to inform every uncertainty.

Third, while there were 79 patients in the study, the number at risk at time zero in the published KM diagrams for OS and PFS (Eyre et al. Figure 1(A) and (B)) is reported as 78. The reason for this discrepancy is not clear. Third, Eyre et al. Figure 1(E) suggests prior therapy PFS/TTP was available from only 74 patients. These limitations should be considered alongside the other limitations and biases associated with Comparison C when interpreting results (Section B.3.8.3).

B.3.4. Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Sections B.2.3–B.2.6, change in HRQL was assessed in Study 101-09 using the FACT-Lym instrument, which comprises multiple domains including physical, social, functional and emotional well-being. As reported in Section B.2.6, overall, HRQL was stable or improved for patients treated with idelalisib[31], and median best change from baseline in FACT-Lym score showed clinically meaningful improvement at least once during follow-up for multiple domains including emotional and functional well-being. Although indicative of the HRQL benefit of idelalisib for double-refractory FL patients in England, these HRQL data in isolation are limited in their usefulness for informing patient utility assumptions in cost-effectiveness analyses, and patient-reported EQ-5D data from the literature, used to inform utility assumptions in TA472 and appraisals of idelalisib in this indication for Scotland, Wales and Ireland[32, 33, 48, 55], are the most relevant, if limited, utility data for this appraisal, as reported in Section B.3.4.3.

B.3.4.2 Mapping

The search for published HRQL evidence identified no studies mapping FACT-Lym patient data to EQ-5D values, and scant published evidence in general, in the specific FL population relevant to this appraisal. There are no mapping algorithms or publicly available and suitable data Gilead are aware of that would allow mapping from Study 101-09 data to UK EQ-5D utility values.

B.3.4.3 Health-related quality-of-life studies

A systematic search for HRQL evidence was conducted in 2014 alongside the 2014 search for economic evidence reported in Appendix G, and identified only one study reporting utility or HRQL data for previously treated FL.[22] In accordance with the economic search update, the search for HRQL evidence was updated on 17 February 2018, but identified no new relevant evidence. The methods and results from both the original evidence review and its update are reported in Appendix H.

There is clear a shortage of HRQL evidence for the specific patient population considered in this submission. Nevertheless, an investigation into the quality of life of 222 UK adults with histologically confirmed FL of various disease stages, reported by

Pettengell et al.[22], has been a useful source of information in (i) informing utility values for the only recent NICE STA in FL[53] and SMC, NCPE and AWMSG appraisals of idelalisib in its licensed FL indication, and in (ii) providing insight into the aspects of FL which most affect patients' quality of life.

Pettengell et al. assessed patient HRQL using the FACT-Lym instrument and also administered the Hospital Anxiety and Depression Scale (HADS)[62], to measure psychological morbidity, and the Work Productivity and Activity Impairment Scale (WPAI)[63], to assess the influence of the disease upon activity and productivity. Over 80% of all patients had mild or normal anxiety levels, and nearly 95% of patients had mild or normal depression scores.[22] Over 25% of activities were impaired for each disease status for those not disease-free in the sample, and for those with relapsed disease, this figure was over 45%, suggesting that FL does affect physical and functional well-being, and increasingly so as the disease progresses.[22]

Pettengell et al. identified a clear relationship between disease status and HRQL in their study.[22] Patients with active relapsed disease reported worse HRQL outcomes across FACT-Lym domains, in comparison to those in remission, partial responders to therapy, and those with newly diagnosed disease, and this result was robust to the authors' statistical analyses (ordinary least squares linear regression of the FACT-Lym Total Outcome Score upon scores from each contributory domain).[22] Following FL progression, disease symptoms will again become apparent, driving the decrease in HRQL observed by Pettengell et al. Response to treatment will drive a decrease in symptoms and an improvement in quality of life. Although the study design was cross-sectional[22], this is highly suggestive of a significant fall in HRQL upon disease progression for Study 101-09 FL patients.

Pettengell et al. categorised patients by the stage of their FL, using the categories 'active disease—newly diagnosed', 'active disease—relapsed', 'partial response', 'complete response' and 'disease free' (no detectable disease beyond first follow-up).[22] However, this patient sample was also combined into two broader groups, to represent the health states "progression-free" (which included those in 'partial response', 'complete response' and 'disease free' categories) and "progression" (which included those in 'active disease—relapsed'), and administered the EQ-5D questionnaire, as reported separately.[54]

Mean (standard error) EQ-5D utility for the "progression-free" group was 0.805 (0.018), and for the "progression" group was 0.618 (0.056).[54] These values are used to capture utility for patients in pre-progressive and progressive disease health states in all cost-effectiveness analyses considered in this submission.

B.3.4.4 Adverse reactions

The HRQL impact of Grade 3 and 4 treatment-emergent AEs related is explicitly incorporated in the cost-effectiveness analysis. The AEs considered were those Grade 3 and higher treatment-emergent AEs in the June 2015 data lock ITT analysis set. Utility decrement estimates for these AEs were sourced from a targeted review of the literature and are reported in Table 39.

Table 39: AE utility decrement estimates

Grade 3/4 AE	Utility decrement	SE	Source
Acute kidney injury	-0.060	0.012[a]	Juday et al. (2013)[64]
Alanine aminotransferase increased	0.000	0.000	Assumption
Anaemia	-0.119	0.020	Swinburn et al. (2010)[65]
Aspartate aminotransferase increased	0.000	0.000	Assumption
Asthenia	-0.115	0.023[a]	Lloyd et al. (2006)[66]
Colitis	-0.047	0.016	Assumed equivalent to diarrhoea
Dehydration	-0.100	0.020[a]	Lloyd et al. (2006)[66]
Diarrhoea	-0.047	0.016	Nafees et al. (2008)[67]
Dyspnoea	-0.050	0.012	Doyle et al. (2008)[68]
Febrile neutropenia	-0.150	0.030[a]	Lloyd et al. (2006)[66]
Hypokalaemia	-0.124	0.018	NICE TA 250 (2012)[69]
Hypotension	-0.057	0.011[a]	Hannouf et al. (2012)[70]
Neutropenia	-0.090	0.015	Nafees et al. (2008)[67]
Pneumonia	-0.200	0.020	Beusterien et al. (2010)[71]
Pyrexia	-0.110	0.022[a]	Beusterien et al. (2010)[71]
Thrombocytopenia	-0.108	0.022[a]	Tolley et al. (2013)[72]

Key: AE, adverse event; ITT, intent-to-treat; SE, standard error.
Note: [a], in the absence of reported SE information, SE is assumed to be 20% of the mean estimate.
Source: CSR Table 3.7.1: Grade [b] 3 or Higher Treatment-Emergent Adverse Events by Preferred Term ITT Analysis Set.

AE utility decrements are applied in the model for the expected duration of each AE. Table 40 shows the average duration estimate for each Grade 3/4 AE considered

and its source. Where an expected duration estimate could not be sourced, mean duration was assumed to be the maximum of the available duration estimates.

Table 40: Duration of AEs

Grade 3/4 AE	Duration (days)	Source
Acute kidney injury	35.33	Assumed to be the maximum of all Grade 3/4 AEs
Alanine aminotransferase increased	35.33	Assumed to be the maximum of all Grade 3/4 AEs
Anaemia	16.07	PIX301 CSR 2010 as reported in NICE TA 306[73]
Aspartate aminotransferase increased	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Asthenia	35.33	PIX301 CSR 2010 as reported in NICE TA 306[73]
Colitis	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Dehydration	8.00	PIX301 CSR 2010 as reported in NICE TA 306[73]
Diarrhoea	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Dyspnoea	12.72	PIX301 CSR 2010 as reported in NICE TA 306[73]
Febrile neutropenia	7.14	PIX301 CSR 2010 as reported in NICE TA 306[73]
Hypokalaemia	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Hypotension	8.00	PIX301 CSR 2010 as reported in NICE TA 306[73]
Neutropenia	15.09	PIX301 CSR 2010 as reported in NICE TA 306[73]
Pneumonia	14.00	PIX301 CSR 2010 as reported in NICE TA 306[73]
Pyrexia	12.30	PIX301 CSR 2010 as reported in NICE TA 306[73]
Thrombocytopenia	23.23	PIX301 CSR 2010 as reported in NICE TA 306[73]
Key: AE, adverse event; CSR, clinical study revolt.		

The cycle-specific probability of each AE, from Study 101-09 data, is multiplied with the QALY decrement of each event to obtain cycle-specific QALY decrements, as reported in Table 41. Since many of these AEs have a duration greater than the 1-week model cycle, all QALY decrements due to AEs are applied at the end of the same cycle it occurs in, for the simplicity of model calculation and to avoid tracking patients through the cycles following an AE. The sum of these cycle-specific QALY decrements is reported as the total QALY decrement per cycle due to AEs for idelalisib in Table 41. This decrement is applied in the model to the proportion of patients in the 'Pre-Progression, On Treatment' health state at the end of each cycle.

In Comparisons A (base case) to C, where the comparison between idelalisib and other treatments including chemotherapy for chemotherapy-suited patients is considered, on-treatment chemotherapy AEs are assumed equivalent to those for idelalisib.

Pettengell et al. observed decreased HRQL during chemotherapy administration, related to the side effects characteristically associated with it, such as nausea and vomiting.[22] In consideration of oral idelalisib versus alternative active treatment for those eligible for chemotherapy, there will likely be a HRQL gain for FL patients receiving a single agent oral therapy, as opposed to complex intravenous base regimens, which necessitate repeated inpatient stays in specialised care units. The cost-effectiveness base case and scenario analyses tested are blind to this likely benefit and so likely underestimate the cost-effectiveness of idelalisib, and this is a relevant consideration when interpreting results.

In Comparison D, where idelalisib is compared to BSC, there are no treatment-related AE effects for patients in the comparator arm.

Table 41: AE utility decrements, cycle probabilities and cycle QALY decrement

Grade 3/4 AE	AE utility decrement	Cycle probability	Cycle QALY decrement
Acute kidney injury	-0.006	0.001	-0.000005
Alanine aminotransferase increased	0.000	0.002	0.000000
Anaemia	-0.005	0.002	-0.000008
Aspartate aminotransferase increased	0.000	0.002	0.000000
Asthenia	-0.011	0.001	-0.000010
Colitis	-0.005	0.001	-0.000004
Dehydration	-0.002	0.001	-0.000003
Diarrhoea	-0.005	0.005	-0.000022
Dyspnoea	-0.002	0.001	-0.000002
Febrile neutropenia	-0.003	0.001	-0.000003
Hypokalaemia	-0.012	0.002	-0.000024
Hypotension	-0.001	0.001	-0.000001
Neutropenia	-0.004	0.006	-0.000023
Pneumonia	-0.008	0.003	-0.000026
Pyrexia	-0.004	0.001	-0.000003
Thrombocytopenia	-0.007	0.002	-0.000012
Total QALY decrement per cycle due to AEs			**-0.0001**

Key: AE, adverse event, QALY, quality-adjusted life year.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 42: Summary of utility values for cost-effectiveness analysis

Disease state	Utility value	Confidence interval	Reference in submission	Justification
Pre-progressive disease	0.81	[0.77,0.84]	Section B.3.4.1	Identified through the systematic search of the literature reported in Appendix H, and consistent with the values used in NICE TA472
Progressive disease	0.62	[0.51,0.72]		
Adverse Event	**Utility Decrement**	**Confidence interval**	**Reference in submission**	**Justification**
Acute kidney injury	-0.06	[-0.04,-0.09]	Section B.3.4.4	Identified through targeted published literature search or assumed equivalent to published estimate for similar AE
Alanine aminotransferase increased	0.00	N/A		
Anaemia	-0.12	[-0.08,-0.16]		
Aspartate aminotransferase increased	0.00	N/A		
Asthenia	-0.12	[-0.07,-0.16]		
Colitis	-0.05	[-0.02,-0.08]		
Dehydration	-0.10	[-0.06,-0.14]		
Diarrhoea	-0.05	[-0.02,-0.08]		
Dyspnoea	-0.05	[-0.03,-0.08]		
Febrile neutropenia	-0.15	[-0.10,-0.21]		
Hypokalaemia	-0.12	[-0.09,-0.16]		
Hypotension	-0.06	[-0.04,-0.08]		
Neutropenia	-0.09	[-0.06,-0.12]		
Pneumonia	-0.20	[-0.16,-0.24]		
Pyrexia	-0.11	[-0.07,-0.16]		
Thrombocytopenia	-0.11	[-0.07,-0.15]		
Key: N/A, not applicable.				

B.3.5. Cost and healthcare resource use identification, measurement and valuation

In line with the NICE Reference Case and reported in Section B.3.2.2, the perspective on costs in all cost-effectiveness analyses is that of the NHS and Personal Social Services (PSS) in England. A systematic search for healthcare

resource use and cost data relevant to this perspective and submission is reported in Appendix I and was conducted alongside the searches for cost-effectiveness and HRQL evidence reported in Appendices G and H. Again, this search was a modified update of a 2014 search. Neither the updated nor original search identified any relevant evidence on the patient population under consideration.

B.3.5.1 Intervention and comparator acquisition and administration costs

Idelalisib

The list price for idelalisib is £3,114.75 per pack of 60 tablets. Assuming a use of two tablets per day and incorporating a mean dose-intensity estimate of 93.75%, taking into account physician-prescribed reductions, escalations and interruptions that occurred in Study 101-09 (June 2015 DBL, ITT [iNHL] analysis set) and are likely to happen in NHS practice, the total drug acquisition cost for the intervention is £681.35 per week. Inclusive of the agreed commercial discount, the NHS England acquisition cost for one patient-week of FL treatment is [redacted]

Chemotherapy Regimens

As described in Section B.3.2.1, comparisons to chemotherapy regimens including the base case cost-effectiveness comparison (Comparison A) assume chemotherapy treatment is represented by the basket of chemotherapies received immediately prior to idelalisib by FL patients in Study 101-09. These comprise 16 different treatment strategies across 72 patients, illustrating the lack of a standard of care in the treatment of refractory FL.

The different treatments used, the number of patients receiving each treatment, and the recommended treatment duration in weeks of each are reported in Table 43. Table 44 shows the weekly doses of component drugs applied for each strategy listed in Table 43. Average patient dose per week in Table 44 was calculated from the does and duration sources cited in Table 43. Table 45 summarises the unit, measure, pack size and cost per mg, for component elements of each chemotherapy regimen. Table 46 shows the administration costs considered for intravenous therapies. To calculate the required weekly dose for regimens whose dose is determined by a patient's body surface area (BSA), the mean baseline BSA from

Study 101-09 was used; the mean BSA in the 72 FL patients in the study was calculated as 1.91m^2.[74] Table 47 summarises the weekly drug acquisition and administration costs associated with *chemotherapy regimens* in the cost-effectiveness model, incorporating all these data.

Table 43: Prior therapy regimens, component drugs and number of patients receiving each regimen, Study 101-09 FL patients

Regimen abbreviation	Component drugs in the regimen	Number of patients	Treatment duration (weeks)	Dose and treatment duration source
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone	25	24	West London Cancer Network[75]
R	Rituximab	10	4	West London Cancer Network[76]
R-B	Rituximab, bendamustine	7	24	Derby-Burton Local Cancer Network[77]
R-CVP	Rituximab, cyclophosphamide, vincristine, prednisolone	7	24	Flinn 2014[78]
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone	6	24	as R-CHOP
Investigative therapy	Unknown	4	-	N/A
R-P	Rituximab, prednisolone	2	24	as R-CHOP
R-CHO	Rituximab, cyclophosphamide, doxorubicin, vincristine	2	24	as R-CHOP
CVP	Cyclophosphamide, vincristine, prednisolone	2	24	as R-CVP
FR	Fludarabine, rituximab	1	16	West London Cancer Network[79]
CHEP	Cyclophosphamide, adriamycin, etoposide, prednisone	1	18	Salles 2008[80]
R-Ch	Rituximab, chlorambucil	1	32	Sachanas 2011[81]
CHOEP	Cyclophosphamide, adriamycin, vincristine, prednisone, etoposide	1	24	as R-CHOP with etoposide (Wunderlich 2003[82])
CHEPi	Cyclophosphamide, adriamycin, etoposide, prednisone, interferon	1	18	as CHEP and SmPC interferon[83]
ChP	Chlorambucil, prednisolone	1	32	West London Cancer Network[84]
FM	Fludarabine, mitoxantrone	1	16	South East London Cancer Network[85]

Table 44: Prior therapy dosing regimens

Regimen abbreviation	Component drug	Average patient dose per week (mg)
R-CHOP	Rituximab	239.26
	Cyclophosphamide	478.52
	Doxorubicin	31.90
	Vincristine	0.89
	Prednisolone (oral)	319.01
R	Rituximab	717.78
R-B	Bendamustine	86.13
	Rituximab	179.45
R-CVP	Rituximab	239.26
	Cyclophosphamide	478.52
	Vincristine	0.89
	Prednisolone (oral)	319.01
CHOP	Cyclophosphamide	478.52
	Doxorubicin	31.90
	Vincristine	0.89
	Prednisolone (oral)	319.01
R-P	Rituximab	239.26
	Prednisolone (oral)	319.01
R-CHO	Rituximab	239.26
	Cyclophosphamide	478.52
	Doxorubicin	31.90
	Vincristine	0.89
CVP	Cyclophosphamide	478.52
	Vincristine	0.89
	Prednisolone (oral)	319.01
FR	Fludarabine	47.85
	Rituximab	179.45
CHEP	Cyclophosphamide	382.82
	Doxorubicin	15.95
	Etoposide	25.52
	Prednisolone (oral)	127.61
R-Ch	Rituximab	179.45
	Chlorambucil	47.85
CHOEP	Cyclophosphamide	478.52
	Doxorubicin	31.90
	Vincristine	0.89

Regimen abbreviation	Component drug	Average patient dose per week (mg)
	Etoposide	191.41
	Prednisolone (oral)	319.01
CHEPi	Cyclophosphamide	382.82
	Doxorubicin	15.95
	Etoposide	25.52
	Prednisolone (oral)	127.61
	Interferon	15 mIU
ChP	Chlorambucil	66.99
	Prednisolone (oral)	267.97
FM	Fludarabine	57.42
	Mitoxantrone	4.79

Table 45: Unit, measure, pack size and cost per mg, *Chemotherapy Regimens*

Drug	Unit	Measure (mg)	Unit cost	Pack size	Cost per mg	Average cost per mg	Source
Rituximab	Concentrate	100	£349.25	2	£1.75	£1.75	MIMS UK Feb 2018[86]
	Concentrate	500	£873.15	1	£1.75		MIMS UK Feb 2018[86]
Cyclophosphamide	Concentrate	500	£8.62	1	£0.02	£0.02	eMIT national database, Feb 2018[87]
	Concentrate	1000	£15.89	1	£0.02		eMIT national database, Feb 2018[87]
	Concentrate	2000	£25.99	1	£0.01		eMIT national database, Feb 2018[87]
Doxorubicin	Concentrate	10	£1.34	1	£0.13	£0.10	eMIT national database, Feb 2018[87]
	Concentrate	50	£3.63	1	£0.07		eMIT national database, Feb 2018[87]
	Concentrate	200	£16.82	1	£0.08		eMIT national database, Feb 2018[87]
Vincristine	Concentrate	1	£15.64	5	£3.13	£3.25	eMIT national database, Feb 2018[87]
	Concentrate	2	£26.59	5	£2.66		eMIT national database, Feb 2018[87]
	Concentrate	5	£98.72	5	£3.95		eMIT national database, Feb 2018[87]
Bendamustine	Concentrate	25	£6.85	1	£0.27	£0.28	MIMS UK Feb 2018[86]
	Concentrate	100	£27.77	1	£0.28		MIMS UK Feb 2018[86]
Cytarabine	Concentrate	100	£17.16	5	£0.03	£0.02	eMIT national database, Feb 2018[87]
	Concentrate	100	£18.90	5	£0.04		eMIT national database, Feb 2018[87]
	Concentrate	500	£21.13	5	£0.01		eMIT national database, Feb 2018[87]
	Concentrate	1000	£6.13	1	£0.01		eMIT national database, Feb 2018[87]
	Concentrate	2000	£12.38	1	£0.01		eMIT national database, Feb 2018[87]
Etoposide	Concentrate	100	£2.30	1	£0.02	£0.02	eMIT national database, Feb 2018[87]
	Concentrate	500	£9.65	1	£0.02		eMIT national database, Feb 2018[87]
Mitoxantrone	Concentrate	20	£58.44	1	£2.92	£3.90	eMIT national database, Feb 2018[87]
	Concentrate	25	£121.79	1	£4.87		eMIT national database, Feb 2018[87]
Interferon alfa 2 (Mega Units)	Concentrate	10 mIU	£41.55	1	£4.16	£4.41 (per mIU)	MIMS UK Feb 2018[86]
	Concentrate	25 mIU	£103.94	1	£4.16		MIMS UK Feb 2018[86]
	Concentrate	18 mIU	£74.83	1	£4.16		MIMS UK Feb 2018[86]

Drug	Unit	Measure (mg)	Unit cost	Pack size	Cost per mg	Average cost per mg	Source
	Concentrate	30 mIU	£124.72	1	£4.16		MIMS UK Feb 2018[86]
	Concentrate	60 mIU	£249.45	1	£4.16		MIMS UK Feb 2018[86]
	Concentrate	3 mIU	£14.20	1	£4.73		MIMS UK Feb 2018[86]
	Concentrate	4.5 mIU	£21.29	1	£4.73		MIMS UK Feb 2018[86]
	Concentrate	6 mIU	£28.37	1	£4.73		MIMS UK Feb 2018[86]
	Concentrate	9 mIU	£42.57	1	£4.73		MIMS UK Feb 2018[86]
Prednisolone	Tablet	1	£0.19	28	£0.01	£0.01	eMIT national database, Feb 2018[87]
	Tablet	2.5	£1.10	30	£0.01		eMIT national database, Feb 2018[87]
	Tablet	2.5	£3.54	100	£0.01		eMIT national database, Feb 2018[87]
	Tablet	5	£0.31	28	£0.00		eMIT national database, Feb 2018[87]
	Tablet	5	£1.15	30	£0.01		eMIT national database, Feb 2018[87]
	Tablet	5	£4.00	100	£0.01		eMIT national database, Feb 2018[87]
	Tablet	25	£23.15	56	£0.02		eMIT national database, Feb 2018[87]
Chlorambucil	Tablet	2	£42.87	25	£0.86	£0.86	MIMS UK Feb 2018[86]
Fludarabine	Tablet	50	£24.16	1	£0.48	£0.47	eMIT national database, Feb 2018[87]
	Tablet	50	£23.01	1	£0.46		eMIT national database, Feb 2018[87]

Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; mIU, million international units; N/A, not applicable.

Table 46: Administration costs

Administration costs for IV therapies	Unit cost	Source
Administration of intravenous R-chemotherapy	£299.68	NHS Reference Cost (2016/17) SB13Z: Deliver more complex Parenteral Chemotherapy at first attendance[88]
Administration of other intravenous chemotherapy	£355.54	NHS Reference Cost (2016/17) SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance[88]
Key: IV, intravenous; NHS, National Health Service; R, rituximab.		

Table 47: Summary of drug and administration costs for each modelled treatment regimen

Regimen	Drug	Active weekly drug costs		Active weekly administration costs
		Each component	Total	
R-CHOP	Rituximab	£417.82	£434.35	£118.51
	Cyclophosphamide	£7.36		
	Doxorubicin	£3.09		
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
R	Rituximab	£1,253.45	£1,253.45	£355.54
R-B	Bendamustine	£23.76	£337.12	£163.81
	Rituximab	£313.36		
R-CVP	Rituximab	£417.82	£431.26	£118.51
	Cyclophosphamide	£7.36		
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
CHOP	Cyclophosphamide	£7.36	£16.54	£99.89
	Doxorubicin	£3.09		
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
R-P	Rituximab	£417.82	£421.01	£118.51
	Prednisolone (oral)	£3.19		
R-CHO	Rituximab	£417.82	£431.16	£118.51
	Cyclophosphamide	£7.36		
	Doxorubicin	£3.09		
	Vincristine	£2.90		
CVP	Cyclophosphamide	£7.36	£13.45	£99.89
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
FR	Fludarabine	£22.57	£335.93	£88.89
	Rituximab	£313.36		
CHEP	Cyclophosphamide	£5.89	£9.25	£99.89
	Doxorubicin	£1.55		

Regimen	Drug	Active weekly drug costs		Active weekly administration costs
		Each component	Total	
	Etoposide	£0.54		
	Prednisolone (oral)	£1.28		
R-Ch	Rituximab	£313.36	£354.39	£88.89
	Chlorambucil	£41.03		
CHOEP	Cyclophosphamide	£7.36	£20.59	£299.68
	Doxorubicin	£3.09		
	Vincristine	£2.90		
	Etoposide	£4.05		
	Prednisolone (oral)	£3.19		
CHEPi	Cyclophosphamide	£5.89	£75.43	£899.04
	Doxorubicin	£1.55		
	Etoposide	£0.54		
	Prednisolone (oral)	£1.28		
	Interferon	£66.18		
ChP	Chlorambucil	£57.44	£60.12	£74.92
	Prednisolone (oral)	£2.68		
FM	Fludarabine	£27.09	£45.73	£74.92
	Mitoxantrone	£18.65		

The weekly cost of chemotherapy regimens is estimated by weighting the total cost of each Study 101-09 prior therapy regimen by the proportion of Study 101-09 FL patients who received it, harnessing the data in Table 43 and Table 47. The four patients who received what was reported as “investigative therapy” (Table 43) were removed from the denominator in calculations of the proportion of patients assigned to each prior therapy.

As described in Section B.3.3.1, ToT data are used to capture expected treatment duration in cost-effectiveness analyses. For *Chemotherapy Regimens*, the length of each treatment regimens from the best available evidence, summarised in Table 43, also informs treatment duration. Recommended maximum treatment durations are assumed to hold in clinical practice in England.

Accounting for the distribution *and duration* of prior treatment regimens in Study 101-09 and the weekly estimated drug acquisition costs in Table 47, Table 48 summarises the weekly prior therapy treatment and administration costs in the model and the model cycles to which they are applied.

Table 48: Weekly prior therapy treatment costs across model cycles

Model weeks	Weekly drug cost	Weekly administration cost	Weekly total cost
1–4	£463.29	£167.56	£630.85
5–16	£278.96	£115.27	£394.23
17–18	£273.35	£112.86	£386.21
19–24	£272.10	£98.17	£370.28
25–32	£6.10	£2.41	£8.50

Monitoring patients treated with idelalisib

To prevent and monitor the occurrence of serious infections, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and CMV, patients treated with idelalisib should receive prophylaxis for PJP and should be screened for CMV infections, as reported in Section B.2.10.

PJP prophylaxis occurs with a continuous treatment with co-trimoxazole (480mg daily) while on idelalisib treatment and 2–6 months thereafter. The model uses a conservative assumption that PJP prophylaxis is continued until 6 months after idelalisib treatment. The cost per pack of 28 tablets is £2.29[86], resulting in a weekly cost of £0.57 per patient. CMV monitoring occurs with a polymerase chain reaction (PCR) test. Several different assumptions can be made on monitoring for CMV. The cost of a PCR test is £7.50 if the NHS reference costs estimate for a microbiology test is used, or £56.00 from the Medtech innovation briefing [MIB24], NICE (2015).[89] In the base case, the more expensive cost per test of £56 is used. Clinical KOL in UK recommended the following frequency of PCR tests per year for patients on idelalisib:

- Months 0-6: one test every month
- Months 6-12: one test every two months
- Months 12+: one test every three months

B.3.5.2 Health-state unit costs and resource use

This section describes the costs associated with the management of FL aside from the costs of treatment that are included in the model. Examples are health care

visits, tests and procedures. Unit cost estimates for resources associated with disease management are presented in Table 49. The unit cost for each element of monitoring was taken from NHS reference costs.[88]

Table 49: Unit costs for resource use

Resource	Unit cost	Source
Haematologist/outpatient visit	£167.83	NHS Reference Costs 2016/17 CL WF01A: 303 (Clinical Haematology)[88]
Specialist nurse	£110.00	PSSRU 2017[90]
Blood test or haematology/blood count or Serum chemistry	£3.06	NHS Reference Costs 2016/17 Directly Accessed Pathology Services; DAPS05[88]
Radiological/CT assessment	£85.56	NHS Reference Costs 2016/17 Computerised Tomography Scan of one area, without contrast, 19 years and over; RD20A[88]
Biopsy	£512.59	NHS Reference Costs 2016/17 SA33Z Diagnostic Bone Marrow Extraction Day Case[88]
Radiotherapy/Palliative Care	£145.12	NHS Reference Costs 2016/17 weighted average of RAD DCRDN[88]
Allogeneic stem cell transplantation	£35,180	NHS Reference Costs 2016/17 Total HRGs: weighted average of SA38A, SA39A and SA40Z[88]
Autologous stem cell transplantation	£17,174	NHS Reference Costs 2016/17 Total HRGs: SA26A[88]
Other chemotherapy	£10,316	Average prior therapy treatment cost
Key: CT, computed tomography; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.		

The costs applied for disease management are reported in Table 50 to Table 53. Table 50 shows disease monitoring costs applied in the “Pre-progression” health states. Table 51 shows the one-off costs associated with disease progression. This one-off cost is applied in the cycle that progression takes place. Table 52 shows the costs associated with disease monitoring in the “Post-progression” health state.

For disease monitoring, the frequency of healthcare provider visits was taken from a previous economic evaluation identified in the review of economic evidence.[91] The frequency of tests and procedures and resource use estimates shown were based on clinical validation of the European Society for Medical Oncology (ESMO) guidelines by UK-based clinical KOL for the diagnosis, treatment and follow-up of FL.[30]

Table 50: Disease management costs per model cycle associated with pre-progressive disease

	0–6 months	6–12 months	12 months onwards
Frequency of blood tests + serum chemistry (per year)[a]	26	12	12
Blood test costs (blood count + serum chemistry) per cycle	£1.52	£0.70	£0.70
Frequency of haematologist visits (per year)[a]	12	12	12
Haematologist costs per cycle	£38.60	£38.60	£38.60
Specialist nurse costs per cycle	£25.30	£25.30	£25.30
Frequency of radiologist visits (per year)[a]	1	1	1
Radiological/CT assessment costs per cycle	£1.64	£1.64	£1.64
Total costs per cycle	£67.06	£66.24	£66.24

Key: CT, computed tomography; KOL, key opinion leader.
Notes: [a], Based on clinical opinion from a UK-based KOL

Table 51: Disease management costs upon disease progression

On progression	% of patients[a]	Unit cost (£)	Total cost on progression (one-time cost applied on disease progression)
Radiological assessments	100%	£85.56	£213.71
Biopsy	25%	£512.59	

Key: KOL, key opinion leader.
Notes: [a], Based on clinical opinion from a UK-based KOL

Table 52: Disease management costs associated with post-progressive disease

Routine management: Progressive disease	Frequency (per year)*	Frequency (per cycle)	% of patients[a]	Unit cost (£)	Total cost (£)
Health care provider visits					
Physician outpatient visit	8	0.15	100%	£167.83	£25.73
Specialist nurse visit	8	0.15	100%	£110.00	£16.87
Tests and procedures					
Haematology/blood count	8	0.15	100%	£3.06	£0.47
Serum chemistry	8	0.15	100%	£3.06	£0.47
Radiological assessments	2	0.04	100%	£85.56	£3.28
Total management costs per week					£46.81

Key: KOL, key opinion leader.
Notes: [a], Based on clinical opinion from a UK-based KOL

Table 53 shows the costs associated with active relapse management in the "Post-progression" health state. Subsequent chemotherapy costs, which are assumed to be applicable to 15% of the progressed patients, were assumed to be the mean cost of prior chemotherapy, as reported in Table 48.

Table 53: Relapse management costs associated with post-progressive disease

Relapse-related	Frequency (per year)*	Frequency (per cycle)	% of patients[a]	Unit cost (£)	Total cost (£)
Radiotherapy	0.50	0.01	70%	£145.12	£0.97
Allogeneic stem cell transplantation	0.50	0.01	5%	£35,180	£16.86
Autologous stem cell transplantation	0.50	0.01	10%	£17,174	£16.46
Subsequent chemotherapy	0.50	0.01	15%	£10,316	£14.83
Total relapse-related costs per week					£49.11
Notes: [a], based on clinical opinion from UK-based KOL					

B.3.5.3 Adverse reaction unit costs and resource use

The AEs considered in the model are those treatment-emergent Grade 3 or 4 AEs reported by the investigator in Study 101-09 occurring in ≥3% of subjects. The unit costs associated with the management of these AEs were sourced from 2016/17 NHS reference costs, NICE guidelines or previous NICE appraisals (see Table 54).

Table 54: Costs associated with AEs in the economic model

Grade 3/4 AE	Cost	Source
Acute kidney injury	£2,618.20	NHS Reference Costs 2016/17 weighted average of LA07H to LA07P[88]
Alanine aminotransferase increased	£115.97	Assumed to have one outpatient visit, consultant led: follow-up attendance non-admitted face-to-face, medical oncology (WF01A); and five outpatient blood monitoring per episode (source: NHS Reference Costs 2016/17)[88]
Anaemia	£2,380.00	NHS Reference Costs 2016/17 NEL SA03H: Haemolytic Anaemia with CC Score 0-2[88]
Aspartate aminotransferase increased	£115.97	Assumed to have one outpatient visit, consultant led: follow-up attendance non-admitted face-to-face, medical oncology (WF01A); and five outpatient blood monitoring per episode (source: NHS Reference Costs 2016/17)[88]
Asthenia	£160.60	ERG report, NICE TA 306 2013; cost inflated from 2010/11 to 2016/17[73]
Colitis	£1,420.56	Assumed to be same as that diarrhoea

Grade 3/4 AE	Cost	Source
Dehydration	£1,423.55	ERG report, NICE TA 306 2013; cost inflated from 2010/11 to 2016/17[73]
Diarrhoea	£1,420.56	NHS Reference Costs 2016/17 NEI_L FD01J: Gastrointestinal Infections, without Interventions, with CC Score 0-1[88]
Dyspnoea	£867.46	ERG report, NICE TA 306 2013; cost inflated from 2010/11 to 2016/17[73]
Febrile neutropenia	£6,421.72	Nice Guidelines NG52; Appendix A; cost inflated from 2014/15 to 2016/17[92]
Hypokalaemia	£331.92	NHS Reference Costs 2016/17 Day cases: Fluid or Electrolyte Disorders weighted average from KC05G to KC05N[88]
Hypotension	£2,139.15	ERG report, NICE TA 306 2013; cost inflated from 2010/11 to 2016/17[73]
Neutropenia	£1,849.09	NHS Reference Costs 2016/17 NEI_L SA08J: Other Haematological or Splenic Disorders CC 0-2[88]
Pneumonia	£2,494.89	NHS Reference Costs 2016/17 NEI_L: weighted average of DZ11K to DZ11V[88]
Pyrexia	£1,500.03	ERG report, NICE TA 306 2013; cost inflated from 2010/11 to 2016/17[73]
Thrombocytopenia	£504.00	NHS Reference Costs 2016/17 NEI_S SA12K: Thrombocytopenia CC 0-1[88]
Key: AE, adverse event; ERG, Evidence Review Group; NHS, National Health Service.		

Applying these costs to the cycle probability of each event produces a total cycle cost of £49.95, as shown in Table 55. The same treatment-related cost is conservatively assumed for the comparator arm in Comparison A. For the comparison to BSC, Comparison D, no AE costs are applied.

Table 55: Cycle cost attributable to treatment-related AEs for active treatments

Grade 3/4 AE	Cycle probability	Cost per cycle
Acute kidney injury	0.001	£2.38
Alanine aminotransferase increased	0.002	£0.29
Anaemia	0.002	£3.78
Aspartate aminotransferase increased	0.002	£0.21
Asthenia	0.001	£0.15
Colitis	0.001	£1.29
Dehydration	0.001	£1.94
Diarrhoea	0.005	£6.76
Dyspnoea	0.001	£1.18
Febrile neutropenia	0.001	£7.29
Hypokalaemia	0.002	£0.68
Hypotension	0.001	£1.94
Neutropenia	0.006	£11.31
Pneumonia	0.003	£8.49
Pyrexia	0.001	£1.36

Grade 3/4 AE	Cycle probability	Cost per cycle
Thrombocytopenia	0.002	£0.91
Total cycle cost		£49.95
Key: AE, adverse event.		

B.3.5.4 Miscellaneous unit costs and resource use

The cost of care immediately prior to death is taken from a King's Fund report into improving choice at end of life[93], and is the average cost of community and acute care for UK patients with cancer in the last eight weeks of their life reported by the authors, inflated to 2017 levels.[90]

The cost for 8 weeks of care is £6,262.43. Assumed to be spread evenly across the last 8 weeks of a patient's life, this cost is applied as £782.80 per week to the proportion of patients in the "Palliative care" health state.

Not all of these costs are direct healthcare costs, with some falling on 'third sector' healthcare organisations; however, their inclusion is relevant to the disease and may introduce only minor bias as almost all patients die within the model time horizon.

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 56 presents a summary of the variables included in the model, their base case values, and the measurement of uncertainty and distribution.

Table 56: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Survival parameters			
Time on treatment idelalisib – Exponential	[redacted]	[redacted]	Section B.3.3
Time on treatment comparator – Exponential	[redacted]	[redacted]	
Time to progression idelalisib – Log-normal	log(scale): 2.513 log(shape): 0.262	log(scale): 0.04, 0.01 log(shape): 0.01, 0.01	
Time to progression	log(scale):	log(scale) log(shape)	

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
comparator – Log-normal	2.513 log(shape): 0.262	log(scale) 0.02 0.00 log(shape) 0.00 0.01	
Post progression survival – Exponential	log(scale): 4.018	Variance (log)scale:	
Adverse events - cycle probabilities			
Cycle probability, Acute kidney injury, Idelalisib	0.00	Beta (0.11,123.89)	Section B.3.4.4
Cycle probability, Alanine aminotransferase increased, Idelalisib	0.00	Beta (0.31,123.69)	
Cycle probability, Anaemia, Idelalisib	0.00	Beta (0.2,123.8)	
Cycle probability, Aspartate aminotransferase increased, Idelalisib	0.00	Beta (0.23,123.77)	
Cycle probability, Asthenia, Idelalisib	0.00	Beta (0.11,123.89)	
Cycle probability, Colitis, Idelalisib	0.00	Beta (0.11,123.89)	
Cycle probability, Dehydration, Idelalisib	0.00	Beta (0.17,123.83)	
Cycle probability, Diarrhoea, Idelalisib	0.00	Beta (0.59,123.41)	
Cycle probability, Dyspnoea, Idelalisib	0.00	Beta (0.17,123.83)	
Cycle probability, Febrile neutropenia, Idelalisib	0.00	Beta (0.14,123.86)	
Cycle probability, Hypokalaemia, Idelalisib	0.00	Beta (0.25,123.75)	
Cycle probability, Hypotension, Idelalisib	0.00	Beta (0.11,123.89)	
Cycle probability, Neutropenia, Idelalisib	0.01	Beta (0.76,123.24)	
Cycle probability, Pneumonia, Idelalisib	0.00	Beta (0.42,123.58)	
Cycle probability, Pyrexia, Idelalisib	0.00	Beta (0.11,123.89)	
Cycle probability, Thrombocytopenia, Idelalisib	0.00	Beta (0.23,123.77)	
Utility			
Utility in pre-progression health state	0.81	Beta (389.21,94.28)	Section B.3.4.5
Utility in post-progression health state	0.62	Beta (45.9,28.37)	
Utility decrement, Acute kidney injury	-0.06	Beta (23.44,367.23)	
Utility decrement, Alanine	0.00	Not included in SA	

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
aminotransferase increased			
Utility decrement, Anaemia	-0.12	Beta (31.07,230.03)	
Utility decrement, Aspartate aminotransferase increased	0.00	Not included in SA	
Utility decrement, Asthenia	-0.12	Beta (22.01,169.38)	
Utility decrement, Colitis	-0.05	Beta (8.61,175.35)	
Utility decrement, Dehydration	-0.10	Beta (22.4,201.6)	
Utility decrement, Diarrhoea	-0.05	Beta (8.61,175.35)	
Utility decrement, Dyspnoea	-0.05	Beta (16.44,312.42)	
Utility decrement, Febrile neutropenia	-0.15	Beta (21.1,119.57)	
Utility decrement, Hypokalaemia	-0.12	Beta (41.45,292.81)	
Utility decrement, Hypotension	-0.06	Beta (23.51,387.55)	
Utility decrement, Neutropenia	-0.09	Beta (30.69,311.37)	
Utility decrement, Pneumonia	-0.20	Beta (79.8,319.2)	
Utility decrement, Pyrexia	-0.11	Beta (22.14,179.13)	
Utility decrement, Thrombocytopenia	-0.11	Beta (22.19,183.29)	
Costs – Drug/admin			
Cycle cost, Idelalisib Drug Treatment	[redacted]	Not included in SA	Section B.3.5.1
Cycle cost, Idelalisib Administration Treatment	£0.00	Not included in SA	
Cycle cost, Previous Therapy Drug Treatment, treatments with 4 weeks duration	£184.33	Normal (£184.33, £36.87)	
Cycle cost, Previous Therapy Drug Treatment, treatments with 16 weeks duration	£5.61	Normal (£5.61, £1.12)	
Cycle cost, Previous Therapy Drug Treatment, treatments with 18 weeks duration	£1.25	Normal (£1.25, £0.25)	
Cycle cost, Previous Therapy Drug Treatment, treatments with 24 weeks duration	£266.01	Normal (£266.01, £53.20)	
Cycle cost, Previous Therapy Drug Treatment, treatments with 32 weeks duration	£6.10	Normal (£6.10, £1.22)	
Cycle cost, Previous Therapy Administration, treatments with 4 weeks duration	£52.29	Normal (£52.29, £10.46)	
Cycle cost, Previous Therapy Administration, treatments with 16 weeks duration	£2.41	Normal (£2.41, £0.48)	
Cycle cost, Previous Therapy	£14.69	Normal (£14.69, £2.94)	

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Administration, treatments with 18 weeks duration			
Cycle cost, Previous Therapy Administration, treatments with 24 weeks duration	£95.76	Normal (£95.76, £19.15)	
Cycle cost, Previous Therapy Administration, treatments with 32 weeks duration	£2.41	Normal (£2.41, £0.48)	
Costs – Resource use			
Cycle cost, routine management, progression-free disease, Months 0-6	£67.06	Normal (£67.06, £13.41)	Section B.3.5.2–B.3.5.4
Cycle cost, routine management, progression-free disease, Months 6-12	£66.24	Normal (£66.24, £13.25)	
Cycle cost, routine management, progression-free disease, Months 12+	£66.24	Normal (£66.24, £13.25)	
One off cost on progression	£213.71	Normal (£213.71, £42.74)	
Cycle cost, routine management, progressive disease	£46.81	Normal (£46.81, £9.36)	
Cycle cost, relapse management, progressive disease	£49.11	Normal (£49.11, £9.82)	
Cycle cost, end of life care	£782.80	Normal (£782.80, £156.56)	
Cost, chemo admin	£299.68	Normal (£299.68, £59.94)	
Cost, rituximab-chemo admin	£355.54	Normal (£355.54, £71.11)	
Cycle cost, PJP prophylaxis	£0.57	Normal (£0.57, £0.11)	
Cycle cost, CMV monitoring Months 0-6	£12.88	Normal (£12.88, £2.58)	
Cycle cost, CMV monitoring Months 6-12	£6.44	Normal (£6.44, £1.29)	
Cycle cost, CMV monitoring Months 12+	£4.29	Normal (£4.29, £0.86)	
Costs – Adverse events			
Total cost per episode, Acute kidney injury	£2,618.20	Normal (£2,618.20, £523.64)	Section B.3.5.3
Total cost per episode, Alanine aminotransferase increased	£115.97	Normal (£115.97, £23.19)	
Total cost per episode, Anaemia	£2,380.00	Normal (£2,380.0, £476.0)	
Total cost per episode, Aspartate aminotransferase increased	£115.97	Normal (£115.97, £23.19)	
Total cost per episode, Asthenia	£160.60	Normal (£160.60, £32.12)	

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Total cost per episode, Colitis	£1,420.56	Normal (£1,420.56, £284.11)	
Total cost per episode, Dehydration	£1,423.55	Normal (£1,423.55, £284.71)	
Total cost per episode, Diarrhoea	£1,420.56	Normal (£1,420.56, £284.11)	
Total cost per episode, Dyspnoea	£867.46	Normal (£867.46, £173.49)	
Total cost per episode, Febrile neutropenia	£6,421.72	Normal (£6,421.72, £1,284.34)	
Total cost per episode, Hypokalaemia	£331.92	Normal (£331.92, £66.38)	
Total cost per episode, Hypotension	£2,139.15	Normal (£2,139.15, £427.83)	
Total cost per episode, Neutropenia	£1,849.09	Normal (£1,849.09, £369.82)	
Total cost per episode, Pneumonia	£2,494.89	Normal (£2,494.89, £498.98)	
Total cost per episode, Pyrexia	£1,500.03	Normal (£1,500.03, £300.01)	
Total cost per episode, Thrombocytopenia	£504.00	Normal (£504.0, £100.80)	
Key: CI, confidence interval; CMV, cytomegalovirus; SA, scenario analysis.			

B.3.6.2 Assumptions

The key assumptions of the economic analysis are described in Table 57. The approach to modelling has been designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of key data, key assumptions have been necessary, and have been made to minimise potential bias in the analysis. These two statements are illustrated by the likely direction of bias and justification for analysis assumptions, summarised in Table 57.

Table 57: Summary of key assumptions of the economic analysis

#	Assumption	Likely bias direction	Justification
Comparison A (base case)			
1	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes	No bias expected	Section B.3.2.2 Model design accepted as a basis for informing decision-making by the SMC, the AWMSG and the NCPE. The health states are also consistent with those considered in in TA472 (Obinutuzumab

#	Assumption	Likely bias direction	Justification
	and NHS/PSS costs.		with bendamustine for treating follicular lymphoma refractory to rituximab).
2	Patient utility is affected by disease progression status only, and captured by the patient reported EQ-5D-3L data reported by Wild et al.	Against idelalisib	Section B.3.4 Patients may be expected to have a higher HRQL than with current care if treated with idelalisib, owing to its favourable toxicity profile versus chemotherapy regimens and the knowledge of being treated with a new, effective treatment. The analyses do not capture this, only capturing HRQL improvements from extensions in time in progression-free health states.
3	Adverse event rates, and health and cost consequences, are assumed to be similar for idelalisib and chemotherapy regimens	Against idelalisib	Sections B.3.4.4, B.3.5.3 The assessment of safety reported in Section B.2.10 highlights that, with the appropriate risk monitoring care, the toxicity profile of idelalisib can be expected to be favourable to chemotherapy regimens.

#	Assumption	Likely bias direction	Justification
4	The relative treatment benefit of idelalisib is assumed to be captured by delaying time to disease progression only	Against idelalisib	Sections B.3.2.1 This simplifying assumption is necessitated by the limits of comparing to prior therapy. The assumptions that pre-progression mortality and post-progression survival are not affected likely bias against idelalisib.
5	TTP on prior therapy is a representative proxy for TTP with currently available chemotherapy options for double refractory FL patients, with a 0.75 hazard ratio adjustment, to account for worsening response to therapy with each line of therapy	No bias expected	Sections B1.3, B.3.2.1, B.3.3.1, B.3.10 TTP is understood to shorten with every line of treatment. This assumption; based on published evidence and input from Dr Robert Marcus, Consultant Haematologist at London Bridge Hospital, in the clinical validation meeting reported in Section B.3.10; attempts to address this to an extent, though whether it overshoots or undershoots is subject to uncertainty.
6	Time to discontinuation on prior therapy is a representative proxy for TTP with currently available chemotherapy options for double refractory FL patients, with a 0.75 hazard ratio adjustment, to account for worsening response to therapy with each line of therapy	No bias expected	Sections B.3.2.1, B.3.3.1 #6 is imposed to align with the rationale and estimate choice for #5
7	Study 101-09 TTP, ToT and PPS for FL patients, modelled following NICE DSU TSD 14, capture expected outcomes for FL patients treated with idelalisib, if it is made available in NHS England practice	No bias expected	Section B.3.3.1 The assumption that regulatory trial outcomes are representative of likely clinical practice outcomes is questioned, but ultimately routinely accepted in NICE single technology appraisals. Here, the assumption is explicitly tested with the use of alternative clinical outcomes data from patients treated in clinical practice, in Comparisons B and C.
8	The basket of chemotherapy treatments received by Study 101-09 FL patients is reflective of the range of chemotherapy options received as best remaining option for double-refractory FL patients in clinical practice in England, for cost estimation purposes	No bias expected	Sections B.3.2.1, B.3.3.1, B.3.5 This assumption is inherent in assuming prior 101-09 prior therapy outcomes are a suitable proxy for active treatment comparator outcomes, in the absence of RCT data. In reality, it is likely a fair proxy, and was considered as such by Dr Marcus, in the clinical validation meeting reported in Section B.3.10.
9	Pre-progression mortality is assumed to be reflective of the scant pre-progression survival event data from Study 101-09, across model arms, irrespective of treatment.	Against idelalisib	Section B.3.2.1, B.3.3.1 Though based on few death events, the approach taken, linking pre-progression survival risk to age-specific general population mortality estimates, ensures the risk of death increases with age, reflecting reality. The number of pre-progression death events in Study 101-09 was also viewed as a likely reflection of the true risk by Dr Marcus, in the clinical validation meeting reported in Section

#	Assumption	Likely bias direction	Justification
			B.3.10. That the same assumption is applied to idelalisib and chemotherapy regimen arms of the model likely biases against idelalisib.

#	Assumption	Likely bias direction	Justification
Comparison B			
10	#1, #2, #3 and #8 also apply to Comparison B	No bias expected	See #1, #2, #3 and #8
11	Study 101-09 PFS, ToT and OS data for FL patients, modelled following NICE DSU TSD 14, capture expected outcomes for FL patients treated with idelalisib, if it is made available in NHS England practice	No bias expected	Sections B.3.2.1, B.3.3.2 This approach provides an alternative structural approach to the base case semi-Markovian analysis, and one more akin to the partitioned survival modelling approaches typical to NICE STA cancer submissions
12	MAIC-adjusted OS and PFS for double refractory FL patients recorded by HMRN, modelled following NICE DSU TSD 14, capture expected outcomes for FL patients treated with currently available chemotherapy regimens in NHS England practice	No bias expected	Sections B.3.2.1, B.3.3.2 In the absence of RCT data, HMRN data from the relevant but small patient group applicable to this appraisal
Comparison C			
13	#1, #2, #3. #4, #5, #6 and #8 and #9 also apply to Comparison C	Against idelalisib	Sections B.3.2.1, B.3.3.3, B.3.5 The expected direction of bias from #1, #2, #3 #4, #5, #6 and #8 and #9 is a mixture of neutral and against idelalisib
14	Pseudo-individual patient data, recreated using a published algorithm from digitised KM curves reported in a peer-reviewed publication, are an accurate reflection of the true patient data from the idelalisib CUP, and analyst assessment of progression versus death events, from comparison of PFS data and OS data, was accurate.	No bias expected	Sections B.3.2.1, B.3.3.3 Recreation of individual patient data in the absence of the data themselves, and in particular for an endpoint that was not explicitly reported, was necessary to allow the analysis carried out, but inevitably means some degree of estimation error, and this adds an extra layer of uncertainty to Comparison C, meaning the results should be interpreted with extra caution.
15	Estimated CUP TTP on idelalisib, modelled following NICE DSU TSD 14, capture expected outcomes for FL patients treated with idelalisib, if it is made available in NHS England practice	Against idelalisib	Sections B.3.2.1, B.3.3.3 The assumption that regulatory trial outcomes are representative of likely clinical practice outcomes is questioned, but ultimately routinely accepted in NICE single technology appraisals. A counterpoint to #7, Comparison C explicitly tests this assumption, highlighting the uncertainty around the size of clinical benefit, but providing further evidence of the existence of such a clinical benefit. Nevertheless, the baseline FLIPI and ECOG scores of CUP patients suggest these patients were predisposed for worse outcomes than both Study 101-09 patients and the group likely to receive idelalisib for FL if recommended, and should be interpreted accordingly.

#	Assumption	Likely bias direction	Justification
16	Estimated CUP TTP on prior therapy, modelled following NICE DSU TSD 14, captures expected outcomes for FL patients treated with idelalisib, subject to #6	No bias expected	Sections B.3.2.1, B.3.3.3 Baseline characteristics prior to last therapy were not reported by Eyre et al., so it is difficult to judge whether and the extent to which the poor predisposition described in #15 held prior to last therapy.
Comparison D			
17	#1, #2, #4 and #7 also apply to Comparison D	No bias expected	See #1, #2, #4 and #7
18	Patients who cannot receive chemotherapy are assumed to be in the progressive disease health state from model outset, with outcomes captured by Study 101-09 post-progression survival data, modelled following NICE DSU TSD 14	No bias expected	Section B.3.2.1 In the absence of comparator data, this assumption it felt to be reasonable, and was sufficient for HTA-based decision-making in Scotland, Wales and Ireland.

Key: DSU, Decision Support Unit; EAP, expanded access program; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HMRN, Haematological Malignancy Research Network; HRQL, health-related quality of life; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; NHS, National health Service; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; RCT, randomised controlled trial; SCT, stem cell transplant; ToT, time on treatment; TTP, time to progression; TSD, Technical Support Document.

B.3.7. Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 58 displays base case cost-effectiveness results, using the clinical comparison defined as Comparator A in Section B.3.2. All results presented are inclusive of the agreed confidential price discount of [redacted] to the list price for idelalisib. Time-preference discounting is applied to all cost and QALY outcomes, unless otherwise stated.

Idelalisib is estimated to offer a high per-patient incremental health benefit, providing over one additional year of life and an additional 0.91 discounted QALYs, versus the chemotherapy regimens typifying currently available care. The estimated incremental cost-effectiveness ratio (ICER) for idelalisib is £26,076 per QALY gained, suggesting idelalisib is a cost-effective option for double refractory FL patients, irrespective of end-of-life criteria for decision making.

As stressed in Section B.3, the limited and non-randomised clinical effectiveness data available for this small population means cost effectiveness estimates are inherently uncertain, and results from analyses using Comparison B and C approaches for comparative clinical effectiveness, shown in Section B.3.8.3, should be considered alongside these results, to paint a fuller picture. Nevertheless, the conservative nature of the comparative effectiveness approaches generally, and Comparison A in particular, outlined in Section B.3.6.2, means even the results in Table 58 in isolation are strongly suggestive that idelalisib is a valuable option for NHS patients in England with double-refractory FL.

Estimates of clinical outcomes compared with trial results and disaggregated results are presented in Appendix J.

Table 58: Base-case (Comparison A) cost-effectiveness results, including idelalisib CCD

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy Regimens	[redacted]	5.01	2.80	-	-	-	-
Idelalisib	[redacted]	6.34	3.71	£23,762	1.33	0.91	£26,076

Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8. Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is reported for the base case analysis only, although the cost-effectiveness model allows the user to generate probabilistic results for any of the programmed settings options, including all scenarios analyses reported in Section B.3.8.3.

PSA results for the base case analysis (Comparison A), based on 4,000 random draws from uncertain input parameter distributions, are summarised across Table 59, Figure 33 and Figure 34. The mean deterministic results in Table 58 are a close

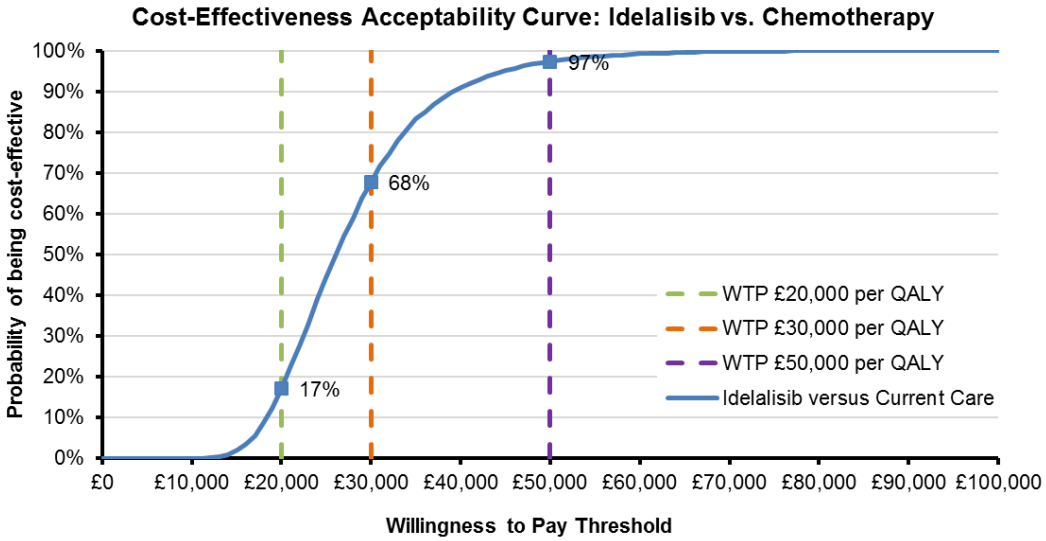
approximation of mean PSA results in Table 59, suggesting mean results are generally robust to uncertainty from parameter distributions. The estimated probability that idelalisib is a cost-effective alternative to current chemotherapy is 17% at a willingness to pay threshold of £20,000 for an additional QALY, 68% at a threshold of £30,000 for an additional QALY, and 97% at a threshold of £50,000 for an additional QALY, as shown in Figure 33. All 4,000 probabilistic results showed that idelalisib offers an incremental QALY benefit versus chemotherapy regimens at a positive incremental cost, as shown in Figure 34.

Table 59: Mean PSA base case (Comparison A) results, including idelalisib CCD

Technologies	Mean costs	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline
Chemotherapy Regimens	£32,535	2.81	-	-	-
Idelalisib	£56,356	3.75	£23,821	0.94	£25,364

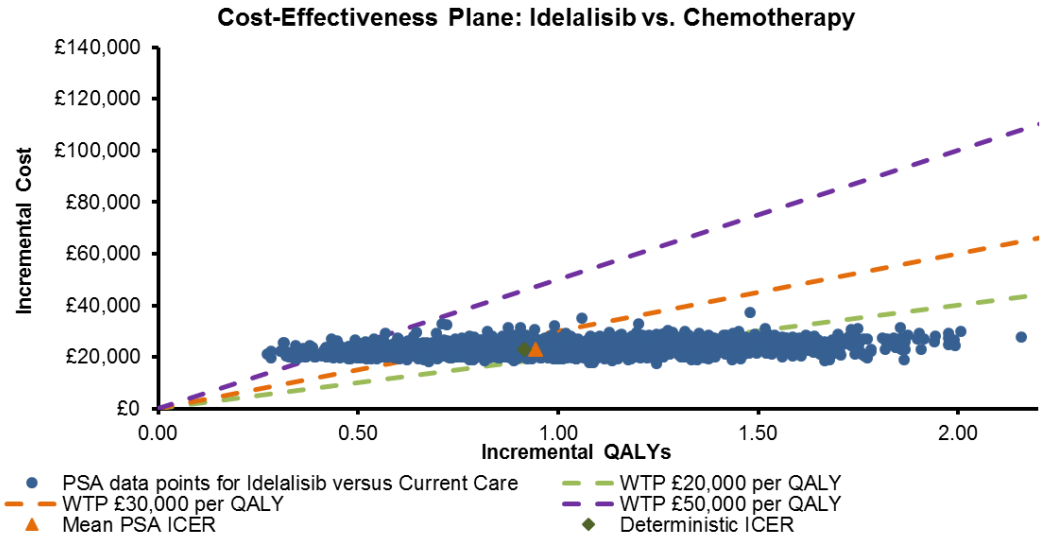
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 33: Cost-effectiveness acceptability curve, from base case (Comparison A) probabilistic results, including idelalisib CCD



Key: CCD, confidential commercial discount; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 34: PSA Scatterplot, from base case (Comparison A) probabilistic results, idelalisib versus chemotherapy regimens, including idelalisib CCD



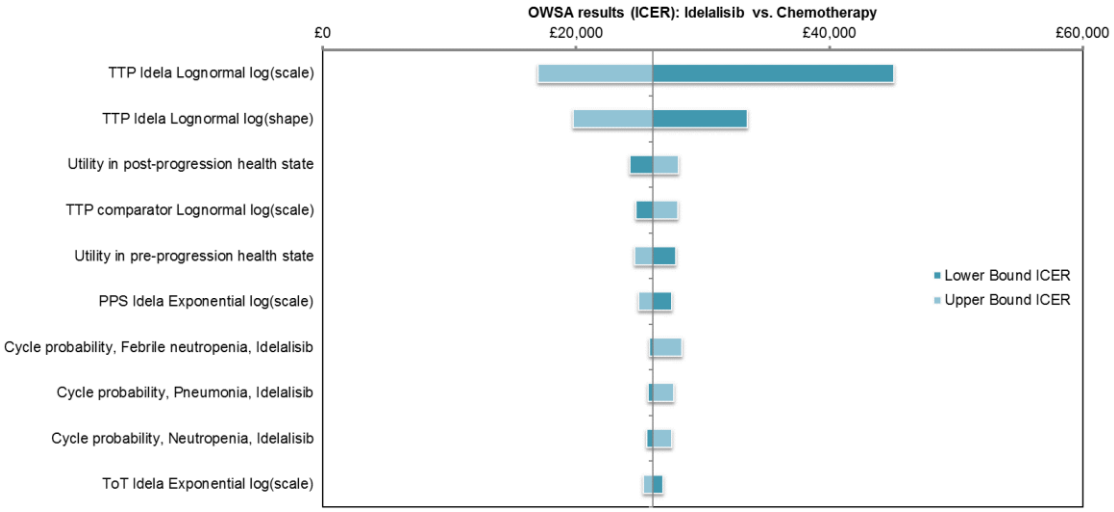
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay.

B.3.8.2 Deterministic sensitivity analysis

Figure 35 shows a tornado diagram depicting the 10 parameters that have the greatest influence on the ICER versus chemotherapy regimens in one-way sensitivity analyses (OWSA), when their values were set to their upper and lower limits of the confidence intervals reported in Section B.3.6.1. We recognise that varying correlated survival analysis model parameters independently in OWSA is theoretically problematic and do this with this knowledge, rather than exclude these influential parameters from OWSA.

The estimated base ICER is shown to be robust to isolated changes to the vast majority of uncertain parameters, somewhat sensitive to uncertainty around TTP parameter estimates, but nevertheless stays below the end of life threshold across OWSA.

Figure 35: Tornado diagram showing OWSA results, base case (Comparison A) cost-effectiveness analysis, including idelalisib CCD



Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALYs, quality-adjusted life years; ToT, time on treatment; TTP, time to progression.

B.3.8.3 Scenario analysis

The scenario analyses reported here together test the sensitivity of cost-effectiveness results to methodological, parameter and structural uncertainties in the cost-effectiveness analysis, and form an important element of this submission. Table 60 describes different scenarios tested, the rationale behind each, and documents the impact upon the base case deterministic ICER of each in turn. Table 61, Table 62 and Table 63 show total and incremental results from Comparisons B, C and D, respectively.

Comparison A results are shown to be robust to different time discounting preference assumptions and a reduced model time horizon, and fairly robust to changes in parametric survival model structural assumptions.

Deterministic results from Comparison B show poor expected health outcomes for chemotherapy regimen patients based on parametric extrapolation of MAIC-adjusted OS and PFS curves, reported in Section B.3.3.2, and lower expected survival and QALYs for idelalisib versus Comparisons A and C, but a far greater estimated incremental health benefit of 1.76 discounted QALYs. Although the incremental

estimated cost of idelalisib is higher in Comparison B versus A or C, owing mostly to the low estimated PFS for HMRN chemotherapy patients, the estimated ICER of £19,872, with expected survival of 2.29 years for HMRN chemotherapy patients, suggests idelalisib is a highly cost-effective end of life treatment for double-refractory FL patients.

Deterministic results from Comparison C suggest a lower QALY benefit associated with idelalisib than suggested by base case Comparison A results, and as a primary result of this, a higher ICER, though one still below the NICE acceptability threshold for end of life health technologies. However, when interpreting, it is important to consider the key limitations specific to Comparison C. The CUP data collection and management may be different to that in a registered clinical trial such as Study 101-09, and the information available is limited to that in a six-page correspondence publication in the British Journal of Haematology, its supplementary materials, and brief but helpful email clarifications with the corresponding author, Dr Toby Eyre. Importantly, the summary baseline characteristics reported by Eyre at al indicate a higher proportion of ECOG 2–4 and FLIPI 3–5 patients in the CUP versus Study 101-09 (25% versus 8% and 75% versus 54%), that may both (i) predispose CUP patients to worse outcomes than in Study 101-09 and (ii) indicate that the CUP patient group has worse predisposition than the FL patient group, who are likely to benefit from idelalisib in practice.

Results from Comparison D suggest idelalisib is a cost-effective treatment option for those high-need patients for whom the risk-benefit ratio for chemotherapy rules out such treatment, but who may have a viable treatment option in idelalisib. The analysis approach for chemotherapy-ineligible patients is clearly subject to strong assumptions and limitations, yet has been sufficient to allow HTA-approved access for such patients in Scotland, Ireland and Wales in recent years.

Table 60: Scenario analyses impact summary, including idelalisib CCD

Scenario	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			£26,076

Comparison B	Haematological Malignancy Research Network (HMRN) chemotherapy KM data digitised and used to create pseudo-IPD after matching adjusted indirect comparison with 101-09 study, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering HMRN chemotherapy clinical effectiveness estimates, where possible	-£6,204
Comparison C	Published UK & Ireland idelalisib CUP KM data digitised and used to create pseudo-IPD, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering published CUP idelalisib clinical effectiveness estimates, where possible	£20,935
Comparison D	Best supportive care (BSC) is considered as a comparator, for the patients who are not eligible for chemotherapy, under the assumptions that patients would progress instantly in the absence of an active treatment.	Exploration of the impact upon CE conclusions of considering best supportive care (BSC) as a comparator	-£804
Comparison A, Hazard ratio adjustment for expected drop in time to progression in the next line of treatment	Hazard ratio set to 1 implying no drop in time to progression in the next line of treatment for chemotherapy.	Exploration of alternative assumption that all patients will respond same in this line of therapy as they have in the previous line of therapy	£1,817
Comparison A, alternative discount rate preferences	Costs and benefits are discounted at 6%.	Discounting the benefits and costs in the future at a higher rate	£2,800
Comparison A, alternative discount rate preferences	Costs and benefits are not discounted.	Undiscounted results	-£4,119
Comparison A, alternative time horizon	Costs and benefits are accumulated for 10 years.	Shorter time horizon	£5,462
Comparison A, alternative pre-progression survival assumptions	Mortality hazard is assumed to be equal to that of a general population to model no risk of higher mortality in the pre-progression population.	Exploration of impact of no higher pre-progression mortality risk assumptions on the CE model conclusions	-£3,208
Comparison A, alternative parametric model choice for TTP	A Generalised Gamma parametric survival model fitted to the time to progression data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time to progression data	-£7,117
Comparison A, alternative parametric model choice for PPS	A Lognormal parametric survival model fitted to the post-progression survival data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of post-progression survival data	£3,785

Comparison A, alternative parametric model choice for ToT	A Lognormal parametric survival model fitted to the time on treatment data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time on treatment data	£2,023
Key: BSC, best supportive care; CCD, confidential commercial discount; CE, cost-effectiveness; CUP, Compassionate Use Programme; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; KM, Kaplan-Meier; UK, United Kingdom.			

Table 61: Comparison B: 101-09 / HMRN (chemotherapy), including idelalisib CCD

	Costs	QALYs	Life years	Incremental			ICER
				Costs	QALYs	Life years	
Chemotherapy Regimens	[redacted]	1.44	2.29	-	-	-	£19,872
Idelalisib	[redacted]	3.19	5.33	£34,924	1.76	3.04	
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.							

Table 62: Comparison C: UK&I CUP / UK&I CUP (chemotherapy), including idelalisib CCD

	Costs	QALYs	Life Years	Incremental			ICER
				Costs	QALYs	Life Years	
Chemotherapy Regimens	[redacted]	2.92	5.18	-	-	-	£47,011
Idelalisib	[redacted]	3.41	5.88	£22,712	0.48	0.70	
Key: CCD, confidential commercial discount; CUP, compassionate use programme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.							

Table 63: Comparison D: 101-09 / 101-09 (BSC), 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	
Key: BSC, best supportive care; CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.							

B.3.8.4 Summary of sensitivity analyses results

Sensitivity analysis results showed base case Comparison A results to be robust to uncertainty around most input parameters. However, survival assumptions are clearly important for cost-effectiveness results, and Comparison B, investigating a comparison to HMRN data within a more traditional partitioned survival analysis model structure, led to different absolute and incremental benefit estimates for idelalisib versus Comparison A, suggesting idelalisib is an even more cost-effective option for FL patients than suggested in the base case Comparison A. When derived CUP TTP data are used as an alternative to Study 101-09 TTP data to capture treatment benefit, in Comparison C, the expected incremental benefit of idelalisib is diminished versus Comparison A (and Comparison B). The resulting ICER estimate remains below the NICE willingness-to-pay threshold for end-of-life technologies, but is likely falsely high, being influenced by differences in prognosis across Study 101-09 and the UK and Ireland CUP, outlined in Sections B.2.6.3, B.3.3.3, B.3.6.2 and B.3.8.3.

A scenario for chemotherapy-ineligible patients who could benefit from idelalisib is naturally subject to uncertainty, but indicates that idelalisib may provide an effective and cost-effective option for a very small group of FL patients who currently have no active treatment options left and who have very poor survival prospects.

While there is clear inherent uncertainty around the clinical- and cost-effectiveness of idelalisib for double-refractory FL patients, care has been taken to investigate the different clinical data available, while taking a transparent approach in illustrating the uncertainty around results. Overall, the sensitivity and scenario analyses explored indicate that under a range of assumptions and across different datasets, idelalisib looks to be a cost-effective treatment that promises a substantial health benefit to a small group of cancer patients with poor end of life prospects under current care.

B.3.9. Subgroup analysis

In accordance with the final scope for this appraisal, and the limited early-Phase clinical data available for idelalisib for FL, while inference is drawn on the likely cost-effectiveness for both chemotherapy-eligible and -ineligible patients, the scant

clinical data for idelalisib in FL were not further stratified to inform cost-effectiveness estimates.

B.3.10. Validation

B.3.10.1 Validation of cost-effectiveness analysis

In the absence of comparator trial data, the use of clinical practice outcomes data from the HMRN database and the UK and Ireland CUP for idelalisib alongside evidence from the latest database-lock of Study 101-09 means all available evidence for a small and high-need group of cancer patients have been presented in this appraisal. While outcomes vary across patients and mean expected outcomes are uncertain, the data presented allow a clear-eyed assessment of the likely value of idelalisib for patients with late-stage FL in England, and for NHS England as a potential treatment option.

Furthermore, the inputs and assumptions of the cost-effectiveness analyses were reviewed during an 8 May 2018 meeting with Dr Robert Marcus, Consultant Haematologist at London Bridge Hospital, referenced in Sections B.3.3.1 and B.3.6.2. In the spirit of transparency we hope to embody in this submission, we enclose the meeting report, signed off by all attendees, as a documented reference.[15]

The cost-effectiveness model itself was quality-assured by the internal processes of the external economists who built the economic model. In these processes, an economist not involved in model building reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also subject to review against a checklist of known modelling errors and questioning of assumptions.

B.3.11. Interpretation and conclusions of economic evidence

As described throughout Section B.3, the methods and data used to analyse the cost effectiveness of idelalisib for double-refractory FL patients are believed to be the best available. The main weaknesses of the economic evidence presented are the lack of randomised, comparative clinical effectiveness data, and the small sample of FL patients within Study 101-09. However, conducting a large, randomised, clinical study in highly refractory FL patients is not feasible, and we have demonstrably

attempted to present all the available clinical evidence for fair and transparent appraisal of a decision problem that affects a small, high-need patient group.

The main strength of the economic evaluation presented is that it attempts to maximise use of the limited evidence from Study 101-09, published idelalisib CUP data, and outcomes for double-refractory FL patients in the HMRN database, to understand and present informative estimates of the likely benefit of idelalisib treatment in a patient group with high unmet need. The base case comparison to previous line of therapy in Study 101-09 is a pragmatic attempt to contextualise the relative clinical and cost-effectiveness of idelalisib. It is also likely to be conservative analysis given that it is accepted that response to treatment decreases following each relapse, though the analysis approach does attempt to adjust for this. Even without adjustment, Study 101-09 showed that idelalisib as a single-agent induced higher response rates and longer duration of response compared to a variety of combination treatments used as prior therapies. Comparisons using idelalisib CUP data and to HMRN patients illustrate the uncertainty around mean estimates and variability in outcomes across patients, but serve as further evidence of the value of idelalisib for FL patients in UK clinical practice. Even in the most pessimistic and flawed analysis presented, Comparison C, idelalisib is projected to provide health benefits at an incremental cost justified for end-of-life therapies in England.

Another potential benefit of idelalisib not captured with this indirect evaluation is the benefit for FL patients of receiving a single agent oral therapy as opposed to complex intravenous base regimens which necessitate repeated inpatient stays in specialised care units. The results from all comparisons to prior therapy data are also achieved without the assumption of post-progression survival benefit, which may prove evident if idelalisib becomes standard practice for double-refractory FL patients.

While outcomes vary across patients and mean expected outcomes are uncertain, the data presented allow a clear-eyed assessment of idelalisib as a cost-effective option for NHS patients with FL that is highly refractory to available therapies, and the evidence necessary to allow idelalisib to be made available to this patient group, aligning care with that currently available to similar patients in Scotland and Wales.

B.4. References

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Standard criteria for lymphoma and Waldenström's macroglobulinaemia

Appendix M: Baseline characteristics of patients enrolled to Study 101-02/99

Appendix N: Previous data from Study 101-02/99

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Single technology appraisal

Idelalisib for treating refractory follicular lymphoma ID1379

Dear Company,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 08/06/2018 from Gilead Sciences Ltd. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **12 July 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Adam Brooke, Technical Lead (Adam.Brooke@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
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Section A: Clarification on effectiveness data

Clinical effectiveness – Searches

A1. Regarding the Medline/Embase strategy reported in Appendices D, G and H for all 2018 update searches. Please clarify if this was a single search conducted simultaneously over both the Embase and Medline individual databases or was it a single search of Embase conducted with the understanding that it now contains all records from Medline?

All 2018 update searches were single searches within the Embase.com platform that covers Embase and Medline databases.

A2. Please resend the original 2014 Embase search (Table 1, Appendices). Line #129 (all facets + RCT filter/English only /1990-2014) reports retrieving 2775 records and line #131 (all facets + Observational studies filters/English only /1990-2014) retrieves 3387. However, the final line which retrieves both sets of results only reports retrieving 368, is this due to a typographical error?

Apologies for the confusion – this is a typographical error and should read 3,688 records. A corrected table is provided in Appendix A2.

A3. Results from a bibliographic search are mentioned in the flow chart for the 2018 update (Figure 11, Appendices), however it was unclear whether reference checking was undertaken for the 2014 searches, please confirm this took place.

The clinical SLR report accompanying the 2014 searches does not explicitly state that reference checking took place and therefore we cannot confirm this took place.

Clinical effectiveness – Inclusion of studies

A4. In appendix D (Page 13, Appendices), it is stated: “At this point of screening, the population was refined to patients with FL refractory to rituximab and an alkylating agent as per the Study 101-09 trial population to identify trials investigating comparable patients.” Please clarify whether any studies meeting the inclusion criteria according to the NICE scope but deemed not similar enough to the Study 101-09 trial population were excluded.

In the original SLR, three further studies to the idelalisib trials were identified which analysed follicular lymphoma (FL) populations where all patients had refractory disease, but not all of them had been treated with 2 prior lines of therapy. Details of these studies are summarised in Table 1.

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Results from these studies should be treated with caution with regard to relevance to the decision problem, as they do not provide data for named comparators of relevance in the population under consideration.

Table 1: Studies identified that investigated patients with refractory follicular lymphoma

Study	Design	Population	Intervention(s)	Prior treatment	Efficacy data
Avilles et al. 2001(1)	Single-arm pilot study	Refractory FL (n=17)	Rituximab	-	ORR, %: 76
Tinmouth et al. 2001(2)	Observational study	Alkylator-resistant FL (n=17)	Fludarabine	≤2 lines = 9 >2 lines = 8	ORR, %: 53 OS, median months: 15.4
Witzig et al. 2002(3)	Single-arm trial	Rituximab-refractory FL (n=57)	Ibritumomab tiuextan RI	Median (range): 4 (1-9)	ORR, %: 74 TTP, median months: 6.8
Key: FL, follicular lymphoma; ORR, overall response rate; OS, overall survival; TTP, time to progression; RI, radioimmunotherapy.					

Clinical effectiveness – Trials

A5. **Priority Question:** Please provide the Clinical Study Report for study 101-02/99.

The CSR synopses for study 101-02/99 have been uploaded along with our responses.

In addition, reference to publications relating to Study 101-02 (NCT00710528) and Study 101-99 (NCT01090414) can be seen below:

- Flinn IW et al. Blood. 2014 May 29;123(22):3406-13
- Kahl BS et al. Blood. 2014 May 29;123(22):3398-405.
- Brown JR et al. Blood. 2014 May 29;123(22):3390-7
- Stevenson FK et al. Blood. 2011 Oct 20;118(16):4313-20
- de Vos S et al.Blood Adv. 2016 Nov 30;1(2):122-131

A6. Please clarify the date of the most recent data lock for study 101-09, and the scheduled date for the next data lock.

The most up to date CSR for Study 101-09 is the version dated 30 June 2015 (see Document B, Section B.2.4).

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A7. a. The NICE scope describes the population as people with follicular lymphoma that is refractory to 2 prior lines of therapy and the marketing authorisation for idelalisib specifies that idelalisib monotherapy is indicated for the treatment of adult patients with FL that is refractory to two prior lines of treatment. In the company submission (CS), the company explains that "Idelalisib is anticipated to fit in the third-line setting" (Page 19, Document B). Please explain why only 57 out of 72 FL patients in study 101-09 (Table 8) were 'Refractory to ≥2 regimens'; while all 72 patients were refractory to rituximab and to an alkylating agent. Were the remaining 15 patients refractory to only 1 regimen, this being rituximab in combination with an alkylating agent, and therefore those patients were at second-line treatment?

Eligibility criteria for enrolment to study 101-09 meant that all patients had received at least two prior lines of treatment and were refractory to rituximab and an alkylating agent.

We would agree with the ERG interpretation of baseline characteristics as above, that is, that there were a small proportion of patients (n=15) that had received two prior lines of treatment, one of which was rituximab in combination with an alkylating agent to which they were refractory.

b. In the CS, it states that the median number of prior therapies among the [redacted] (Table 16, Document B). However, in the HMRN submission (Figure 18, HMRN submission), which describes the treatment pathways for the [redacted] who had received two or more prior chemotherapy/immunochemotherapy or maintenance, were refractory to both rituximab and an alkylating agent, or had a relapse within 6 months after receipt of those therapies and were subsequently treated with chemotherapy, a different number of treatments appear to be presented [redacted] Please clarify the minimum and maximum number of prior lines of therapy for the HMRN dataset that was used in economic comparison B

[redacted]

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[redacted]

A8. With regards to the incidence data provided in section B.1.3 of document B and the budget impact assessment, the HMRN dataset (reference 4 of Document B) is used to inform the expected number of cases of follicular lymphoma and large cell follicular lymphoma per year (n=1,930). This number is further used to inform the calculation of the estimated number of patients with double-refractory FL in the UK (n=52 in the UK, n=43 in England). However, the most recent Office of National Statistics (ONS) 2016 dataset (release date: 4th June 2018) suggests a higher prevalence, with 2,194 newly diagnosed cases of follicular NHL plus 380 newly diagnosed cases of large cell follicular lymphoma in 2016, giving a total of 2,574. Since the ONS dataset pertains to the whole of England rather than the UK, the values do not have to be adjusted by 84.2% to arrive at estimates for England. Consequently, please use this observed rather than estimated data to inform incidence values, and update the budget impact accordingly.

The ONS dataset was published only few days prior to the submission, hence not included in the submission for the lack of time. After going through the ONS dataset, we concluded that the reported incidence is only numerically higher (59 patients instead of 43 patients) without any major change in the reported budget impact. In our analysis the cumulative budget impact over a period of 5 years will rise from £5.2 million to £5.9 million; £0.14 million per year on average after incorporating this new incidence rate.

For the above calculation an incidence of 2,194 was used and 380 newly diagnosed cases of large cell follicular lymphoma was not added since it is already included in the reported incidence of 2,194. Please refer to Table 2 for further detail.

Table 2: Registrations of newly diagnosed cases of cancer; England, 2016

ICD-10 code	Cancer	Newly diagnosed cases
C82	Follicular [nodular] non-Hodgkin's lymphoma	2,194
C82.0	Small cleaved cell, follicular	451
C82.1	Mixed small cleaved and large cell, follicular	804
C82.2	Large cell, follicular	380
C82.7	Other types of follicular non-Hodgkin's lymphoma	0
C82.9	Follicular non-Hodgkin's lymphoma, unspecified	559

Source: Office for National Statistic, UK(4)

It is well recognised that national cancer registration has struggled with classification of non-Hodgkin lymphoma to WHO classification https://www.nature.com/articles/bjc201594 and the

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data presented by ONS are by ICD-10 classification rather than current classification of cancer (ICD-O-3) used clinically. Bridge coding between the two different classification systems isn't straight forward and so this may have resulted in different estimates.

A9. **Priority question**: With regards to the prevalence data provided in the budget impact assessment, the CS states that the number of people living with double-refractory FL in England who are eligible to receive idelalisib is 342. However, since this number is based on a top level prevalence of 15,232 patients living with FL in the UK *over 10 years* (as specified on the HMRN website; reference 9 of the budget impact assessment document), this number does not appear to be correct, and 342 should be the number of people living with double-refractory FL in England over 10 years. Therefore, the per-year value should be 34.2. Please clarify if this is correct, and update the budget impact accordingly.

The estimate of 342 number of patients living with double-refractory FL in England over 10 years is correct, since these are the patients who were diagnosed in the previous 10 years and still alive at the end of the 10 year. Since all 342 patients are alive at the end of 10 years, all of them are eligible to receive idelalisib, hence this was not divided by 10. The change suggested by ERG is likely to favour idelalisib, showing lower budget impact due to lower number of patients. However, no changes were made to the budget impact model in this regard to capture the expected impact of idelalisib on the budget impact.

A10. a. To support the statement, "the burden of illness in patients with double-refractory FL is expected to be particularly high (though data outside of the Study 101-09 trial is limited)" (Page 17, Document B), Please provide any comparative burden of illness data available for double-refractory FL patients undergoing chemotherapy regimens or best supportive care.

We are not aware of any comparative burden of illness data for double-refractory FL patients undergoing chemotherapy regimens or best supportive care. This expectation is based on comparative data presented within the CS, broken down as follows:

- Patients with relapsed FL are more likely to experience worse HRQL compared to FL patients who were newly diagnosed, in partial or complete remission or disease-free(5)
- Significant differences are observed in assessment of physical well-being, emotional well-being, functional well-being, lymphoma concerns, anxiety and depression(5)
- Double-refractory FL patients have aggressive disease with limited treatment options and poor prognosis(6-9); we may expect this to further exacerbate emotional well-being, anxiety and depression, and lymphoma concerns associated with relapsed disease

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- Double-refractory FL patients have experienced at least two periods of time since diagnosis where their disease has been controlled for less than six months. During periods of active disease, patients may experience B-symptoms and further clinical manifestations of lymphadenopathy and bone marrow failure(5, 10-12); we may expect this to further exacerbate physical well-being, functional well-being, and lymphoma concerns associated with relapsed disease

b. Similarly, please specify why "best change from baseline" was chosen as the readout for the health-related quality of life values (Table 13, Document B; reference 31 of Document B) and the specific definition of "best change"? Please provide mean or median changes for HRQL (FACT-Lym) over the whole follow-up period or the area-under-the curve values for FL patients in this study.

The FACT-Lym questionnaire was administered on a 4-weekly basis throughout the duration of the study. The best change from baseline is defined as the highest change score at post-baseline. This was chosen as the measurement given the fluctuation in symptoms that patients may experience during the course of follicular lymphoma (double-refractory) which can be incremental. Best change may detect the subtle qualitative improvements in QoL which may be missed by analysing the difference in mean/ median.

A11. Figure 4 (Appendices) appears to contradict Table 19 (Document B) about adverse events leading to study drug discontinuation. Please clarify the number of FL patients that discontinued idelalisib in study 101-09 and the reasons for these discontinuations.

We have investigated this apparent contradiction and can confirm that there were three patients who experienced Grade 5 AEs that led to death. These patients were included as discontinuations due to death in subject disposition analyses (captured in Figure 4 of the appendices) but were included as discontinuations due to AE in safety analyses.

The total number of FL patients that discontinued idelalisib in study 101-09 are correctly reported in Figure 4 (Appendices). Due to the above, the reasons for these discontinuations could also be considered correctly reported or three of the discontinuations due to death could be transferred to the reported discontinuations due to adverse events.

A12. In Figure 7 (Document B), data is presented for patients in study 101-02/99 across a range of doses, some of which do not appear to be clinically relevant for this submission. Please provide a revised version of this figure that only presents data for outcomes at the recommended 150mg twice daily dose level, or that highlights which individual patients are dosed at this level.

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Unfortunately, subject disposition data for the 10 patients treated with idelalisib at the recommended 150mg twice daily dose level are not available from the Study 101-02/99 reports, and therefore we cannot provide the requested figure.

A13. The overall response rate to idelalisib is reported to be 45% for the FL population in study 101-02/99 (Table 14, Document B), 55.6% in the FL population in study 101-09 (Table 15, Document B) and 57% in the CUP retrospective cohort (Table 15, Document B). Please comment on why the response rate reported in study 101-02/99 is lower than that reported in 101-09 and CUP.

As discussed in the CS, differences observed in absolute outcomes across trials are likely influenced by a number of factors (see Section B.2.13). Specific to this question, the overall response rate in study 101-02/99 may be lower than that reported in 101-09 and CUP as a result of:

- Differences in baseline characteristics, particularly the high rates of bulky disease observed in the study 101-02/99 population (44%)(13)
- Differences in dosing, with 22 patients (34%) in study 101-02/99 receiving a lower dose of idelalisib than the recommended dose of 150mg twice daily(13)
- Differences in treatment duration, with a lower median duration on treatment observed in the 101-02/99 study (3.8 months(13)) than the 101-09 study (6.5 months(14)) or the CUP (4.3 months(15))
- General differences in study design and conduct across the three trials

A14. In Table 15 (Document B), the proportions of patients achieving a complete response or an unconfirmed complete response are presented for study 101-09 and the CUP cohort. Please clarify the difference between complete response and unconfirmed complete response. If data is available, please provide the statistics for patients with a *confirmed complete response* only.

In study 101-09, response was assessed using standard criteria for lymphoma(16) and Waldenström's macroglobulinaemia(17), which does not allow for an assessment of unconfirmed complete response (see Appendix L). Table 15 of the CS (Document B) therefore only reports confirmed complete response data for study 101-09.

Reference to unconfirmed complete response is therefore only applicable to the CUP data. A definition for unconfirmed complete response and the number of patients that were assessed as having an unconfirmed versus a confirmed complete response are not available from the published evidence for this study(15), and thus cannot be provided.

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A15. In terms of the serious adverse events reported in the FL population of study 101-09 (50.0%; n=36) (Table 19, Document B), how many of these were considered treatment-related? Similarly, for adverse event data that is available in other cohorts (101-2/99, CUP), how many of these were considered to be related to idelalisib treatment?

As summarised in the CS (Table 19, Document B), treatment-related SAEs were experienced by 45 (36.0%) patients in the total population of Study 101-09, and 24 (33.3%) patients in the FL population.

Treatment-related adverse event data are not available for the iNHL population of Study 101-02/99. Across all patients enrolled to Study 101-02 (which included patients with confirmed relapsed or refractory CLL, NHL, AML or MM), 45 received idelalisib at the 150mg twice daily dose and in this group, the most common Grade ≥3 TRAEs were increased ALT, reported for 4 patients (8.9%) and abnormal LFT, reported for 2 patients (4.4%).

Assessment of the relationship of adverse events to study drug was not reported in the CUP manuscript, and the authors note in their discussion that part of the weakness of their retrospective study was the lack of prospective AE reporting.

Matched adjusted indirect comparison (MAIC)

A16. The HMRN report is a draft version. Is there a final version available? If so, please provide it.

The final HMRN report has been uploaded along with our responses. Please treat this report as academic in confidence at the request of the HMRN group.

A17. **Priority question:** Please clarify why data from the database lock of June 2014 were used in the MAIC but the reported results for Study 101-09 in the submission are from the latest database lock of June 2015. Why does the MAIC not use the most recent data, and are there more recent data available than June 2015?

There are no more recent data available than June 2015, and these could not be made available to the HMRN group at the time of MAIC initiation as they have not been published.

Looking across the June 2014 and June 2015 data, results are very similar and if anything PFS and OS rates were slightly underestimated in the earlier data set used for MAIC analyses. For example, the 1-year PFS estimate reported from the June 2014 database lock was 43% (see Appendix N of the CS) and the 48-week PFS estimate reported from the June 2015 database lock was 51% (see Table 12 of Document B).

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A18. Please clarify whether there are any patients in the total HMRN population ([redacted]) who fall under the population defined in the NICE scope but are not included in the [redacted]. If so, please provide the number of patients and full baseline characteristics of all these patients.

[redacted]

A19. a. Please explain the rationale for using individual population data from the HMRN and matching it to summary data from Study 101-09 in the MAIC. If access was available to the trial data for Study 101-09 why was this not used as the source of IPD, especially as it would have resulted in a larger dataset for analysis?

Using individual population data from the HMRN and matching it to summary data from study 101-09 result in the outcomes directly relating to the patient population used to estimate the clinical- and cost-effectiveness of idelalisib versus current care; that is, the MAIC provides an estimate of the treatment effect for if patients enrolled in study 101-09 had been treated with current care in NHS England.

b. **Priority Question:** Please re-run the MAIC using the Study 101-09 data as the source of IPD and matching it to summary HMRN data. Please use the most recent data for study 101-09.

Given the limited time available for clarification, we have tried to prioritise analyses to be run based on the value of their contribution to the decision problem, and thus NICE's decision making. While reversing the MAIC may have resulted in a larger dataset for analysis, weighting based on HMRN summary statistics would have been limited due to the small patient population. It was therefore considered that minimal value would be gained from re-running the MAIC and time would be better spent on other analyses contributing to the decision problem.

A20. **Priority Question:** There are no methods for the MAIC described either in the submission or the HMRN report. Please provide full details of the statistical methods, including the type of statistical model, the rationale for variable selection, the weighting applied and the statistical software packages used, in sufficient detail to enable replication by an independent statistician. Please also provide all the relevant datasets (both IPD and summary statistics) and analysis code to enable the ERG to check the analyses.

The statistical methods are taken from Signorovitch et al.(18) and analyses conducted using *R*. Briefly, study patients are described by a random triple (X, T, Y) where X is the vector of

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baseline characteristics, T the treatment received (or in this case the group HMRN, T=0 vs trial group, T=1) and Y the outcome. So (x_i, t_i, y_i) for i=1, …, n, but is only observed when t_i = 0 whereas mean baseline characteristics and outcome, $\bar{x}_1$ and $\bar{y}_1$ respectively, are observed when t_i = 1, given this the causal effect of treatment T=0 versus T=1 on the mean of Y can be estimated as follows:

$$\hat{\theta} = \frac{\sum_{i=1}^{n} y_i\,(1-t_i)w_i}{\sum_{i=1}^{n}(1-t_i)w_i} - \bar{y}_i$$

Where:

$$w_i = \frac{\Pr(T_i = 1|x_i)}{\Pr(T_i = 0|x_i)}$$

i.e. the odds of receiving trial 1 versus trial 0 given the baseline characteristics x_i, so in essence the patients in "trial" 0, the HMRN patients, are reweighted so that there baseline characteristics match those of the trial patients. The weight w_i is assumed to follow a logistic regression $w_i = \exp(\alpha + x_i'\beta)$ and so find the value of β such that reweighting the IPD for patients where T=0 by $w_i = \exp(x_i'\beta)$ exactly matches their mean baseline characteristics to where T=1. Therefore the estimate of β, $\hat{\beta}$, is found by solving the equation:

$$0 = \frac{\sum_{i:t_i=0} x_i exp(x_i'\hat{\beta})}{\sum_{i:t_i=0} exp(x_i'\hat{\beta})} - \bar{x}_1 \qquad (1)$$

This is equivalent to solving

$$0 = \sum_{i:t_i=0} (x_i - \bar{x}_1)\exp(x_i'\beta)$$

Setting $\bar{x}_1 = 0$ gives

$$0 = \sum_{i:t_i=0} \exp(x_i'\beta)$$

Where the right hand side is the first derivative of

$$Q(\beta) = \sum_{i:t_i=0} \exp(x_i'\beta)$$

With second derivative

$$Q''(\beta) = \sum_{i:t_i=0} x_i x_i' \exp(x_i'\beta)$$

Since $Q''(\beta)$ is positive define for all β, then the solution to (1) can be found by minimising $Q(\beta)$

In this case, *R* is used to find the solution using the Broyden–Fletcher–Goldfarb–Shanno algorithm and the *R* code is shown in the appendix.

Finally from the Signorovitch methodology, an effective sample size for the re-weighted sample can be calculated to assess the impact of the re-weighting process:

"To gauge the impact of re-weighting on the available statistical information in the IPD, an effective sample size can be computed as the square of the summed weights divided by the sum of the squared weights. If the weights are treated as fixed, this effective sample size

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provides the correct sample size for converting the standard deviation of the re-weighted outcome to a standard error. The maximum effective sample size occurs when all patients have equal weight. The occurrence of a small effective sample size can indicate that some patients are receiving extreme weights, and there may be little statistical power to detect differences between treatments."(18)

[redacted]

[redacted] Please provide further information about the adjustment model of the HMRN dataset used in the MAIC, particularly how the model reduces equivalent sample size [redacted]

Please see details of effective sample size computation in the response to A20.

A22. Why were MAICs performed for only two outcomes, OS and PFS?

These were the two outcomes available in the HMRN dataset.

A23. Previous ASCT, previous therapy, and number of prior lines were excluded from the MAIC for either a lack of data or correlation with another variable. Please provide the supporting correlation coefficient and p-value for the correlation between number of prior lines and time from diagnosis. These variables might still be important in the MAIC, please provide MAIC results including all variables for comparison purposes.

[redacted]

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Figure redacted – academic in confidence

[redacted]

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Table 3: Characteristics of patients pre- and post-matching including all variables, HMRN cohort, FL population with disease refractory to rituximab and an alkylating agent

Characteristic	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

A24. **Priority Question:**

a. The efficacy comparison to previous line of therapy (Page 46, Document B). There are also no methods for this. There appear to be two sources of data for the previous line of therapy (Study 101-09 as shown in figure 5 for PFS; and CUP as shown in figure 9E). Please provide full details of the statistical analysis methods and how the data for the previous line of therapy were obtained. Were they derived retrospectively or reported in the study, how were missing data handled?

The efficacy comparison to previous line of therapy is available from study 101-09 and the CUP. This comparison was reported in each of the studies with data for previous line of therapy specific to the patients enrolled in each study. Details of the statistical analysis methods and how the data for the previous line of therapy were obtained are not reported in full, but in both studies they are thought to have been derived retrospectively (definitely in the case of the CUP where all data were collected retrospectively).

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In study 101-09, descriptive statistics were provided to the last regimen patients received prior to study entry. The best response to last therapy (n, %) and duration of response to the last therapy were summarised, primarily based on clinician recall (presumably supported with data collected in routine clinical practice). Duration of response was calculated as the date of response to previous treatment to date of progression; where progression dates were not recorded, the end date of previous treatment was used as the date of progression. Progression-free survival (PFS) to the last therapy were further explored post-hoc, although as noted in the CS, this should be considered more reflective of time to progression (TTP) as patients could not have died on previous line of therapy. While not reported, it is assumed that this was calculated as the date of initiation of previous treatment to date of progression. Missing data for previous treatment to date of progression was avoided as it was the end date of previous treatment was taken conservatively as the date of progression. In general, within the study data quality assurance programmess (as per written standard operating procedures generated by INC Research) were used to identify missing data and request for data clarification were forwarded to investigator sites for resolution.

In the CUP, PFS of the prior treatment is reported, though as above this should be considered more reflective of TTP. While no details of the methods around these data were reported in the published reference, this was queried with the primary author who confirmed that this was calculated as the date of initiation of previous treatment to date of progression, and that these data were routinely recorded and well documented on the data collection proforma.

> b. The results for PFS for idelalisib in Figures 5 and 9E (Document B) are different, PFS on idelalisib is better in Study 101-09. Please explain possible reasons for this difference, how the two populations differ and which idelalisib population is considered to be most representative of the UK population.

This difference is discussed in the CS (see Sections B.2.6.3 and B.2.13), and possible reasons for this difference considered, which are summarised below for ease of reference:

- Differences in the quality of study designs and rigour of progression assessment methods across the studies
- Differences in baseline prognosis, with a higher proportion of patients in the CUP having a high-risk FLIPI score and/or ECOG performance status of 2 or more(15)
- Differences in treatment duration, with a lower median duration on treatment observed in the CUP (4.3 months(15)) than the 101-09 study (6.5 months(14))
- Differences in data maturity, with 35 patients (44%) remaining on idelalisib without progression in the CUP compared to 4 patients (6%) in the latest DBL of study 101-09(14, 15)

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While the CUP was conducted across the UK and Ireland, the baseline characteristics of the population enrolled to study 101-09 are considered more representative of the FL population that would be treated with idelalisib, should it become routinely available in NHS England. All patients had disease refractory to rituximab and an alkylating agent, and most (86%) had disease refractory to their most recent regimen but still presented with a good performance status (ECOG 0-1)(19), warranting consideration of further active treatment.

> c. The numbers at risk on figure 9E (Document B) do not match the sample sizes of Study 101-09 and the CUP cohort. On figure 9E the numbers at risk are 78 for idelalisib and 74 for prior therapy but the sample sizes in Table 15 (Document B) are 72 for study 101-09 and 65 for the CUP cohort. Please explain the discrepancy.

Please see the response to Question A24a for clarification that the data for previous line of therapy are specific to the patients enrolled in each study; that is, the study 101-09 population is not a consideration when reviewing the sample sizes for idelalisib and previous line of treatment in the CUP.

The discrepancy is a reporting error in Table 15 (Document B) where the assessable population for ORR (n=65) have incorrectly been associated to all efficacy analyses. The numbers at risk on Figure 9E report the correct sample sizes for the assessable population for PFS in the CUP; that is, 78 patients treated with idelalisib and 74 (of the same) patients for which previous line of treatment data were available.

> d. (Page 52, Document B) There is a p-value reported for the comparison of PFS (Figure 9E; p=0.82) between idelalisib and prior treatment but there are no details of the corresponding statistical methods. Please provide details of the analysis method.

The p-value is taken from the published reference for the CUP study but no further details of the corresponding statistical methods are reported that can be provided.

Of note, while Gilead provided idelalisib for use in the CUP, data from this study are not the property of Gilead and investigators conducted all analyses.

A25. **Priority Question:** MAIC results: please provide the 95% CI for the results for 1-year PFS, 2-year OS and median OS for both idelalisib and chemotherapy.

- [redacted] Median chemotherapy OS: 4.2months [95% CI: 0.4,9.1]

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Section B: Clarification on cost-effectiveness data

Cost effectiveness - Searches

B1. Please provide details of the database hosts for the 2014/2018 searches.

In the 2014 search, the following databases and conference proceedings were searched to identify available evidence published until 17 February 2014:

- Embase and MEDLINE (using Embase.com)
- MEDLINE In-Process (using Pubmed.com)
- EconLit (using EBSCO.com)
- The Cochrane Library:
  - National Health Service Economic Evaluation Database (NHS EED)

The updated 2018 search was run from 1 January 2014 on all these databases plus the Health Technology Assessment database (HTAD). **Table 4** summarises the databases searched in the 2018 update, including database host/interface.

The 2018 search also accessed conference proceedings. The following conference websites were searched for last 2 years from 2016-2017 using the search terms [NHL; non-Hodgkin's lymphoma; follicular lymphoma; follicle centre lymphoma; centroblastic follicular; centrocytic follicular; nodular lymphoma].

- American Society of Clinical Oncology (ASCO) Annual Meeting: https://meetinglibrary.asco.org/
- American Society of Hematology (ASH): http://www.hematology.org/Annual-Meeting
- European Society for Medical Oncology (ESMO) Congress: http://www.esmo.org/Conferences/Past-Conferences/ESMO-2017-Congress/Meeting-Resources
- International Conference on Malignant Lymphoma (ICML): http://www.lymphcon.ch/icml/website/icml-abstracts-books/icml-abstract-books-1981-2011.html
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual and European Congress: www.ispor.org

Table 4: 2018 search: databases searched

S. No.	Database/ website	Provider/Interface	Filter used for study design	Coverage	Hits
1. Economic evaluation					
2.	3. Medline & EMBASE	4. EMBASE.com	5. SIGN based economic evaluations filter (20)[a]	6. Year 2014 onwards	7. 225

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8.	9. Medline-in-process	10. Pubmed.com	11. -	12. No limit	13. 91
14.	15. HTAD	16. onlinelibrary.wiley.com	17. -	18. Year 2014 onwards	19. 3
20.	21. NHS EED	22. onlinelibrary.wiley.com	23. -	24. Year 2014 onwards	25. 1
26.	27. Econlit	28. EBSCO.com	29. -	30. Year 2014 onwards	31. 1
32. **TOTAL**					**33. 321**
34. Resource use					
35.	36. Medline & EMBASE	37. EMBASE.com	38. SIGN based resource use filter (20)[a]	39. Year 2014 onwards	40. 464
41.	42. Medline-in-process	43. Pubmed.com	44. -	45. No limit	46. 91
47.	48. HTAD	49. onlinelibrary.wiley.com	50. -	51. Year 2014 onwards	52. 3
53.	54. NHS EED	55. onlinelibrary.wiley.com	56. -	57. Year 2014 onwards	58. 1
59.	60. Econlit	61. EBSCO.com	62. -	63. Year 2014 onwards	64. 1
65. TOTAL					**66. 560**
67. Utility					
68.	69. Medline & EMBASE	70. EMBASE.com	71. HRQL/utility filter (21)[b]	72. Year 2014 onwards	73. 206
74.	75. Medline-in-process	76. Pubmed.com	77. -	78. No limit	79. 91
80.	81. HTAD	82. onlinelibrary.wiley.com	83. -	84. Year 2014 onwards	85. 3

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86.	87. NHS EED	88. onlinelibrary.wiley.com	89. -	90. Year 2014 onwards	91. 1
92.	93. Econlit	94. EBSCO.com	95. -	96. Year 2014 onwards	97. 1
98. TOTAL					**99. 302**

Key: HRQL, Health-Related Quality of Life; HTAD, Health Technology Assessment Database; NHS EED, National Health Services Economic Evaluation Database.
Notes: [a], search filters were taken from the website: http://www.sign.ac.uk/search-filters.html and additional terms were used to make filter more comprehensive.
[b], search filters utility/HRQL is based on the utility studies search method and terms developed by ScHARR (university of Sheffield).

B2. (Tables 25/26, Appendix G) – search line numbers appear incorrect (do not start at #1). Line combinations appear correct. Please provide revised strategies.

We thank the ERG for identifying this. The search line numbers for these tables should start from #1. Revised versions of Tables 25 and 26 from Appendix G are provided below, correcting for this simple reporting error.

Table 5: ***Table 25 of Appendix G: MEDLINE In-Process search for all study designs (13 February 2018)*****, Corrected**

Sr. No.	Query	Hits
1.	(Lymphoma, Non-Hodgkin[MeSH Terms]) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	5,784
2.	(("Non Hodgkin Lymphoma"[Title/Abstract] OR "Non-Hodgkin Lymphoma"[Title/Abstract] OR "Non Hodgkin's Lymphoma"[Title/Abstract] OR "Non-Hodgkin's Lymphoma"[Title/Abstract] OR "Non Hodgkin Lymphomas"[Title/Abstract] OR "Non-Hodgkin Lymphomas"[Title/Abstract] OR "Non Hodgkin's Lymphomas"[Title/Abstract] OR "Non-Hodgkin's Lymphomas"[Title/Abstract] OR "NonHodgkin Lymphoma"[Title/Abstract] OR "NonHodgkin's Lymphoma"[Title/Abstract] OR "NonHodgkin Lymphomas"[Title/Abstract] OR "NonHodgkin's Lymphomas"[Title/Abstract])) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-	3,534

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Sr. No.	Query	Hits
	growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	
3.	(NHL[Title/Abstract]) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	1,759
4.	(Lymphoma[MeSH Terms]) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	6,696
5.	((Lymphoma[Title/Abstract] OR Lymphomas[Title/Abstract])) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	8,199
6.	Lymphoma, Follicular[MeSH Terms]	5,345
7.	((Lymphoma[Title/Abstract] OR Lymphomas[Title/Abstract])) AND (follicular[Title/Abstract] OR nodular[Title/Abstract])	11,764
8.	(Lymphoma[MeSH Terms]) AND (follicular[Title/Abstract] OR nodular[Title/Abstract])	10,762
9.	(Lymphoma, Mantle-Cell[MeSH Terms]) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	275
10.	(Lymphoma, B-Cell, Marginal Zone[MeSH Terms]) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	1,133
11.	(Waldenstrom Macroglobulinemia[MeSH Terms]) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	165
12.	(("mantle cell"[Title/Abstract] OR MCL[Title/Abstract])) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	683
13.	(("marginal zone"[Title/Abstract] OR malt[Title/Abstract] OR "nodal MZL"[Title/Abstract])) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	1,786

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Sr. No.	Query	Hits
14.	(("waldenstrom macroglobulinemia"[Title/Abstract] OR "waldenstroem macroglobulinemia"[Title/Abstract] OR "waldenstrom's macroglobulinemia"[Title/Abstract] OR "waldenstroem's macroglobulinemia"[Title/Abstract] OR lymphoplasmacytic[Title/Abstract])) AND (indolent[Title/Abstract] OR "low grade"[Title/Abstract] OR "slow growth"[Title/Abstract] OR "slow-growth"[Title/Abstract] OR "slow growing"[Title/Abstract] OR "slow-growing"[Title/Abstract])	366
15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	20,832
16.	((recur*[Title/Abstract] OR recurr[Title/Abstract] OR recurrent[Title/Abstract] OR recurrence[Title/Abstract] OR relaps*[Title/Abstract] OR relapse[Title/Abstract] OR relapsed[Title/Abstract] OR repeat*[Title/Abstract] OR repeat[Title/Abstract] OR repeated[Title/Abstract] OR repetitive[Title/Abstract] OR refract*[Title/Abstract] OR refractory[Title/Abstract] OR regular*[Title/Abstract] OR regular[Title/Abstract] OR regularly[Title/Abstract] OR regularity[Title/Abstract] OR recrudesc*[Title/Abstract] OR persis*[Title/Abstract] OR persist[Title/Abstract] OR persistent[Title/Abstract] OR persistence[Title/Abstract] OR freq*[Title/Abstract] OR frequent[Title/Abstract] OR frequently[Title/Abstract])) OR Recurrence[MeSH Terms]	3,142,046
17.	#15 AND #16	7,439
18.	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	435,522
19.	**#17 AND #18**	**91**

Table 6: ***Table 25 of Appendix G: Cochrane search (NHS EED and HTAD) for all study designs (13 February 2018)*****, Corrected**

Sr. No.	Query	Hits
1.	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees	1,414
2.	(indolent* or "low grad*" or "slow grow*"):ti,ab,kw	2,658
3.	#1 and #2	171
4.	(("non hodgkin* lymph*" or "nonhodgkin* lymph*") and (indolent* or "low grad*" or "slow grow*")):ti,ab,kw	212
5.	(nhl and (indolent* or "low grad*" or "slow grow*")):ti,ab,kw	210
6.	MeSH descriptor: [Lymphoma] explode all trees	2,446
7.	(indolent* or "low grad*" or "slow grow*"):ti,ab,kw	2,658
8.	#6 and #7	182
9.	(lymph* near/3 (indolent* or "low grad*" or "slow grow*")):ti,ab,kw	380

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10.	MeSH descriptor: [Lymphoma, Follicular] explode all trees	201
11.	(lymph* near/3 (follicul* or nodular*)):ti,ab,kw	856
12.	(follicul* or nodular*):ti,ab,kw	4,249
13.	#6 and #12	300
14.	MeSH descriptor: [Lymphoma, Mantle-Cell] explode all trees	64
15.	#7 and #14	22
16.	MeSH descriptor: [Lymphoma, B-Cell, Marginal Zone] explode all trees	19
17.	#7 and #16	7
18.	MeSH descriptor: [Waldenstrom Macroglobulinemia] explode all trees	20
19.	#7 and #18	2
20.	(("mantle cell*" or mcl*) and (indolent* or "low grad*" or "slow grow*")):ti,ab,kw	121
21.	(("marginal zone" or malt or "nodal mzl*") and (indolent* or "low grad*" or "slow grow*")):ti,ab,kw	80
22.	(("waldenstro* macroglobulinemia" or lymphoplasmacytic) and (indolent* or "low grad*" or "slow grow*")):ti,ab,kw	27
23.	#3 or #4 or #5 or #8 or #9 or #10 or #11 or #13 or #15 or #17 or #19 or #20 or #21 or #22	1,300
24.	(recur* or relaps* or repeat* or repetitive or refract* or regular* or recrudesc* or persis* or freq*):ti,ab,kw	225,840
25.	MeSH descriptor: [Recurrence] explode all trees	11,935
26.	#24 or #25	225,851
27.	#23 and #26	659
28.	#27 [Publication Year from 2014 to 2018]	354
29.	**#28 in Technology Assessments**	**3**
30.	**#28 in Economic Evaluations**	**1**

B3. The 2014 Embase and Medline searches for Economic evaluation, HRQL and Resource Use data contained a clear and comprehensive facet for Resource Use terms. The 2018 update searches do not appear to contain the same facet. Please confirm which strategy was intended to address this element and what effect the different approach may have had on the recall of results.

The search facet for the resource use terms in the 2018 search was similar to that in 2014. Table 7 highlights the search strategy used in the 2018 update to search resource use studies. We apologise for the omission of this table from Appendix I of the CS, which was an unintended oversight.

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Table 7: MEDLINE and Embase search for resource use studies (13 February 2018)

Sr. No.	Query	Hits
1.	'nonhodgkin lymphoma'/exp AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	9,602
2.	('non hodgkin* lymph*':ab,ti OR 'nonhodgkin* lymph*':ab,ti) AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	2,172
3.	nhl:ab,ti AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	2,910
4.	'lymphoma'/exp AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	12,104
5.	(lymph* NEAR/3 (indolent* OR 'low grad*' OR 'slow grow*')):ab,ti	6,923
6.	'follicular lymphoma'/exp	13,895
7.	(lymph* NEAR/3 (follicul* OR nodular*)):ab,ti	14,997
8.	'lymphoma'/exp AND (follicul*:ab,ti OR nodular*:ab,ti)	19,940
9.	'mantle cell lymphoma'/exp AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	1,245
10.	'marginal zone lymphoma'/exp AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	2,315
11.	'waldenstroem macroglobulinemia'/exp AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	617
12.	('mantle cell*':ab,ti OR mcl*:ab,ti) AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	1,541
13.	('marginal zone' OR malt OR 'nodal mzl*') AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	3,142
14.	('waldenstro* macroglobulinemia':ab,ti OR lymphoplasmacytic:ab,ti) AND (indolent*:ab,ti OR 'low grad*':ab,ti OR 'slow grow*':ab,ti)	598
15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	35,283
16.	recur*:ab,ti OR relaps*:ab,ti OR repeat*:ab,ti OR repetitive:ab,ti OR refract*:ab,ti OR regular*:ab,ti OR recrudesc*:ab,ti OR persis*:ab,ti OR freq*:ab,ti	4,059,826
17.	'recurrent disease'/exp OR 'cancer recurrence'/exp OR 'relapse'/exp	402,271
18.	#16 OR #17	4,142,643
19.	'health care utilization'/exp OR 'health care cost'/exp OR 'hospitalization cost'/exp OR 'resource allocation'/exp OR 'resource management'/exp OR (((('health care' OR resourc* OR service* OR hospital*) NEAR/2 (utili* OR cost* OR us*)):ab,ti) OR 'nursing cost'/exp	2,627,962
20.	#15 AND #18 AND #19	1,268
21.	**#15 AND #18 AND #19 AND [english]/lim AND [2014-2018]/py**	**464**

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Comparators

B4. Please clarify the following with regards to comparators:

a. Please explain to what extent the chemotherapy regimens used in Study 101-09, Eyre et al. (CUP UK & Ireland) and HMRN database registry are reflective of the UK clinical practice.

As reported in the CS (Page 19, Document B), it is challenging to fully define the relevant comparator treatments for NHS England outside of 'chemotherapy regimens' as there is no standard of care for double refractory FL patients and treatments are either repeated (from first- or second-line) or administered in a different combination according to individual clinician choice. Evidence from the 8 May 2018 meeting with Dr Robert Marcus indicates that data from these studies fairly reflects current care, and certainly represent the best available proxy for current care in UK clinical practice.(9)

b. Some of the recently approved treatments (e.g. obinutuzumab) were missing in Table 43 (Document B). If available, please report any other more recent values (e.g. UK market share or clinical audit results) which can be used to inform the distribution of 3rd line treatments in FL patients whose disease is refractory to rituximab and another alkylating agent refractory and who had received 2 prior treatments before.

Obinutuzumab with bendamustine has been available to treat rituximab-refractory FL only since August 2017 (22). In addition, we expect and understand from the respective license terms and the 8 May 2018 meeting with Dr Robert Marcus that obinutuzumab with bendamustine will be used earlier in the treatment pathway than idelalisib monotherapy, and as such does not represent an appropriate comparator.(9)

We are not aware of more recent values to inform the distribution of current treatments for patients who stand to benefit from idelalisib monotherapy if it made available to NHS England patients within its license terms. If any such data were available it would be important to consider the implications for costs and well as patient outcomes; however, we understand from the 8 May 2018 meeting with Dr Robert Marcus that the current care data we submitted, representing our understanding of the latest available clinical effectiveness data in line with NICE requirements, are a fair reflection of the current treatment options available for the high-need patient group under consideration.(9)

Model Structure

B5. In Figure 14 (Document B), it can be seen that a patient can be on treatment only in the pre-progression state. In some instances, treatment is not discontinued

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immediately upon progression. Please clarify that none of the patients in Study 101-09, CUP and HMRN data registry received treatment after disease progression.

In clinical practice according to license terms, treatment with idelalisib monotherapy should be continued until disease progression or unacceptable toxicity. The cost-effectiveness model, represented by Figure 14, reflects this. In Study 101-09, treatment rules allowed subjects to receive idelalisib indefinitely, however,

- Subjects had the right to withdraw from the study at any time
- Subjects who experienced progression of disease were withdrawn from the study treatment.
- Subjects whose condition substantially changed after entering the study were carefully evaluated by the investigator in consultation with the study sponsor medical monitor. Such subjects were withdrawn from study treatment if continuing placed them at risk.
- Subjects who became pregnant were to be removed from study treatment.
- Subjects who became significantly noncompliant with study drug administration, study procedures, or study requirements was withdrawn from study treatment if these circumstances increased risk or substantially compromised the interpretation of study results.
- The investigator, in consultation with the study sponsor medical monitor, could withdraw any subject from the study treatment, if, in the investigator's opinion, it was not in the subject's best interest to continue.
- Subjects who were unable to tolerate the protocol-described, dose-modified IDELA Dose Level -2 of 75 mg/dose BID was withdrawn from study treatment.

ToT data are not available to us from the CUP or HMRN databases. Though we hoped they were clear from the CS, our data access restrictions are reiterated in our response to B9.

Clinical effectiveness inputs used in the economic model

B6. **Priority Question:** Please clarify which type of progression event definitions were used (i.e. IRC or investigator-assessed) in 'time to progression' (TTP) , 'post-progression survival' (PPS), 'pre-progression survival' (PrePS), 'progression free survival' (PFS) data used in the cost-effectiveness analyses in Comparisons A, B, C and D (from Study 101-09, Eyre et al. (CUP UK & Ireland) and HMRN database registry) and provide the results based on both IRC and investigator-assessed progression event definitions.

The June 2015 clinical effectiveness data analyses to inform the cost-effectiveness analyses ['time to progression' (TTP), 'post-progression survival' (PPS), 'pre-progression survival'

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(PrePS), 'progression free survival' (PFS)] used progression events defined based on IRC assessment, in line with the assessment approach for the primary endpoint.

The definition of progression events in the CUP and HMRN datasets is not definitively stated in any documentation available to us, but by definition these databases will not record IRC-assessed outcomes.

a. Please incorporate TTP, PPS, PrePS, PFS data based on both definitions into the economic model.

As indicated by the results in Table 12 of Document B of the CS, summary investigator-assessed PFS results were very similar to summary IRC-assessed results. We ask the ERG to reconsider their request in this context, with consideration of the scope of substantive work required to fulfil this request.

B7. **Priority Question** Please confirm that all clinical data used from Study 101-09 in the cost-effectiveness analyses are based on the latest data cut-off available (June 2015).

TOT, PrePS, OS, PFS, TTP, PPS for idelalisib based on Study 101-09 are derived from the June 2015 data cut-off.

In Section B.3.3.1 of the CS, we were careful to document database lock wherever we presented clinical data graphically. From this and the surrounding text, it was hopefully clear that all Study 101-09 TTP, ToT, PPS, PrePS and OS data for idelalisib patients presented and incorporated into the economic model are from the latest available dataset (June 2015). Where prior therapy data on TTP and ToT were used, these were, by definition, complete in the June 2014 dataset, and so there was no call to analyse these data from the June 2015 dataset.

Aside from the key clinical outcomes data reported in Section B.3.3.1 of the CS, other clinical data from Study 101-09 used in the cost-effectiveness analysis were adverse event (AE) data (Section B.3.4.4 and B.3.5.4) and dose intensity data (Section B.3.5.1). As reported in these sections, the adverse event frequency data and the data informing estimated dose-intensity are from the June 2015 dataset. Reporting in the Economic Model has been reviewed and updated to clarify database lock for AE data, on sheet "Adverse_Events".

There are two exceptions to the use of the June 2015 database wherever it represented an update. First, as addressed in question A.17 above, the HMRN MAIC used data from the June 2014 dataset. Second, though reported only in the economic model (Economic Model, Sheet "Adverse Events", cell "C:14"), mean ToT data from the Primary Analysis Clinical

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Study Report (June 2013) were used in combination with AE frequency data to calculate a weekly probability of occurrence for each AE considered. This historical estimate was not updated prior to submission. Using mean idelalisib ToT from the CS base case analysis ([redacted] months, Economic Model, Sheet "PF_Idela", cell "CV:7") instead of the June 2013 estimate reduces the CS base case ICER from £26,076 to £25,559. When considering limitations in the base case approach here, the conservative limitations inherent in the approach to adverse event cost and QALY estimation in the absence of chemotherapy AE data should also be borne in mind. As described in Section B.3.4.4 of the CS, the cycle probability for each AE for idelalisib is applied to the comparator arm in Comparisons A, B and C to account for chemotherapy AEs, when the AE profile of idelalisib monotherapy is expected to be both different and preferable to currently available options. The approach to AEs in the economic analysis clearly underestimates the likely value of idelalisib.

B8. **Priority Question** The clinical effectiveness model inputs (TTP, 'time on treatment' (ToT), PPS, PrePS, PFS, 'overall survival' (OS) and 'adverse events' (AEs)) used in the economic model are based on the non-randomized evidence from different trials (Study 101-09 in Comparison A; Study 101-09 and HMRN database in Comparison B; CUP and Study 101-09 in Comparison C, Study 101-09 in Comparison D):

a. Please provide all details (datasets used, statistical codes compiled as well as the outputs of these codes) of the analyses conducted to obtain comparable KM curves for idelalisib and chemotherapy arms in each of the comparisons (A, B, C and D). Please ensure these analyses are in line with the NICE Decision Support Unit Technical Support Document 17 (specifically method selection algorithm explained in Section 4.1, and Figures 1, 2, 3 of TSD 17).

We took care to follow the principles and guidance in NICE TSD 17 to obtain comparable KM curves for idelalisib and chemotherapy in each of the comparisons (A, B, C and D) that inform the parametric survival analysis. The approach was exhaustive of data selection and adjustment options in line with the criteria laid out by TSD 17. As the response to B9 describes, data availability limits the options to produce data that is truly comparable. Due to the fact that Study 101-09 is a single arm trial, there does not exist a randomised chemotherapy/comparator arm, as such comparisons between idelalisib and chemotherapy (Comparisons A, B, C) and the comparison to BSC for chemotherapy-ineligible patients (Comparison D) have been synthesized in 4 ways.

Comparison A forms the base case comparison between idelalisib and chemotherapy within the cost-effectiveness model and is informed fully by Study 101-09. Survival outcomes associated with idelalisib are compared to outcomes recorded for the same cohort in their previous line of therapy, hence considerable overlap between treated and untreated groups. Parametric survival models were fitted to the idelalisib and prior line of therapy data separately to provide extrapolations of survival outcomes for use in the cost-effectiveness model as described in B8b and B8c. Given that non-randomised IPD for survival outcomes are available for each arm of the comparison, TSD 17 advises that multivariate regression,

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regression adjustment (RA), inverse probability weighting (IPW), doubly robust (IPW + RA) or matching should be considered to produce more comparable treatment arms. Covariate-adjusted survival analysis, as requested in B9b, would fulfil the regression adjustment advised by TSD 17. The response to B9b outlines why covariate-adjustment was ruled out. While baseline characteristic data is available for the cohort before initiation of idelalisib, similar characteristics are not available before initiation of the prior line of therapy. Therefore, we would compare to the same patients one therapy ago, so each chemotherapy patient, by definition, has had one more prior therapy when they receive idelalisib. Thus, treatment and line of therapy are intractably correlated and the inclusion of line of therapy is unlikely add worth to the models. Other covariates would not change. The lack of baseline characteristics at the prior line of therapy stage data is the limiting factor of this analysis. If the baseline characteristic data described above were available then it is unlikely that the values for each covariate (time since diagnosis, SCT history, FLIPI score etc.) for each patient would change largely, and variability of covariates is preferable for predictive models.

Comparison B forms the comparison between idelalisib and chemotherapy by comparing survival outcomes associated with idelalisib in Study 101-09 and those of patients from HMRN with comparable indication. As suggested in TSD 17 survival data is adjusted to make KM curves more comparable. An MAIC was conducted matching HMRN data to summary statistic reported from 101-09. Justification for matching in this way is given in response to A19a.

For comparison C, KM curves for idelalisib and prior line of therapy were synthesized from the publication by Eyre et al.(15) As set out throughout Section B.3 of the CS, the only CUP effectiveness data available for the submission were those reported in the publication by Eyre et al.(15) As such, baseline characteristics and associated PLD were to available to allow adjustment.

Comparison D, similarly to comparison A, is informed fully by Study 101-09. This approach equates the comparator arm for patients who are ineligible for chemotherapy (i.e. only survival without idelalisib) to the survival observed post-progression in Study 101-09, and assumes that if patients were not treated, they would have simply experienced post-progression survival. Again, baseline characteristics are recorded before initiation of idelalisib, but are not available at progression. Consequently, covariate adjustment is not possible.

Attached is;
Eyre et al. publication, synthesised data, KM plot and cumulative hazard plot code and output;
HMRN report, synthesised data, KM plot and cumulative hazard plot code and output;
101-09 KM plot and cumulative hazard plot code and output, this makes use of the time to event efficacy data set provided by Gilead based on June 2015 data cut-off.

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b. Please provide all details (datasets used, statistical codes compiled as well as the outputs of these codes) of the survival analyses conducted to obtain parametric extrapolations for idelalisib and chemotherapy arms in each of the comparisons (A, B, C and D). Please ensure that these analyses are in line with the NICE Decision Support Unit Technical Support Document 14 (specifically survival model selection process algorithm explained in Section 6.1 and 6.2, and Figures 3 and 4 in TSD 14).

In section 6.1, NICE TSD 14 advises given the availability of PLD log-cumulative hazards plots should be fit as an initial selection tool for appropriate survival models. If the plots give straight lines, but parallel lines of treated and untreated patients are not possible individual models for the treatment and comparator are should be used.

Log-cumulative hazard plots (attached in response to previous question) for each outcome appear reasonably straight (excluding PrePS) and do not provide evidence to suggest that more flexible models than the standard parametric survival models are required. PrePS log cumulative hazard plot is not linear due to the immature data, KM data was used directly for PrePS rather than a parametric model fit to the data. Given that each outcome modelled with parametric extrapolations was not part of a randomised trial, separate models for each arm of each comparison were fitted; this removes any assumption of proportional hazards. Additionally, parametric extrapolations fit the KM curves well, any diversion from the KM curves were not sufficiently large to imply that more flexible extrapolation models should be considered. Further details regarding model selection are provided in response to B8c, below.

Attached is;
CUP parametric extrapolation code and output for TTP prior line of therapy and TTP idelalisib;
HMRN parametric extrapolation code and output for OS chemotherapy and PFS chemotherapy;
Study 101-09 parametric extrapolation code and output for OS, PFS, PPS, TOT and TTP idelalisib.
These analyses are based on data provided or referenced in response to B8a.

c. The parametric distributions in survival modelling do not appear to have been chosen systematically (e.g. sometimes it was justified as reflecting “conservative” assumptions while in other cases it was based on the best statistical fit only). While the fit of the parametric curves should be assessed based on statistical, visual and clinical plausibility, not all these assessments were reported in detail. Please provide external data or clinical expert estimates to validate the parametric PFS, OS, ToT, PrePS, PPS and TTP curves for the licenced indication (third line, double-refractory FL patients) for idelalisib and current care (e.g. PFS % at 1, 5, 10 and 15 years).

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We took care to follow the principles and guidance in NICE TSD 14 in application of parametric survival analysis to KM data and in subsequent model selection to inform base case and scenario cost-effectiveness analyses, and to document our approach to decision-making clearly in Section B.3.3.1 or the CS. The approach was systematic. Where KM data were complete or close to completion, statistical goodness-of-fit was relatively more useful for understanding the validity of the (whole) parametric survival curves. Where KM data were less complete, based on fewer events, and substantial extrapolation was required, clinical plausibility gained relative importance in informing model selection.

We documented our approach to clinical expert validation in the CS (Sections B.3.3 and B.3.10) and included the meeting report from the key meeting with Dr Robert Marcus, signed off by all attendees, as reference #15. As documented therein, the plausibility of each base case parametric survival model choice was considered; this informed eventual model selection.

We encourage the ERG to consider the usefulness of the additional "external…or clinical expert" data requested. As clearly outlined throughout or submission, the clinical evidence on outcomes for the small patient group under consideration are highly limited. We included all the clinical data available to us; beyond the pivotal Study 101-09 dataset, published CUP data and HMRN data. It is not clear which 'external data' could be used to validate the modelling methodology we have chosen. Moreover, the usefulness of expert clinician predictions on outcomes is affected by the limited nature of the data available. We have gained clinical expert perspective on the data available and have documented our work clearly to allow the ERG and Committee to gain further expert clinical perspectives on the same data if deemed necessary. Mindful of ERG question wording, we encourage caution if the ERG look to validate Study 101-09, CUP or HMRN data with other data or clinical experts unfamiliar with results from these studies, in such a small and poorly evidenced patient group.

B9. **Priority Question:** Please clarify why the time to event data from different studies (e.g. CUP and Study 101-09) were not pooled in any of the analyses.

Data availability ruled out pooling of time-to-event data from different studies. For clarity, Gilead Sciences do not have ownership of the CUP data, nor any HMRN data. As set out throughout Section B.3 of the CS, the only CUP effectiveness data available for the submission were those reported in the publication by Eyre et al.(15) To incorporate HMRN data, we could engage analysts at the University of York with access to the dataset to request analyses; Gilead Sciences were not and are not permitted to access patient-level HMRN data.

a. Please provide de novo survival regression analyses (datasets used, statistical codes compiled as well as the outputs of these codes) on the pooled TTP, OS, PFS, PrePS and PPS datasets (panel data from CUP, Study 101-09 and HMRN

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studies), where the treatment received (idelalisib or chemotherapy), the number of prior lines of treatments, study ID and other important covariates, (e.g. patient ID, time since diagnosis, SCT history, FLIPI score etc., which were selected after a systematic selection process) are added as explanatory variables.

Given the differences across the idelalisib evidence base with regard to study design, patient populations and patient-level data availability that are discussed within the CS (Document B), it is not considered appropriate to pool data from different datasets.

Due to the data availability described above, pooling of patient data was never a possibility. The request for further survival regression analyses, irrespective of pooling, is addressed within the response to part b, below.

b. If pooling data from different datasets cannot be conducted due to patient-level data unavailability or data type mismatch, please conduct the survival regression analyses on the panel TTP, OS, PFS, PrePS and PPS datasets from the Study 101-09 only, where the treatment received (idelalisib or chemotherapy), the number of prior lines of treatments, and other important covariates, (e.g. patient ID, time since diagnosis, SCT history, FLIPI score etc., which were selected after a systematic selection process) are added as explanatory variables.

An important conceptual point to the approach to economic analysis, that we were careful to stress in Section B.3.2.1, rules out much of this request. From the outcomes requested, the only chemotherapy patient data available from Study 101-09 is, by definition, TTP. These are prior therapy data. No one died, there were no survival events. This is central to the base case Comparison A approach to modelling.

Beyond this, if we are to consider the request only for TTP, consider the conceptual steps. First, we suggest the ERG do not consider, or describe, TTE data as panel data. They are recorded differently. It is possible to create panel data from TTE data, but your description of “the panel TTP, OS, PFS, PrePS and PPS datasets” suggests the ERG are already considering them as such.

We anticipate that what you are requesting is covariate-adjusted survival analysis, where TTP is modelled as a function of treatment (idelalisib or chemotherapy), number of prior lines of treatment, and other explanatory variables. We are comparing to the same patients one therapy ago, so each chemotherapy patient, by definition, has had one more prior therapy when they receive idelalisib. What could the suggested analysis of these data tell us about the effect of number of prior therapies versus treatment received upon TTP, when the two factors are intractably correlated? It is not possible to differentiate the effect of idelalisib versus chemotherapy upon patient outcomes from the effect of an additional line of therapy on patient outcomes using Study 101-09 data. This point is important in the context of numerous questions posed here, and in the difficulty of answering the decision problem generally.

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c. Please incorporate the most plausible (based on statistical, clinical and visual plausibility) survival regression analysis results for PPS, TTP, OS, PFS and PrePS above into the economic model, by assuming the baseline characteristics of the Study 101-09 trial (or CUP or HMRN database, depending on the comparison) for both arms, and by assuming idelalisib treatment coefficient 1 for the idelalisib arm and 0 for the chemotherapy arm.

We refer the ERG to our response to part b.

B10. **Priority Question:** The ERG has some concerns regarding the HR=0.75 used for the chemotherapy arm, to adjust for the number of prior treatments received (Table 57, assumption #5).

a. In reference 15 of Document B, it is reported that the Scottish, Welsh and Irish HTA submissions for idelalisib applied a hazard ratio (HR) of 0.9 to last prior therapy time-to-event outcomes when using them as current therapy outcomes. Based on feedback from the company's clinical expert, a HR of 0.75 was suggested as an alternative and was consequently used in this NHS England submission. Please provide an economic sensitivity analysis for all scenarios based on a HR of 0.9, in line with previous submissions for this patient population.

Figure 2 and Figure 3 shows a tornado diagram depicting the 10 parameters that have the greatest influence on the ICER versus chemotherapy regimens in one-way sensitivity analyses (OWSA) with drop in response HR set to 0.75 and 0.9 respectively. The order of the value drivers changes between scenarios however their net impact is still comparable. The alternative analysis suggests very little change in the sensitivity around the base case results presented in the Document B and thus demonstrating robustness of the base case results.

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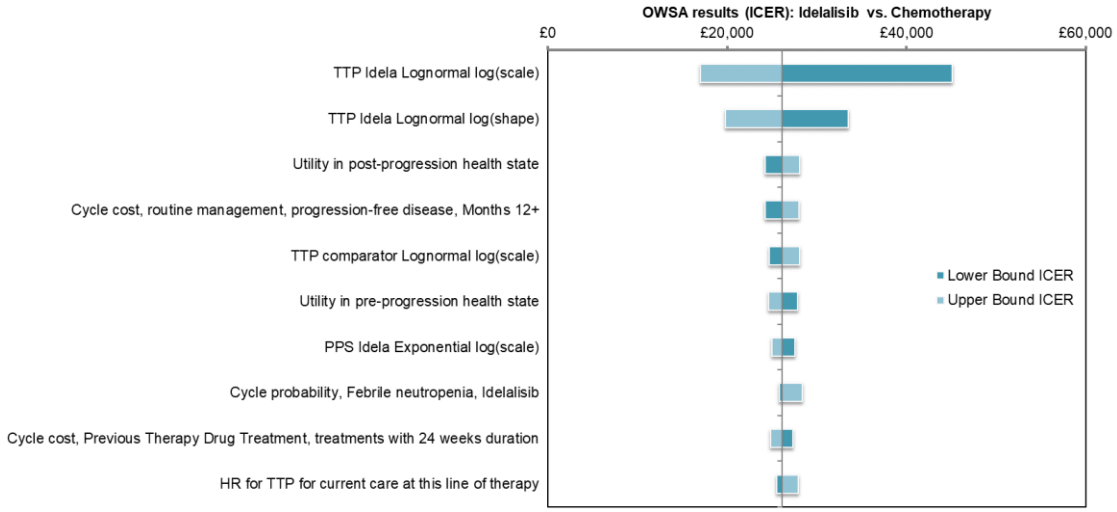
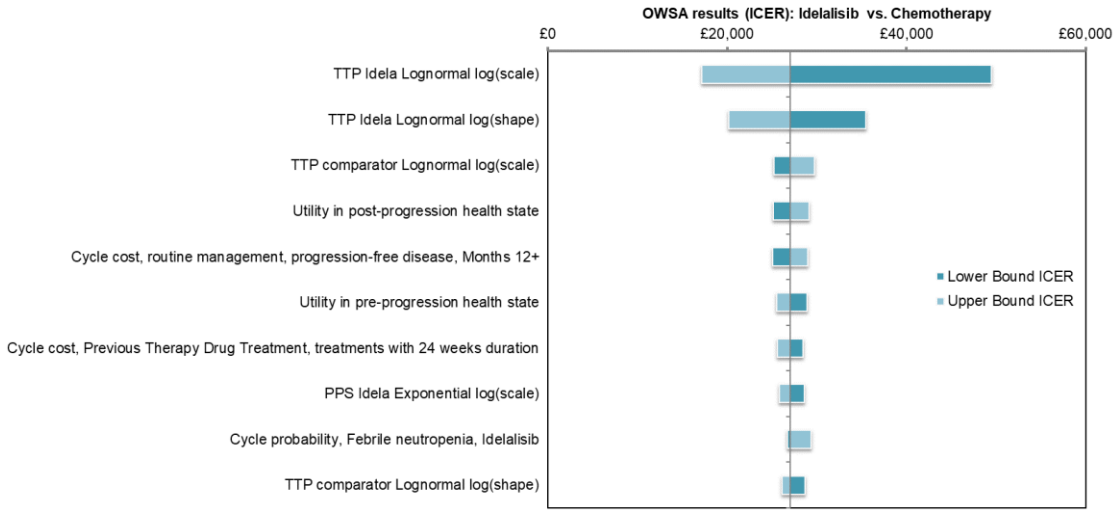
Figure 2: Tornado diagram showing OWSA results, base case (Comparison A) cost-effectiveness analysis, including idelalisib CCD (alternative analysis with drop in response HR set to 0.75)



Key: CCD, confidential commercial discount; OWSA, one-way sensitivity analysis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; TTP, time to progression.

Figure 3: Tornado diagram showing OWSA results, base case (Comparison A) cost-effectiveness analysis, including idelalisib CCD (alternative analysis with drop in response HR set to 0.9)



Key: CCD, confidential commercial discount; OWSA, one-way sensitivity analysis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; TTP, time to progression.

Please note that while implementing this scenario, the team noticed that upper bounds and lower bounds of the cost inputs were missing from the one-way sensitivity analysis in the CS

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cost-effectiveness model. We apologise for this oversight. Correction affects one-way sensitivity analysis results only and does not impact base case results, scenario analysis results or probabilistic sensitivity analysis results as reported in the Document B. Figure 35 in the Document B should be discounted due to this change and Figure 2 should be instead considered in its place.

Table 8 shows impact on base case ICER for different scenarios tested under two assumptions: drop in response HR=0.75 and drop in response HR=0.9. The analysis suggests that the impact of change in HR is not significant in most of the scenarios except comparison C, which can be explained by the small QALY benefit under comparison C. Due to the smaller QALY benefit, any smaller change in the denominator results into a wide variation in the ICER. We believe that comparison A and B presents a more robust result and thus should be used for decision making.

Table 8: Scenario analyses impact summary, including idelalisib CCD (alternative analysis with drop in response HR set to 0.9)

Scenario	Scenario detail	Brief rationale	Impact on base-case ICER (HR=0.75)	Impact on base-case ICER (HR=0.9)
Base case			£26,076	£27,026
Comparison B	Haematological Malignancy Research Network (HMRN) chemotherapy KM data digitised and used to create pseudo-IPD after matching adjusted indirect comparison with 101-09 study, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering HMRN chemotherapy clinical effectiveness estimates, where possible	-£6,204	-£7,154
Comparison C	Published UK & Ireland idelalisib CUP KM data digitised and used to create pseudo-IPD, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering published CUP idelalisib clinical effectiveness estimates, where possible	£20,935	£31,415
Comparison D	Best supportive care (BSC) is considered as a comparator, for the patients who are not eligible for chemotherapy, under the assumptions that patients would progress instantly in	Exploration of the impact upon CE conclusions of considering best supportive care (BSC) as a comparator	-£804	-£1,754

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	the absence of an active treatment.			
Comparison A, Hazard ratio adjustment for expected drop in time to progression in the next line of treatment	Hazard ratio set to 1 implying no drop in time to progression in the next line of treatment for chemotherapy.	Exploration of alternative assumption that all patients will respond same in this line of therapy as they have in the previous line of therapy	£1,817	£866
Comparison A, alternative discount rate preferences	Costs and benefits are discounted at 6%.	Discounting the benefits and costs in the future at a higher rate	£2,800	£3,045
Comparison A, alternative discount rate preferences	Costs and benefits are not discounted.	Undiscounted results	-£4,119	-£4,451
Comparison A, alternative time horizon	Costs and benefits are accumulated for 10 years.	Shorter time horizon	£5,462	£6,068
Comparison A, alternative pre-progression survival assumptions	Mortality hazard is assumed to be equal to that of a general population to model no risk of higher mortality in the pre-progression population.	Exploration of impact of no higher pre-progression mortality risk assumptions on the CE model conclusions	-£3,208	-£3,417
Comparison A, alternative parametric model choice for TTP	A Generalised Gamma parametric survival model fitted to the time to progression data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time to progression data	-£7,117	-£7,880
Comparison A, alternative parametric model choice for PPS	A Lognormal parametric survival model fitted to the post-progression survival data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of post-progression survival data	£3,785	£5,803
Comparison A, alternative parametric model choice for ToT	A Lognormal parametric survival model fitted to the time on treatment data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time on treatment data	£2,023	£2,178

Key: BSC, best supportive care; CCD, confidential commercial discount; CE, cost-effectiveness; CUP, Compassionate Use Programme; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; KM, Kaplan-Meier; UK, United Kingdom.

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b. Please provide specific details on the "M7 FLIPI" study (including the relevant publication(s)), which was provided by their clinical expert as published evidence to support the use of a HR of 0.75.

"M7 FLIPI" is a follicular lymphoma risk model first published in 2015.(23) Parameters of the risk model were estimated from Phase III trial data on previously untreated Stage III/IV follicular lymphoma patients, and the model results were validated by data from a similar but smaller cohort from a separate study.(23) The M7 FLIPI model is useful for understanding of prognostic factors for follicular lymphoma patients, but is limited in its application to this appraisal of a treatment option for follicular lymphoma refractory to two prior lines of therapy.

c. Please justify why the same HR = 0.75 was applied to ToT.

As stated in Section B.3.3.1 of the CS, as well as less effective, we expect treatment at subsequent lines be less costly, with a reduction in treatment exposure at each subsequent line. This is an expectation based on rationale in the context of limited data. The only clinical effectiveness data for chemotherapy in patients refractory to two prior therapies are the HMRN data; ToT KM data are not available from this dataset. Using prior therapy data as proxy data for current therapy requires assumptions, for both TTP and ToT.

Are approach is intended to be fair and even-handed. If the adjustment to prior therapy outcomes is maintained for TTP but relaxed for ToT (HR=1), the CS base case ICER falls from £26,076 to £25,021.

d. Please clarify if HR=0.75 was applied for the TTP/PFS derived from the CUP study for chemotherapy patients in Comparison C to adjust for the number of prior treatment lines.

Yes, that is the case, and we apologise for not explicitly stating this in Section B.3.3.3 of the CS. We feel this is and was logical and appropriate. In the economic model, this is applied in columns S and T of worksheet "PF_CurrCare".

e. Please derive the HR pertaining to the prior number of treatment lines from a Cox PH model conducted on the panel data from Study 101-09 for each of the following curves, ToT, TTP, PFS, PPS and PrePS.

As outlined in our response to B.9, it is not possible to differentiate the effect of idelalisib versus chemotherapy upon patient outcomes from the effect of an additional line of therapy on patient outcomes using Study 101-09 data.

B11. **Priority Question:** Please provide other mortality estimates for the chemotherapy receiving patients in the pre-progression and post-progression states to be used in the economic model (currently they are based on idelalisib PrePS and PPS mortality estimates). These estimates should be based on the PrePS and PPS survival data from Study 101-09, related to the chemotherapy treatment before idelalisib. These estimates can be adjusted using the HRs (due to the effect of an additional line of therapy) as derived in B10.e.

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We refer the ERG to our response to B.9.b, and related response to B.10.e, and ask that the ERG carefully consider Section B.3.2 of the CS. This question and others indicates that the ERG do not fully appreciate the definitive limitations of data from last line of therapy in a clinical trial.

B12. **Priority Question:** Please provide results of a partitioned survival modelling approach, (based on PFS, OS and ToT) from Study 101-09 only, where the PFS, OS and ToT data from the prior chemotherapy lines are used, adjusted according to the effect of an additional line of therapy derived from the regression coefficient of the covariate as specified in B10.e. As emphasized in B8, please follow the recommendations in TSD 14 while following survival modelling of the PFS, OS and ToT curves.

Again, we refer the ERG to our response to B.9.b, and related response to B.10.e, and reiterate our request that the ERG carefully consider Section B.3.2 of the CS. This question and others indicates that the ERG do not fully appreciate the definitive limitations of data from last line of therapy in a clinical trial.

B13. **Priority Question:** Please provide all details of the communication between the company and the clinical experts. The details include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or TC, list of expert recommendations and justifications for clinical assumptions used in the model.

We were careful to describe how clinical expert opinion informed our approach to cost-effectiveness analysis throughout Section B.3 of the CS. Beyond building on learning and validation through the technology appraisal processes that have led to the recommendation of idelalisib for follicular lymphoma refractory to two prior lines of treatment in Scotland, Wales and Ireland, preparation of submission materials was informed during the 8 May 2018 meeting with Dr Robert Marcus, described in Section B.3.10.1 of the CS. The meeting report from this engagement represents the sum of its documentation and was included as reference 15 of the CS. In Table 57 of the CS (Section B.3.6.2), we were careful to detail modelling assumptions, stating the justification for, and likely direction of bias implied by, each assumption.

B14. In the model, it is implicitly assumed that a patient who progressed from idelalisib and a patient who progressed from chemotherapy spend the same amount of time before death in the PPS state. This would lead to a situation where a gain in PFS would translate fully to a gain in OS (i.e. full OS Surrogacy approach, Davis et al.[1]). Please explain the OS surrogacy approach followed in the economic model and validate from other FL studies (OS gain/PFS gain) whether the approach followed in the economic model is plausible.

The model does not assume a full surrogacy approach. It only assumes that the rates of death are similar among patients upon progression, since they are likely to receive similar

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treatment regimens upon progression. The base case results (see Table 9) from the model suggests that PFS gain on idelalisib arm is 1.84 years compared to 1.33 years of OS gain.

Table 9: Life years breakdown for the model in the base case

Health states	Idelalisib	Chemotherapy
Pre-progression (On treatment)	0.90	0.23
Pre-progression (Off treatment)	1.44	0.24
PFS gain	1.84	-
Post progression	4.00	4.54
Overall survival	6.34	5.01
Overall survival	1.33	-

B15. In the CS, it was mentioned that: "*ToT assumptions are used solely to inform estimated treatment cost in the model*" (Page 99, Document B). Please explain the reasoning behind this approach and justification for why time on treatment does not impact time to progression in the model.

We recognise that by modelling ToT and TTP independently, we are assuming their independence. However, the approach allows the model to accurately reflect the ToT and TTP observed in the trial. This is key strength of partitioned survival modelling generally, and a part of the story behind these types of models having informed so many NICE oncology technology appraisals. To attempt to capture a relationship between the outcomes would itself require assumptions, and data. We encourage the ERG to consider this and the practical implications for modelling, if they are minded to advise against our approach.

a. Please provide details on how an "event" and a "censor" were defined in the KM curves for the ToT from CUP, HMRN and 101-09 trial given in the CS.

ToT was not reported or derived for CUP and HMRN. ToT was derived from the 101-09 patient level data as follows;

ToT = Treatment end date – treatment start date + 1

At the June 2015 data cut-off all patients have completed/discontinued treatment, so all observations are considered events; there are no censors.

Utilities

B16. **Priority Question:** Please incorporate age adjusted decline in the utilities to the economic model and justify why it was not incorporated in the base case.

Understanding of how patient utility changes over time, beyond typical trial endpoints and particularly in late-stage cancer patients, remains low, as a recent review of evidence in this area attests.(24) Assuming that utility for the patient group under consideration at hand will

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change over time in the fashion observed in general population samples is in itself an untested and unevidenced assumption. While we stress this, as requested, the "Control" sheet in the revised model includes an option to choose whether to include age adjusted decline in the utility in the model or not.

Age adjusted decline in the utilities to the economic model is implemented using the formula from Ara and Brazier (2010):

General population utility = $\beta_0 + \beta_1 * age + \beta_2 * age^2$

Where coefficient values are:

Coefficient	Value	Standard error
Age (β_1)	0.000173	0.000374
Age^2 (β_2)	-0.000034	0.000004
Constant (β_0)	0.958459	0.007743

Source: Ara and Brazier (2010)(25)

The revised base case result including age-adjusted utility decline is presented in Table 10.

Table 10: Base-case (Comparison A) cost-effectiveness results, including idelalisib CCD (after only including age adjusted decline in the utility)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy Regimens	[redacted]	5.01	2.72	-	-	-	-
Idelalisib	[redacted]	6.34	3.60	£23,762	1.33	0.87	£27,158

Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B17. Please explain why published mapping algorithms based on FACT-G (e.g. Yost et al.[2], Cheung et al.[3] and Teckle et al.[4]) were not used to derive utility estimates (FACT-G scores should be available from the FACT-Lym results in the Study 101-09).

As indicated within the question, FACT-Lym is an extension of the FACT-G questionnaire; it comprises FACT-G plus 15 questions specified for lymphoma patients. As stated in Section B.3.4.2, we are aware of no studies mapping FACT-Lym patient data to EQ-5D values. The ERG highlight two studies that mapped FACT-G results to EQ-5D(-3L) results (Cheung et al

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and Teckle et al) and one study that assessed the validity of the FACT-G questionnaire for monitoring quality of life in lymphoma patients (Yost et al). Limitations associated with the use of the mapping algorithms reported by to Cheung et al or Teckle et al derive utility estimates from Study 101-09 quality of life data to inform this NICE appraisal include:

- Ignorance of the elements of quality of life captured by the 15 questions specified for lymphoma patients to create FACT-Lym
- The limitations of Teckle et al and Cheung et al mapping algorithms in their ability to predict EQ-5D utility from FACT-G response within their patient samples
- Key differences between the samples in Cheung et al (n=367 cancer patients, none of whom were lymphoma patients, let alone refractory FL patients) and Teckle et al (n=558 cancer patients, 4.1% of whom were lymphoma patients (FL subset not reported)) and the Study 101-09 FL sample, and ultimately the FL patients who stand to benefit from NHS England availability of idelalisib monotherapy

As described in Sections B.3.2.2 and B.3.4.3 of the CS, the utility values selected for analysis were chosen to align with the NICE Reference Case and for consistency with the only recent NICE STA in FL, TA472 (26) and with the SMC, NCPE and AWMSG appraisals of idelalisib in this indication.

Costs:

B18. **Priority Question:** Please clarify the following with regards to drug prices:

a. Please verify that the rituximab prices used in the economic model were not based on biosimilar prices, and incorporate the biosimilar prices, if available.

In the economic model cost of biosimilar rituximab was not used in the base case. We have now included biosimilar cost in the model and in application assumed a simple average of the cost of rituximab and its biosimilars constitutes the acquisition cost for rituximab. The user can use the option provided in the “Control” sheet of the revised model to choose whether to include biosimilar cost or not. The cost per mg or rituximab has decreased as a result, from £1.75 to £1.66 resulting in an increase of £193 in the total per patient, discounted estimated incremental cost of idelalisib. The overall impact on results is an increase of £212 in the base case ICER. Revised results with this change implemented to the base case are presented in Table 11.

Table 11: Base-case (Comparison A) cost-effectiveness results, including idelalisib CCD (after only including rituximab biosimilar costs)

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Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy Regimens	[redacted]	5.01	2.80	-	-	-	-
Idelalisib	[redacted]	6.34	3.71	£23,955	1.33	0.91	£26,288

Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

b. Please verify that the chemotherapy options incorporated in the economic model are not followed by maintenance treatment with rituximab

No maintenance treatment with rituximab is included in the model. The chemotherapy options included incorporated in the model include rituximab-based regimens but do not include the costs of rituximab maintenance therapy.

Idelalisib as per study 101-09 Study is given as monotherapy – Study Protocol: Concomitant Therapy: No other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind were permitted while the subject received IDELA. Subjects were not allowed to participate concurrently in any other therapeutic clinical study.

The question of use of rituximab as a maintenance treatment is a topic of clinical debate – e.g. trials such as the PRIMA have shown benefit whist other regimens have not.(27)

c. Please incorporate the drug wastage costs for the idelalisib arm (for the unused drugs left in a package)

The cost for 28-days of idelalisib is applied at the beginning of the cycle to account for drug wastage cost. The “control” sheet in the revised model now includes an option to choose whether to include drug wastage cost for idelalisib or not. The revised base case results after including drug wastage is presented in the Table 12.

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Table 12: Base-case (Comparison A) cost-effectiveness results, including idelalisib CCD (after only including idelalisib drug wastage costs)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy Regimens	[redacted]	5.01	2.80	-	-	-	-
Idelalisib	[redacted]	6.34	3.71	£25,075	1.33	0.91	£27,516

Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

d. Please provide the details on how the 'mean dose intensity' from Study 101-09 is derived and check if other mean dose intensity estimates are available from the CUP study for idelalisib

As described in Section B.3.5.1 of the CS, "mean dose intensity" was incorporated into cost-effectiveness analyses to account for physician-prescribed reductions, escalations and interruptions that occurred in Study 101-09 and are likely to reflect clinical practice. The estimate was taken from planned study drug exposure analysis of the June 2015 ITT analysis set, calculated at the patient level as {sum of pills dispensed minus pills returned for each dosing period} divided by {sum over all dosing period of (total daily pills x dosing duration)} taking into account physician-prescribed reductions, escalations and interruptions.

As set out throughout Section B.3 of the CS and noted above, the only CUP data available for the submission were those reported in the publication by Eyre et al (15). No drug exposure data were reported.(15)

e. Please explain why 'mean dose intensity' was not used for the chemotherapy arm.

As described above, data availability from Study 101-09 prior therapy is very different to data availability from Study 101-09 investigation therapy. As for the HMRN dataset, such data were not reported. Cost-effectiveness results are less sensitive to dose-intensity assumptions for chemotherapy estimates. In the absence of data, assuming the CS base case mean dose intensity estimate of 93.75% applies to chemotherapy as well as idelalisib increases the CS base case (Comparison A) ICER by only £278, from £26,076 to £26,354 (see Table 13). The "Control" sheet in the revised model includes an option to choose whether to apply idelalisib mean dose intensity for chemotherapy or to follow dose information as per the recommendations in the relevant guideline.

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Table 13: Base-case (Comparison A) cost-effectiveness results, including idelalisib CCD (after applying mean dose intensity estimate of 93.75% to chemotherapy)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy Regimens	[redacted]	5.01	2.80	-	-	-	-
Idelalisib	[redacted]	6.34	3.71	£24,016	1.33	0.91	£26,354

Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B19. Please clarify whether the costs in the comparator are overestimated in the model. (Page 99, Document B) It is mentioned that: "*As well as less effective, treatment at subsequent lines is likely to be less costly, with a reduction in treatment exposure at each subsequent line*". This seems to be inconsistent with the approach taken in the model where the same distribution of prior ("second-line") treatments was assumed for the comparator arm (Table 43, Document B).

The model is consistent with the statement. To model less effective and less costly treatments at subsequent lines a drop in response HR of 0.75 is applied. With 0.75 HR, total treatment drug costs for PFS is [redacted] with no reductions in effectiveness or costs (HR=1.00). Thus, the approach of applying 0.75 HR ensures costs on the comparator arm are not inappropriately estimated.

B20. Please explain how the last 4 cost items in Table 49 (Document B) are included in the electronic model?

The last 4 costs items in Table 49 (Document B) is used to estimate total relapse related costs per week of £49.11 which is in turn applied to the number of relapses per week in the model.

Adverse events

B21. Please clarify whether additional death due to AEs is included in the model. Page 67 (Document B) mentions that "In the FL population, six (8.3%) patients had an AE that resulted in death; fatal AEs were multi-organ failure, acute abdomen, cardiac arrest, cardiac failure, pneumonitis and splenic infarction".

a. Page 100 (Document B) says only 4 pre-progression deaths were recorded. On Page 67 (Document B) it is mentioned that 6 patients had AEs resulting in death. Please clarify whether these 6 AE-related deaths are pre-progression.

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We confirm that there were exactly 4 pre-progression deaths recorded in the latest (June 2015) database lock of Study 101-09, as shown in Figure 23 of the Document B of the CS. Concerning the two post-progression (PD) and AE-related deaths, one subject had PD (2013-03-11) before death (2013-03-19). The other was censored due to 'Missed >=2 Consecutive Tumor Assessments'.

Validation:

B22. **Priority Question:** Please provide all the details of the validation exercise mentioned in the CS. Does the validation exercise include all the steps (internal validation, cross-validation, etc…) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool? If not, please include these steps as well.

We developed our submission in accordance with the NICE Single technology appraisal user guide for company evidence submission template (nice.org.uk/process/pmg24) and guide to the methods of technology appraisal (nice.org.uk/process/pmg9). The exact details of the model quality control process are the confidential commercial property of the company who built the economic model and cannot be shared, but we can confirm that the aspects of validation outlined in the AdvisHE publication the ERG refers to were considered as standard. We encourage the ERG to provide independent and fair comment on the validity of our approach to cost-effectiveness analysis as part of their function in this appraisal process, to help the committee to reach a fair and important decision.

B23. **Priority Question:** Table 35 (Appendices) shows that the "*comparator PFS may seem to be underestimated in the base case cost-effectiveness analysis, versus the trial data upon which it is based. However, given that 4.6 months of median PFS is based on the progression-only data for prior therapy and clinical opinion suggested a 25% drop in response from prior therapy to current line of care, 3.7 months of PFS on chemotherapy may in fact be an overestimation of PFS for double-refractory FL patients*". While this might be the case, Table 35 (Document B) also shows that the model overestimates PFS (in 1.35 months) and especially OS (in almost 20 months) for idelalisib. Please comment on the validity of the model results with regards to this.

Though not explicitly clear from Appendix J reporting, Appendix Table 35 compares mean model predictions with median trial results. Mean PFS and OS exceeding median PFS and OS is commonly observed across cancers, and a familiar phenomenon in NICE appraisals. We acknowledge the limitations of the Study 101-09 survival data and in particular the PPS data clearly throughout Section B.3.3.1 and commented on cost-effectiveness model validity in Section B.3.10 in particular. It is important to consider that we explicitly tested structural and data uncertainties in the CS, and that in the base case (Comparison A) analysis and the Comparison C scenario analysis, Study 101-09 PPS informs both the intervention and comparator arm of the analysis; any validity concerns apply to both arms.

Sensitivity analyses:

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B24. In Table 56 (Document B), it is indicated that a large number of costs parameters have been modelled using a Normal distribution. This could lead to sampling negative values for the costs. Please consider using a different distribution (e.g. Gamma) to model these cost parameters.

Assumption of normal distribution for the cost parameters is appropriate as these costs are mean costs of all such events in the UK reported in the NHS reference cost. Central limit theorem suggests that such sample statistics follow a normal distribution, hence the assumption. Theoretically it is a possibility that such assumption may produce a negative cost value, but the probability of such occurrence is very low. Please refer to the Table 14 for further details.

Table 14: Probability of random draw of costs to be negative under the assumption of normal distribution

	Mean	**Standard error**	**Probability that a random draw to be ≤ 0**
Cycle cost, routine management, progression-free disease, Months 0-6	£67.06	£13.41	0.0000003
Cycle cost, routine management, progression-free disease, Months 6-12	£66.24	£13.25	0.0000003
Cycle cost, routine management, progression-free disease, Months 12+	£66.24	£13.25	0.0000003
One off cost on progression	£213.71	£42.74	0.0000003
Cycle cost, routine management, progressive disease	£46.81	£9.36	0.0000003
Cycle cost, relapse management, progressive disease	£49.11	£9.82	0.0000003
Cycle cost, end of life care	£782.80	£156.56	0.0000003
Cost, chemo admin	£299.68	£59.94	0.0000003
Cost, rituximab-chemo admin	£355.54	£71.11	0.0000003
Cycle cost, PJP prophylaxis	£0.57	£0.11	0.0000003
Cycle cost, CMV monitoring Months 0-6	£12.88	£2.58	0.0000003
Cycle cost, CMV monitoring Months 6-12	£6.44	£1.29	0.0000003
Cycle cost, CMV monitoring Months 12+	£4.29	£0.86	0.0000003

Budget Impact Assessment

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B25. In Table 2 (Budget Impact Assessment), the final row contains a value that is reported to represent the number of double-refractory FL patients, calculated as 38.2% of the larger population of patients who were expected to be treated at third line or beyond. Please clarify if this 38.2% includes patients who are either double-refractory to rituximab and an alkylating agent **or** had a relapse within 6 months after receipt of those therapies, in line with the HMRN population that is included in the economic model? Or if this number is exclusively the number of patients who are refractory to two lines of (any) therapy, in line with the final NICE scope?

In the HMRN study, of patients receiving active treatment at first- and second-line, 68 patients went on to receive further treatment at third-line. Of these 68 patients, only 26 patients met the Study 101-09 population criteria: patients who had received ≥2 prior lines of chemotherapy/immune-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent, or had a relapse within 6 months after receiving those therapies, and were subsequently treated with chemotherapy. Thus 38.2% (=26/68) was estimated to be the proportion of third-line follicular lymphoma patients who were refractory to two prior lines of treatment, and therefore eligible for idelalisib.

Section C: Textual clarifications and additional points

C1. Please report Table 60 (Document B) where the last column shows all potential ICERs and add an additional column showing the % change with respect to the base case ICER.

Please refer to the Table 14 which includes an additional column showing the % change with respect to the base case ICER. However, please note that these % changes should be used with caution as the % change of a ratio is often difficult to interpret and could be potentially misleading.

Table 15: Scenario analyses impact summary, including idelalisib CCD (with added column showing the % change with respect to the base case ICER)

Scenario	Scenario detail	Brief rationale	Impact on base-case ICER	% change with respect to the base case ICER
Base case			£26,076	-
Comparison B	Haematological Malignancy Research Network (HMRN) chemotherapy KM data digitised and used to create pseudo-IPD after matching adjusted indirect comparison with 101-09 study, to which	Exploration of the impact upon CE conclusions of considering HMRN chemotherapy clinical effectiveness	-£6,204	-23.8%

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	parametric survival models were fitted, and incorporated into the economic analysis	estimates, where possible		
Comparison C	Published UK & Ireland idelalisib CUP KM data digitised and used to create pseudo-IPD, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering published CUP idelalisib clinical effectiveness estimates, where possible	£20,935	80.3%
Comparison D	Best supportive care (BSC) is considered as a comparator, for the patients who are not eligible for chemotherapy, under the assumptions that patients would progress instantly in the absence of an active treatment.	Exploration of the impact upon CE conclusions of considering best supportive care (BSC) as a comparator	-£804	-3.1%
Comparison A, Hazard ratio adjustment for expected drop in time to progression in the next line of treatment	Hazard ratio set to 1 implying no drop in time to progression in the next line of treatment for chemotherapy.	Exploration of alternative assumption that all patients will respond same in this line of therapy as they have in the previous line of therapy	£1,817	7.0%
Comparison A, alternative discount rate preferences	Costs and benefits are discounted at 6%.	Discounting the benefits and costs in the future at a higher rate	£2,800	10.7%
Comparison A, alternative discount rate preferences	Costs and benefits are not discounted.	Undiscounted results	-£4,119	-15.8%
Comparison A, alternative time horizon	Costs and benefits are accumulated for 10 years.	Shorter time horizon	£5,462	20.9%
Comparison A, alternative pre-progression survival assumptions	Mortality hazard is assumed to be equal to that of a general population to model no risk of higher mortality in the pre-progression population.	Exploration of impact of no higher pre-progression mortality risk assumptions on the CE model conclusions	-£3,208	-12.3%
Comparison A, alternative parametric model choice for TTP	A Generalised Gamma parametric survival model fitted to the time to progression data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time to progression data	-£7,117	-27.3%

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Comparison A, alternative parametric model choice for PPS	A Lognormal parametric survival model fitted to the post-progression survival data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of post-progression survival data	£3,785	14.5%
Comparison A, alternative parametric model choice for ToT	A Lognormal parametric survival model fitted to the time on treatment data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time on treatment data	£2,023	7.8%
Key: BSC, best supportive care; CCD, confidential commercial discount; CE, cost-effectiveness; CUP, Compassionate Use Programme; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; KM, Kaplan-Meier; UK, United Kingdom.				

C2. Figures 15, 30, 31 and 32 (Document B) are captioned TTP but the y-axis is labelled progression-free. Please clarify this.

Figure 15, 30, 31 and 32 (Document B) present time-to progression (TTP) data where the area under the curve represents the proportion of patients who are progression-free thus the y-axis is appropriately labelled.

ERG References:

1) Davis S, Tappenden P, Cantrell A. (Eds). A Review of Studies Examining the Relationship between Progression-Free Survival and Overall Survival in Advanced or Metastatic Cancer. London: National Institute for Health and Care Excellence (NICE); 2012 Aug. NICE Decision Support Unit Methods Development.

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3) Paulos Teckle, Helen McTaggart-Cowan, Kim Van der Hoek, Stephen Chia, Barb Melosky, Karen Gelmon and Stuart Peacock. Mapping the FACT-G cancer-specific quality of life instrument to the EQ-5D and SF-6D. Health and Quality of Life Outcomes 2013;11:203

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Appendix A2

Table 16: Systematic search strategy for Embase: OVID (w/c 5 February 2014)

Disease Terms	
1. exp nonhodgkin lymphoma/ and (indolent$ or low grad$ or slow grow$).mp.	6,986
2. ((non hodgkin$ lymph$ or nonhodgkin$ lymph$) and (indolent$ or low grad$ or slow grow$)).mp.	4,435
3. (NHL and (indolent$ or low grad$ or slow grow$)).mp.	2,241
4. exp lymphoma/ and (indolent$ or low grad$ or slow grow$).mp.	8,404
5. (lymph$ adj3 (indolent$ or low grad$ or slow grow$)).mp.	5,793
6. exp follicular lymphoma/	8,681
7. (lymph$ adj3 (follicul$ or nodular$)).mp.	14,880
8. Exp lymphoma/ and (follicul$ or nodular$).mp.	15,677
9. mantle cell lymphoma/ and (indolent$ or low grad$ or slow grow$).mp.	794
10. exp marginal zone lymphoma/ and (indolent$ or low grad$ or slow grow$).mp.	564
11. exp Waldenstroem macroglobulinemia/ and (indolent$ or low grad$ or slow grow$).mp.	308
12. ((mantle cell$ or MCL$) and (indolent$ or low grad$ or slow grow$)).mp.	1,028
13. ((marginal zone or malt or nodal mzl$) and (indolent$ or low grad$ or slow grow$)).mp.	2,270
14. ((Waldenstro?m macroglobulinemia or lymphoplasmacytic) and (indolent$ or low grad$ or slow grow$)).mp	501
15. OR/1-14	25,521
Disease Stage Terms	
16. (recur$ or relaps$ or repeat$ or repetitive or refract$ or regular$ or recrudesc$ or persis$ or freq$).mp.	2,769,190
17. recurrent disease/	118,352
18. exp recurrent cancer/	11,448
19. relapse/	56,515
20. OR/16-19	2,825,059
Intervention Terms	
21. exp idelalisib/	201
22. (cal 101 or cal101 or gs 1101 or gs1101).mp.	361
23. idelalisib.mp.	199
24. exp rituximab/	35,817
25. rituximab.mp.	36,937
26. (idec c2b8 or mabthera or monoclonal antibody idec c2b8 or reditux or rituxan or rituxin).mp.	3,762
27. exp fludarabine/	16,087
28. fludarabine.mp.	17,205
29. exp lenalidomide/	7,480
30. lenalidomide.mp.	7,749

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31. exp lenalidomide/ and exp rituximab/	1,079
32. (lenalidomide and rituximab).mp.	1,119
33. CVP.mp.	2,981
34. exp vincristine/ and exp cyclophosphamide/ and exp prednisone/	18,761
35. (vincristine and cyclophosphamide and prednisone).mp.	20,182
36. CHOP.mp.	8,990
37. exp doxorubicin/ and exp cyclophosphamide/ and exp prednisone/ and exp vincristine/	15,607
38. (doxorubicin and cyclophosphamide and prednisone and vincristine).mp.	16,776
39. R-CVP.mp.	132
40. exp prednisone/ and exp rituximab/ and exp cyclophosphamide/ and exp vincristine/	5,961
41. (prednisone and rituximab and cyclophosphamide and vincristine).mp.	6,473
42. R-CHOP.mp.	1,803
43. exp doxorubicin/ and exp prednisone/ and exp cyclophosphamide/ and exp vincristine/ and exp rituximab/	5,412
44. (doxorubicin and prednisone and cyclophosphamide and vincristine and rituximab).mp.	5,850
45. RFMD.mp.	4
46. exp rituximab/ and exp fludarabine/ and exp mitoxantrone/ and exp dexamethasone/	471
47. (rituximab and fludarabine and mitoxantrone and dexamethasone).mp.	489
48. exp rituximab/ and exp bendamustine/	1,132
49. (rituximab and bendamustine).mp.	1,168
50. exp rituximab/ and exp fludarabine/ and exp cyclophosphamide/	3,413
51. (rituximab and fludarabine and cyclophosphamide).mp.	3,561
52. R-FC.mp.	100
53. FCMR.mp.	18
54. exp rituximab/ and exp fludarabine/ and exp mitoxantrone/ and exp cyclophosphamide/	964
55. (rituximab and fludarabine and mitoxantrone and cyclophosphamide).mp.	1,007
56. exp fludarabine/ and exp rituximab/	4,418
57. (fludarabine and rituximab).mp.	4,648
58. exp mitoxantrone/ and exp dexamethasone/	2,193
59. (mitoxantrone and dexamethasone).mp.	2,230
60. R-IEV.mp.	2
61. ifosfamide/ and epirubicin/ and etoposide/ and exp rituximab/	180
62. (ifosfamide and epirubicin and etoposide and rituximab).mp.	182
63. R-DHAP.mp.	70
64. exp dexamethasone/ and cytarabine/ and cisplatin/ and exp rituximab/	743
65. (dexamethasone and cytarabine and cisplatin and rituximab).mp.	749
66. BVR.mp.	247
67. exp bendamustine/ and exp bortezomib/ and exp rituximab/	256

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68. (bendamustine and bortezomib and rituximab).mp.	267
69. exp bortezomib/ and exp rituximab/	1,968
70. (bortezomib and rituximab).mp.	2,031
71. exp bortezomib/	14,825
72. bortezomib.mp.	15,281
73. exp interferon/	320,535
74. interferon$.mp.	244,085
75. alpha interferon/	42,473
76. exp stem cell transplantation/	82,441
77. exp allotransplantation/	13,331
78. ((stem cell or allo$ or homo$) adj3 (transplan$ or therap$ or treat$)).mp.	170,531
79. exp radioimmunotherapy/	4,503
80. radioimmunotherapy.mp.	5,205
81. tositumomab/	498
82. ibritumomab tiuxetan/	2,463
83. (tositumomab or ibritumomab tiuxetan).mp.	2,981
84. ((wait and see) or wait to see).mp.	1,559
85. (watch and wait).mp.	644
86. (no$ adj1 (treat$ or therap$)).mp.	336,249
87. standard of care.mp.	26,895
88. support$ care.mp.	13,494
89. bsc.mp.	1,798
90. clinical observation/	17,860
91. clinical observation$.mp.	32,043
92. OR/21-91	958,252
RCT Terms	
93. randomized controlled trial/	337,241
94. exp clinical trial/	940,941
95. double blind procedure/	108,342
96. single blind procedure/	18,082
97. crossover procedure/	38,115
98. randomization/	59,660
99. experimental design/	8,371
100. control group/	46,898
101. placebo/	190,455
102. (clin$ adj3 trial$).mp.	1,038,282
103. randomi?ed controlled trial$.mp.	406,111
104. RCT.mp.	12,915
105. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	177,310
106. placebo$.mp.	268,084
107. (random$ adj2 allocat$).mp.	22,705
108. ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	5,619,270

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109. (crossover$ or (cross adj over$)).mp.	67,743
110. OR/93-109	5,976,237
Observational Terms	
111. exp clinical study/	5,161,641
112. exp case control study/	88,469
113. family study/	9,614
114. longitudinal study/	61,571
115. retrospective study/	325,975
116. prospective study/	240,225
117. randomized controlled trial/	337,241
118. 116 not 117	209,899
119. cohort analysis/	155,798
120. (cohort adj (study or studies)).mp.	104,455
121. (case control adj (study or studies)).tw.	69,514
122. (follow up adj (study or studies)).tw.	35,282
123. (observational adj (study or studies)).tw.	56,891
124. (epidemiologic$ adj (study or studies)).tw.	63,815
125. (cross sectional adj (study or studies)).tw.	76,234
126. OR/111-115, 118-125	5,530,637
127. #110 (RCT Terms) OR #126 (Observational Terms)	8,234,183
128. #15 (Disease Terms) AND #20 (Disease Stage Terms) AND #92 (Intervention Terms) AND #110 (RCT Terms)	2,898
129. Limit #128 to English language and years 1990 to 2014	2,775
130. #15 (Disease Terms) AND #20 (Disease Stage Terms) AND #92 (Intervention Terms) AND #126 (Observational Terms)	3,609
131. Limit 130 to English language and years 1990 to 2014	3,387
132. #15 (Disease Terms) AND #20 (Disease Stage Terms) AND #92 (Intervention Terms) AND #127 (RCT OR Observational Terms)	3,933
133. Limit 132 to English language and years 1990 to 2014	3,688

[redacted]

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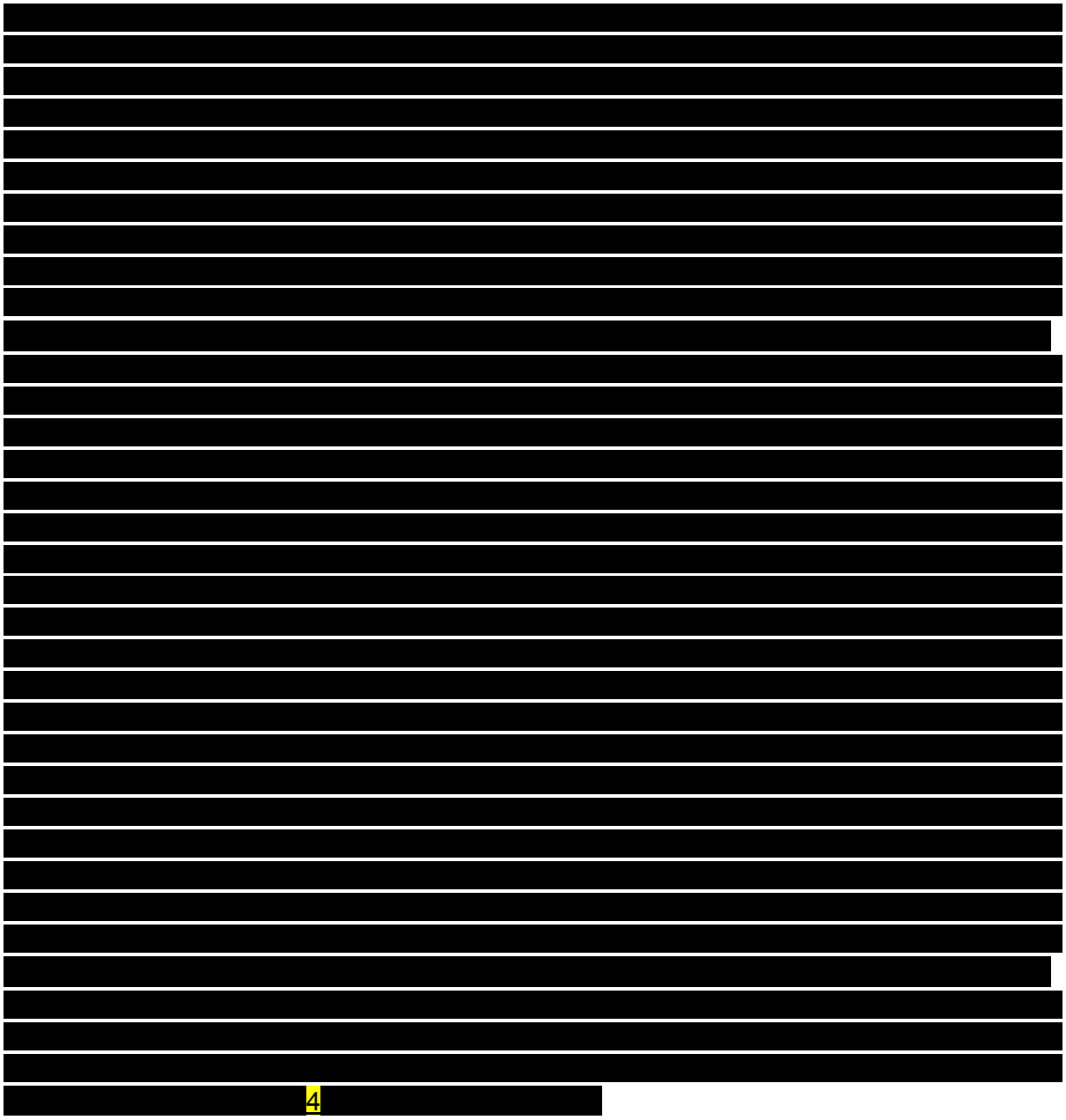

Figure redacted – academic in confidence

NICE National Institute for Health and Care Excellence

Professional organisation submission

Idelalisib for treating refractory follicular lymphoma [ID1379]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	BSH and the RCPath

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	√ an employee or representative of a healthcare professional organisation that represents clinicians? √ a specialist in the treatment of people with this condition? √ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To improve the progressive free survival of patients with 'double refractory' follicular lymphoma (FL): i.e. FL that has been treated with alkylating agents and rituximab and has relapsed or become refractory to both agents.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Patients that obtain a partial or complete response according the Revised response criteria for malignant lymphoma criteria (Cheson et al 2007). Effectiveness of treatment response is to some extent treatment specific, but response to idelalisib with a > 50% reduction in tumour volume (sum of the products of diameters) is generally considered a reasonable bench march for a 'clinically significant' treatment response.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there are 3 key groups that are areas of unmet need (although these do have considerable overlap). 1. Patients that progress after first line therapy with 24 months (POD24). These patients typically have a 5 year overall survival that is significantly inferior to patients that relapse post-first line therapy after 24 months (Casulo et al, JCO, 2015). 2. Patients that relapse after having received an autologous stem cell transplant in 2nd remission (the typical time point to receive an ASCT) 3. Patients that are 'double-refractory' to alkylators and an anti-CD20 monoclonal antibody (mab).
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	- Asymptomatic patients with low volume disease do not require treatment and often undergo a period of active observation (approximately 20% of patients do not require treatment at 10 years follow up). - Patients with stage I or some patients with stage II disease can undergo involved field radiotherapy (24 Gy). These patients typically have a 40-50% long term chance of disease control i.e. cure. - For patients with advanced stage disease requiring treatment, first line therapy is typically with an anti-CD20 mab given in combination with chemotherapy (CVP, CHOP or Bendamustine are most typically used in the first line setting). - Obinutuzumab alongside chemotherapy (CVP, CHOP or Bendamustine) has only recently been approved by NICE in the first line setting for patients with a FLIPI score of 2 or more. This is an evolving field with little real world data available to date. - Patients are often offered maintenance rituximab or obinutuzumab following first line immunochemotherapy based on the PRIMA trial and the GALLIUM trial results respectively. - Salvage chemotherapy (examples include GDP-R, ICE-R, IGEV-R, ESHAP-R if a peripheral blood stem cell harvest (PBSCH) and an autologous stem cell transplantation (ASCT) approach is followed) is often used at first relapse, with the length of first remission and the patient age and relative fitness being key determinates of the intensity of the approach at first relapse. As a general rule if patients have an early but chemotherapy-sensitive relapse, most patients who are fit enough, under the age of 65 years will be considered for an autologous stem cell transplant. A selective group of fit patients under the age of 65

	years with a sibling matched donor may be suitable for allogenic stem cell transplant. Practice certainly varies across the UK in the NHS. - Patients with longer first remissions (e.g. > 5 years) may well do very well from repeat treatment with a standard immunochemotherapy approach with an anti-CD20 mab and chemotherapy (Bendamustine, CVP, CHOP being the standard options). The length of first remission can often guide clinicians as to whether the patient may benefit from an intensified approach. There are no absolute hard and fast rules about which patients should be intensified to salvage therapy and an ASCT, but it is considered the standard approach in those relapsing within 2-3 years post first line therapy. - Obinutuzumab-Bendamustine followed by obinutuzumab maintenance is a relatively newly NICE approved option in patients that are 'refractory' to rituximab i.e. relapsing within 6 months of maintenance or sooner (i.e. on therapy). This combination therefore can be used in patients that are pre-treated who are rituximab refractory. - Patients that relapse after the above therapies are often those with an 'unmet' clinical need and will be subject to investigative agents, fludarabine-based therapy, further salvage treatment with an aim to perform an allogenic SCT or indeed palliative approaches.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSCH guidance ESMO guidance

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is partly defined although not absolutely: please see the answer to question 9 which refers to some key differences.
• What impact would the technology have on the current pathway of care?	Idelalisib would almost certainly be used in one or more of these settings: 1. Patients that relapse after having received an autologous stem cell transplant in 2nd or subsequent remissions (2nd remission is the typical time point to receive an ASCT) 2. Patients that are 'double-refractory' to alkylators and an anti-CD20 monoclonal antibody (mab). 3. Patients with immune-chemotherapy refractory disease that have relapsed at later lines of therapy. At present the only clear other therapeutic option in the rituximab refractory setting is the use of obinutuzumab and bendamustine as an option in suitable patients relapsing within 6 months of rituximab (there is an overall survival benefit to this approach when compared to single agent bendamustine). These patients treated with this approach will relapse and it is likely that a number of those patents will be suitable for idelalisib at subsequent relapse. It is unlikely that the use of idelalisib will precede the use of bendamustine-obinutuzumab in patients that are eligible and suitable for bendamustine-obinutuzumab.

	There is a small amount of evidence that patients with progression of disease within 12 or 24 months - POD12 or POD24 - have a similar response rates, tumour reduction and progression free survival as each other and indeed not dissimilar from the whole FL cohort in the phase II clinical trial.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – it should be used in the 'double refractory setting'.
• How does healthcare resource use differ between the technology and current care?	N/A
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics in secondary care: the agent would be advised by specialists in regional lymphoma MDT meetings.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	N/A. Education on the toxicities and nature of idelalisib for those not using the agent in CLL will be important

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – there is currently no standard therapies available in patients that have been treated with the standard lines of immunochemotherapy +/- autologous stem cell transplantation. The overall response rate of 56% and CR rate was 13.9% was documented in the FL patients treated in the phase II DELTA trial (Gopal et al, 2014). Responses were seen across patients regardless of the number of prior therapies, refractoriness to previous regimens, bulky disease, and age.
• Do you expect the technology to increase length of life more than current care?	Idelalisib has the potential to extend the life for patients treated in the immunochemotherapy refractory setting. There are no randomised clinical trial data available comparing a standard approach with idelalisib monotherapy and therefore answering this with absolutely certainty is difficult.
• Do you expect the technology to increase health-related quality of life more than current care?	In those patients that the agent controls the refractory follicular lymphoma with minimal toxicity, then yes. Idelalisib has a known, well described toxicity prolife that requires careful monitoring. Patients that develop grade 3-4 immuno-related toxicities are likely to have a significantly impaired quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is my estimate that most clinicians will feel more comfortable using idelalisib in younger, fitter patients, particularly those in which they wish to add to bridge to allogenic stem cell transplantation. Conversely there will also be patients that will not be treated with idelalisib because of concerns regarding immune related toxicities. It is my estimate that these will be patients with known immune related disorders e.g. ulcerative colitis, but also those that are more frail and older e.g. over 80 years.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Closer monitoring for immune related idelalisib induced side effects (pneumonitis, colitis, hepatitis, skin rash) will be required. Cytomegalovirus (CMV) PCR monitoring and PJP prophylaxis will also be needed. These side effects have been well publicised following the closure of idelalisib studies due to excess infections and deaths and as such education for physicians around the UK using idelalisib in CLL and FL has been very important. Local protocols should be established for monitoring CMV, PJP and other immune side effects should ideally be in place for patients treated with idelalisib for FL.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – only standard CT based response criteria should be used.
15. Do you consider that the use of the technology will	No

result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any	

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	See answer 13.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the phase II clinical trial (Gopal et al, 2014, NEJM) investigated idelalisib in a 'double refractory' population and as such this remains a reasonable group with an unmet need according to standard UK practice. These data from the trial are applicable to UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, duration of response, overall survival, toxicity profile of the agent.
• If surrogate outcome measures were used, do	

they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	See answer to 13. CMV reactivation and PJP infection are 2 key new adverse effects that were not highlighted in the published clinical trial.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s)	There are published data on the novel Pi3K (predominant activity against PI3K-α and -δ isoforms) inhibitor copanlisib which has recently received an FDA license for patients with relapsed FL who have received at least two prior systemic therapies. The clinical trial data supporting copanlisib is strikingly similar in terms of ORR, PFS and OS when compared to idelalisib. 142 patients were treated with copanlisib monotherapy: the ORR was 59% across all patients in indolent NHL. In the 104 patients with follicular lymphoma, the objective response rate was 59%, including 15 patients (14%) with a complete response and 46 (44%) with a partial response. Patients with follicular lymphoma had a median duration of response of 12.2 months (range, 0 to 22.6 months; 95% CI, 6.9 to 22.6 months; n = 61). Median progression-free survival was 11.2

and renumber subsequent sections]	months (range, 0.2 to 24.0 months) and median overall survival had not yet been reached (Dreyling et al, JCO 2017). Similar response rates, DOR and PFS were also seen with Duvelisib (PI3K-δ) and PI3K-γ) inhibitor in a recent publication (Flinn et al, 2018, Blood) (indolent NHL overall response rate, 58% (n = 31) with 6 complete responses (CRs)). This agent hasn't received a license to date.
21. How do data on real-world experience compare with the trial data?	Data published in 2017 (Eyre et al, 2017) show that the response rates in the 'real world' are strikingly and reassuringly similar to the data published in the phase II DELTA trial. Post hoc analyses from the clinical trial have shown that the PFS for idelalisib is improved compared to the prior line of therapy (the opposite to what one might expect from historical data series). The real world data shows that the PFS is the same as that of the prior line of therapy and as such, partially bucks that trend. The PFS in the real world data is shorter (7.1 months) compared to the clinical trial, but in some respects that is not suprising given the nature of 'real world' patients: high FLIPI scores at start of idelalisib (75% FLIPI 3-5 vs 54% FLIPI 3-5), more patients with prior ASCT (27% vs 17%) for example.
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Idelalisib is an effective agent in relapsed, refractory, heavily pre-treated follicular lymphoma.
- Idelalisib has a license and efficacy data in a key area of unmet need in the follicular lymphoma treatment pathway
- Real world data suggests that the response rate for idelalisib is similar to the clinical trial data although the PFS is shorter in a higher risk population
- The toxicity profile for idelalisib is well described and local protocols should be in place to monitor for specific immune related side effects, CMV reactivation and PJP. Patients must receive PJP prophylaxis on idelalisib
- 10% patients in the real world setting were able to use idelalisib to bridge to allogenic stem cell transplantation

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Professional organisation submission

Idelalisib for treating refractory follicular lymphoma [ID1379]

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NCRI/RCP/RCR/ACP

3. Job title or position	Professor of Haematology, University of Liverpool Honorary Consultant Haematologist, Clatterbridge Cancer Centre NHS Foundation Trust Chair, NCRI Lymphoma Clinical Studies Group
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): I am the Chief Investigator for 2 consecutive phase III NCRI trials investigating initial therapy for follicular lymphoma (PACIFICO and PETReA), as well as a phase III NCRI trial in chronic lymphocytic leukaemia which investigated idelalisib (RIAltO).
5a. Brief description of the organisation (including who funds it).	NCRI/RCP/RCR/ACP
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To improve quality of life by inducing remission and in doing alleviating disease-related symptoms. 2. To prolong life by extending the natural history of the disease and preventing disease-related complications.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would normally be defined as a complete (CR) or partial (PR) anatomical response (a PR requires at least 50% shrinkage of 2-dimensional tumour size). However, in a post-hoc analysis of the 72 patients with FL in the pivotal DELTA trial, the PFS and OS of patients with stable disease (defined as less than 50% shrinkage of 2-dimensional tumour size) was very similar to that of patients who achieved a PR (Haematologica 2017;102:e156–e159). This suggests that freedom from disease progression may not be coupled to response in this setting.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Unlike other mature B-cell malignancies such as chronic lymphocytic leukaemia, mantle-cell lymphoma and lymphoplasmacytic lymphoma, patients with follicular lymphoma who have failed chemoimmunotherapy do not have any further treatment options available to them.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Advanced-stage follicular lymphoma (FL) is generally considered to an indolent but incurable disease with a clinical course characterised by recurrent relapses and remissions. Treatment is usually deferred in asymptomatic patients with low tumour burden, although rituximab monotherapy is approved by NICE as an option for this indication. Initial treatment of high tumour burden FL is with a CD20 antibody in combination with one of 3 different chemotherapy regimens: bendamustine or cyclophosphamide, doxorubicin and prednisolone with or without vincristine (CHOP and CVP, respectively). Until recently, the only CD20 antibody available for frontline chemoimmunotherapy was rituximab, but obinutuzumab (GA101) was recently NICE approved as an option for patients with high or intermediate FLIPI scores. Patients who respond to chemoimmunotherapy have the option of continuing the CD20 antibody as maintenance therapy for 2 years, although this is increasingly controversial. The choice of subsequent therapy depends on a number of factors including the type of first-line therapy given, how well it worked and how much and what type of toxicity it caused. General fitness and comorbidity are also important factors. Treatment options for relapsed or refractory follicular lymphoma include further rituximab-based chemoimmunotherapy (with or without rituximab maintenance), obinutuzumab plus bendamustine (NICE approved for rituximab-refractory patients only), or chemoimmunotherapy followed by autologous stem-cell transplantation (ASCT) for patients who are sufficiently fit. Rituximab monotherapy is available for patients who have exhausted other treatment options but is rarely used as such patients are usually rituximab resistant. Occasional patients may undergo allogeneic stem-cell transplantation. This is a potentially curative treatment but requires patients to be in remission and is associated with significant morbidity and mortality. Some targeted agents (e.g. lenalidomide and idelalisib) may be available through patient access schemes.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	European guidelines for FL were published in 2016 by the European Society for Medical Oncology (ESMO). The current UK Guidelines were published by the British Society for Haematologists (BSH) in 2011 and updated in 2017 to include frontline bendamustine plus rituximab. Both guidelines encompass most of the ideas outlined above.
• Is the pathway of care well defined? Does it	Frontline therapy is reasonably well defined but subsequent pathways of care are poorly defined owing to the large number of variables that impact on treatment decisions in the relapsed/refractory setting.

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Furthermore, opinion is split regarding issues such as rituximab maintenance and whether obinutuzumab has any advantages over rituximab. These controversies are global.
• What impact would the technology have on the current pathway of care?	Idelalisib would have a big impact on treatment pathways for FL as patients who fail chemo-immunotherapy currently have no other treatment options available to them apart from palliation, clinical trials or novel agents via patient access schemes.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Idelalisib is already NICE approved for chronic lymphocytic leukaemia.
• How does healthcare resource use differ between the technology and current care?	Idelalisib should require less healthcare resource than rituximab or chemoimmunotherapy as it is taken orally.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care (haemato-oncology outpatient clinics).

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is needed to introduce the technology as idelalisib is already NICE approved for CLL and clinicians are therefore already familiar with it in many centres.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	Yes. The pivotal phase II study of idelalisib in 125 patients with indolent NHL (DELTA) showed an overall response rate of 57% and a median PFS and OS of 11m and 12 months, respectively (NEJM, 2014;370:1008-18). A post-hoc analysis showed very similar results in the subgroup of 72 patients with FL (Haematologica 2017;102:e156–e159). In this analysis, the median PFS following idelalisib was more than twice as long as the PFS following the most recent therapy prior to idelalisib. Furthermore, OS and PFS in patients who achieved SD were similar to the OS and PFS of patients who achieved a partial response. Overall, these results are much better than would be expected with palliation or further chemoimmunotherapy.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Active follicular lymphoma often produces symptoms such as pain and fatigue which reduce quality of life. These symptoms usually increase with tumour burden. Technologies that induce remissions and prevent disease progress should therefore reduce such symptoms and in doing so improve quality of life.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In the DELTA trial, the OR rate was unaffected by age, gender, tumour burden, number of prior therapies, bendamustine exposure and refractoriness to last therapy (NEJM, 2014;370:1008-18). In the post-hoc analysis of 72 patients with FL, the OR rate was unaffected by age, gender, race, histological grade, FLIPI score, tumour bulk, lines of prior therapy and refractoriness to the most recent therapy (Haematologica 2017;102:e156–e159). The only variables associated with a lower response rate were ECOG status of 2 and high LDH.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Idelalisib administration should not pose any problems for patients or healthcare professionals as it is taken orally and does not require any intravenous infusions. Idelalisib is associated with some notable toxicities including infection (including pneumocystis jirovecii pneumonia and CMV reaction) and immune-mediated complications (skin rash, hepatitis, colitis and pneumonitis). Consequently, it is generally recommended that patients receiving idelalisib should be prescribed antimicrobial prophylaxis with co-trimoxazole (or equivalent) and undergo regular monitoring for CMV reactivation and immune-mediated complications. Patients should also be monitored for haematopoietic suppression and supported with G-CSF and/or blood transfusion if required. Healthcare professionals should have an awareness of these potential toxicities, and patients should be managed appropriately if they occur.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Idelalisib would be suitable for most patients with relapsed/refractory follicular lymphoma. However, because of its toxicity profile, caution should be used in patients with a significant history of infection, haematopoietic suppression or co-existing skin, gut, liver or lung conditions. Treatment should be paused in the event of significant toxicity and stopped altogether if the toxicity is life-threatening.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Signalling inhibitors are not currently available in the NHS as a treatment option for patients with follicular lymphoma. Given that idelalisib is a first-in-class signalling inhibitor with significant activity in double-refractory FL and taking into account the paucity of alternative treatment options for such patients, the drug can be regarded as a genuine breakthrough in the treatment of this disease.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, it would be the first signalling inhibitor to be NICE approved for FL.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, idelalisib is suitable for older, less fit patients who would not tolerate further chemoimmunotherapy. This is pertinent given that the median age of patients with newly diagnosed FL is about 60.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the DELTA trial, the most common adverse events of any grade were diarrhoea (43%), fatigue (30%), nausea (30%), cough (29%), and pyrexia (28%). The most common grade 3 or higher toxicities were neutropenia (27%), elevated transaminase (13%), thrombocytopenia (6%), diarrhoea (13%), pneumonia (7%), and dyspnoea (3%). Some of these toxicities are likely to have a negative impact on quality of life and treatment efficacy (idelalisib was discontinued due to toxicity in 20% of patients).
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The entry criteria for the DELTA trial stipulated ≥2 prior lines chemotherapy- or immunotherapy-based treatment, with refractoriness to both rituximab as well as an alkylating agent. The main exclusion criteria were histological transformation, central nervous system lymphoma, a history of hepatic dysfunction, and active systemic infection. The profile of patients with double-refractory FL in the post-hoc analysis is fairly representative of routine clinical practice (median age 62, high FLIPI score in 54%, reduced performance status in 57%, median of 4 lines of prior therapy). However, it may not be representative of the entire

	population of patients with FL who have exhausted conventional treatment options as many such patients will have failed their last treatment due to intolerance or early progression without fulfilling the rather narrow definition of “refractory” used in the DELTA trial.
• If not, how could the results be extrapolated to the UK setting?	It would be reasonable to extend the definition of “refractory” to include patients who are intolerant of rituximab-containing chemoimmunotherapy or who have progressed within 12 months of responding to it as treatment options for these patients are equally as limited as those for patients who fulfil the definition of “refractory” in the DELTA trial.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Given the poor outcome of refractory FL and lack of therapy options for these patienst, the most important trial outcomes relate to treatment efficacy and include response, PFS and OS. All of these outcomes were measured in the DELTA trial along with toxicity. Quality of life was not measured directly but would be difficult to interpret owing to the absence of a comparator treatment.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Several trials of frontline idelalisib combination therapy in indolent NHL and CLL were halted in March 2016 owing to an increased rate of serious and fatal infection. Infections included pneumocytis jirovecii pneumonia and CMV reactivation. Marketing authorisation for idelalisib monotherapy in relapsed/refractory FL was nevertheless retained owing to its favourable risk:benefit profile in this setting.
19. Are you aware of any relevant evidence that might	No.

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No.
21. How do data on real-world experience compare with the trial data?	A UK real-world study of 79 patients with relapsed/refractory FL who received idelalisib via a patient access scheme was recently published (Br J Haematol 2018;181:555-559). Patient characteristics, efficacy and toxicity were mostly similar to those observed in the DELTA trial, although patients in the real-world study had higher FLIPI scores and a shorter median PFS. The safety profile of idelalisib was in keeping with that reported in the DELTA trial.
Equality	
22a. Are there any potential equality issues that should be	No.

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	No.
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages
24. In up to 5 bullet points, please summarise the key messages of your submission. • Idelalisib represents a step-change in the treatment of relapsed/refractory follicular lymphoma owing to its novel mechanism of action and its effectiveness in patients who have exhausted conventional treatment options. • Idelalisib has an acceptable safety profile but an awareness of its potential toxicities is required. • Idelalisib is administered orally and should therefore place a minimal additional burden on hospital pharmacies and day wards. • Extending the definition of “refractory” would allow more patients who have exhausted conventional treatment options to benefit from this new technology. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Idelalisib for treating refractory follicular lymphoma

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rider on responsibility for report

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nasuh Büyükkaramikli acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Isaac Corro Ramos, Steve Ryder, Nigel Armstrong, Marscha Holleman and Gimon de Graaf acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Stephanie Swift acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse events
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
bd/b.i.d	Twice daily
BI	budget impact
BIC	Bayesian information criterion
BSA	body surface area
BSC	Best supportive care
CDF	Cancer Drugs Fund
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CHMP	Committee for Medicinal Products for Human Use
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CUP	Compassionate use programme
DBL	Database lock
DHAP	Dexamethasone, cytarabine, cisplatin
DOR	Duration of response
DSU	Decision Support Unit
EAP	Early access programme
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European quality of life-5 dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FACT-Lym	Functional assessment of cancer therapy: lymphoma
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
iNHL	Indolent non-Hodgkin's lymphoma
IPD	Individual patient data
IRC	Independent review committee
ITC	Indirect treatment comparison

ITT	Intention to treat
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
NA	Not applicable
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PJP	Pneumocystis jirovecii pneumonia
PPS	Post-progression survival
PR	Partial response
PRESS	Peer review of electronic search strategies
PSA	Probabilistic sensitivity analyses
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-CVP	Rituximab, cyclophosphamide, vincristine, prednisone
RCT	Randomised controlled trial
RS	Relative survival
RWE	Real world evidence
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SCT	Stem cell transplantation
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
STA	Single technology appraisal
ToT	Time on treatment
TSD	Technical support document
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
WHO	World Health Organisation

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The NICE scope describes the decision problem as the clinical and cost effectiveness of idelalisib within its marketing authorisation for people with follicular lymphoma (FL) that is refractory to two prior lines of therapy.

The population in the submission is in line with the scope. However, the submission mainly relies on one single arm study, the Phase II study 101-09 which provides data on the use of idelalisib monotherapy for the treatment of double-refractory FL. The population of double-refractory FL patients in this study may not be representative of UK patients in the typical clinical setting (see section 3.1).

The comparators listed in the NICE scope are: chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil); and, in people for whom chemotherapy is unsuitable: best supportive care (BSC). For the main comparator (chemotherapy regimens) the company provided data collected via the disease registry for the Haematological Malignancy Research Network (HMRN) to provide real world evidence for chemotherapy regimens currently used to treat double-refractory FL in UK practice. These data are subsequently used to perform a matching-adjusted indirect comparison (MAIC), providing an estimate of comparative effectiveness for chemotherapy regimens (HMRN data) versus idelalisib (study 101-09 data). No evidence was provided for best supportive care in people for whom chemotherapy is unsuitable.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company presented evidence from four idelalisib studies. The main trial is study 101-09, this is a multi-centre, single arm study investigating the efficacy and safety of idelalisib in patients with iNHL refractory to rituximab and an alkylating agent. Study 101-09 enrolled patients with different types of iNHL, but the FL population was the largest population (72 of 125). The other three studies were:

- A phase Ib dose escalation and extension study (study 101-02/99), which included 64 patients with relapsed iNHL, refractory to or relapsed after at least one prior chemotherapy regimen and rituximab (histological subtypes included FL). Data are presented for patients across a range of doses, with only 10 patients receiving idelalisib at the recommended 150mg twice daily dose level.
- A retrospective data collection from real world patients (Compassionate use programme: UK(CUP-UK)), including 79 patients with refractory or relapsed FL.
- A retrospective data collection from real world patients (Europe and Australia Early Access Programme (EAP)), providing further safety data for idelalisib monotherapy. Efficacy data are not available from this non-UK programme, and data have only been presented at conferences to date.

Data collected via the disease registry for the HMRN ([redacted]) was included to provide evidence for the comparator: chemotherapy regimens currently used to treat double-refractory FL in UK practice.

Results from study 101-09 based on the June 2014 database lock were used in the HMRN matching-adjusted indirect comparison and in the economic analyses. Results based on the June 2015 database lock were presented in the main submission. Where possible we have presented both data sets. Median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks. Median PFS was 11.0 months in the FL population for both data sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 dataset, this was not reported for the June 2014 dataset.

In the FL population, the overall response rate (ORR, 95% CI) was 55.6% (43.4, 67.3) as assessed by the independent review committee (IRC), comprising 10 complete responses (CRs, 13.9%) and 30 partial responses (PRs, 41.7%) in the June 2015 data cut. Response data from June 2014 are similar using IRC assessment, but were not reported for investigator assessment.

Health-related quality of life (HRQL) was assessed with the Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) scale. Median best change from baseline in FACT-Lym total score was 7.5 (95% CI: -39.0 to 47.0). The confidence interval was quite wide and the median did not exceed the minimally important difference threshold of 10-11.

The company performed a matching-adjusted indirect comparison (MAIC), comparing idelalisib with alternative chemotherapy, using data from the 101-09 study for idelalisib and HMRN data for the comparator. The MAIC included 72 patients with FL from study 101-09 and [redacted] Variables for matching included in the MAIC were [redacted] The respective two-year OS rate of FL patients treated with idelalisib in study 101-09 was 69.8% and the one-year PFS rate was 43.0%, in the data cut used for the MAIC (11 June 2014 DBL).

The majority of patients enrolled in study 101-09 experienced at least one adverse event (AE), many of which were deemed to be treatment-related; 25% of FL patients discontinued treatment due to an AE. In both the total population and the FL population, the most common Grade ≥3 AE was neutropenia, occurring in 27 (21.6%) and 16 (22.2%) patients, respectively. Other common Grade ≥3 AEs included diarrhoea and pneumonia, both reported by more than 10% of patients.

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 chemotherapy or best supportive care.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company submission (CS) and response to clarification provided sufficient details for the ERG to appraise the searches for eligible studies. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4 using a good range of databases. Additional searches of conference proceedings were reported.

The ERG had several problems with the way the company performed the MAIC. First of all, it seems counter-intuitive to try to match the HMRN data to the baseline characteristics of study 101-09 patients. The HMRN population includes all relevant patients who have been prescribed idelalisib in a real world UK setting; as such the HMRN population seems more representative of the population defined in the NICE scope than the 101-09 study population. Study 101-09 had specific inclusion criteria, such as, 'Karnofsky performance score of 60 or higher (on a scale of 0=death and 100=complete absence of symptoms)' and 'radiographically measurable disease (defined as ≥1 lymph node with perpendicular

dimensions measuring ≥2.0 x ≥1.0cm)', that may have influenced patient characteristics. Therefore, the ERG would have preferred to match the 101-09 study population to the characteristics of the HMRN population. That way, the resulting adjusted population might have been larger than the resulting adjusted HMRN sample size of [redacted].

Secondly, the ERG did not agree with the exclusion of variables from the MAIC. [redacted] However, given the small sample sizes, not taking characteristics from one or a few patients into account in the analyses may similarly give too much weight to the characteristics of the remaining patients. [redacted] However, even though variables may be correlated, these variables might still be important for matching the populations in the MAIC. Therefore, we asked the company to repeat the MAIC by using the study 101-09 data as the source of IPD and matching it to summary HMRN data, using the most recent data for study 101-09; and to provide MAIC results including all variables (see Clarification letter questions A19b and A23). However, the company declined to repeat the MAIC by using the study 101-09 data as the source of IPD and matching it to summary HMRN data. The analysis including all variables in the MAIC model [redacted]. These differences illustrate the concerns about the reliability of the MAIC analyses.

Overall, the reliability of the MAIC is uncertain, primarily stemming from the small sample of FL patients with disease refractory to rituximab and an alkylating agent identified in the HMRN cohort; some variables were excluded from the MAIC which meant that differences in treatment history could not be adjusted for; and the fact that the effective adjusted HMRN sample size was only [redacted] which reduces the statistical power.

1.4 Summary of cost effectiveness evidence submitted by the company

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. Searches were reported for a good range of databases. Additional searches of conference proceedings and reference checking were also reported. The ERG was concerned that the inclusion of a facet for disease stage may have been overly restrictive, however the broad range of searches and additional reference checking may have mitigated against some loss of recall.

The company developed a cohort-level state transition decision analytical model to assess the cost effectiveness of idelalisib for double-refractory FL, compared to the standard of care. The standard of care is chemotherapy regimens for chemotherapy eligible patients and best supportive care for patients who are not eligible for chemotherapy.

The model used a cycle length of one week and the horizon of the analysis was 39 years. It consisted of five health states: pre-progression on treatment, pre-progression off treatment, post-progression, palliative care, and death. The simulation cohort enters the model in the 'pre-progression on treatment' state. In this state patients can either stop treatment (transition to the pre-progression without treatment state), experience disease progression (transition to post-progression state) or enter end-of-life palliative phase before death. In the pre-progression off treatment state, patients can experience disease progression or enter the before death palliative phase. In progressed disease, patients can only stay in

the progressed disease state or go to pre-death palliative care state. Patients remain in the palliative care state for eight cycles/weeks.

In the CS, four different comparisons were defined: A) idelalisib vs. chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09, B) idelalisib from Study 101-09 vs. chemotherapy regimens as observed in the HMRN database, C) idelalisib vs. chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme, and D) idelalisib from Study 101-09 vs. best supportive care.

Each comparison has a unique structure and different underlying set of modelling/input assumptions. Earlier versions of the same model were used in submissions to the SMC, NCPE and AWMSG for idelalisib in the same patient population.

Transition between model states under idelalisib treatment is based predominantly on Study 101-09.

Only in Comparison C (idelalisib compared to chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme) time to progression under idelalisib is based on data from the UK and Ireland compassionate use programme.

Different sources of data (prior line therapy from Study 101-09 for Comparison A, MAIC adjusted the Haematological Malignancy Research Network dataset for Comparison B, and prior line therapy from the UK and Ireland compassionate use programme) are used to describe the transition of the cohort through the model under standard of care, depending on the comparison.

Parametric extrapolations were used for all transitions in the economic model. No evidence on post treatment survival for patients on standard of care was available for Comparisons A, C and D. Therefore, in these comparisons, no difference in post progression survival between treatment alternatives was assumed. Differences in survival between treatment alternatives in those comparisons are driven by differences in progression free survival.

The company founded its base-case on comparison A results. Comparison C differed from comparison A only in terms of the idelalisib and prior line therapy TTP inputs. The TTP inputs for the latter (comparison C) might be more reflective of the UK population. Comparison B uses different inputs (PFS and OS), with different modelling assumptions (area under the curve approach), and different evidence sources (MAIC adjusted HMRN database for chemotherapy). Hence it is impossible for the ERG to pinpoint the exact reason of the substantial gap between the cost-effectiveness outcomes from this comparison and the other comparisons. Comparison D provides estimates for chemotherapy ineligible patient population, and hence its results are not comparable with comparisons A, B and C.

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 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. This was omitted based on the opinion of one clinical expert, and this might be subject to substantial uncertainty.

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.

The ERG identified some programming errors in all comparison. In Comparison D, it was assumed that patients who are receiving best supportive care progress immediately, the ERG considers that this assumption was too strong. In the literature it was suggested that some patients may respond well to the palliative care, and thus these patients receiving palliative care do not necessarily progress immediately.

The ERG concluded that the evidence and assumptions underlying each of the four different comparisons, each have their own limitations and shortcomings. Therefore, the decision should be based on the cost-effectiveness estimates coming from all four comparisons.

Regarding the survival modelling conducted on data from Study 101-09, the ERG noted that the parametric distributions do not appear to have been chosen systematically. Additionally, the ERG thought that different distribution possibilities (joint modelling or separate modelling with the flexibility of choosing different types of distributions per arm) could have been explored by the company. The "sample inflation" method applied in the survival analysis of the MAIC adjusted data from the HMRN database and its implications could not be verified, since the necessary details were not provided to the ERG. The ERG also has some concerns regarding the underestimation of parametric uncertainty of the survival regression coefficient estimates, due to the use of a sample inflation approach leading to artificially reduced variance. Concerning the survival analyses conducted on the Eyre et al. 2017 data, it was unclear to the ERG how the analyst classified the idelalisib progression and death events from the OS and PFS idelalisib KM curves.

The adverse event profile for idelalisib and chemotherapy were assumed to be the same in the CS, due to lack of data. The company argued that this is conservative for idelalisib. The ERG considers that this statement is speculative as it was not grounded on any evidence.

The utility inputs used in the model were based on a conference proceeding from 2004, and the actual values were not reported in the abstract. The ERG questioned why the company did not use some of the mapping algorithms published in the literature. When the ERG requested from the company to use one of the published mapping algorithms in the literature, the company declined to do so, arguing that these mapping algorithms had their own limitations and the population samples used in these algorithms are not reflective of the double refractory FL population. However, the ERG thought that the estimates obtained from this mapping exercise would be still useful, because there is a lack of transparent, verifiable utility inputs in the literature. The ERG identified some additional utility sources from a previous appraisal in refractory FL. Also, the ERG considered that an age-based utility decline should be implemented, since assuming the same utility for a patient who stays in the same health state for consecutive years would overestimate the actual utility that a patient experiences. The company suggested that there might be a HRQoL gain due to oral therapy (in comparison to intravenous administration of other chemotherapy options), however without lack of comparative HRQoL evidence, the ERG cannot comment on the plausibility of this gain.

In terms of resource use, the ERG identified that wastage costs for idelalisib and mean dose intensity for chemotherapy were not included in the economic model. Furthermore, the rituximab prices were not reflecting the cost of biosimilar rituximab available on the market. Overall, the ERG deemed that the choice of inputs for the resource use estimates from the literature and expert meetings were rather arbitrary.

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

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Overall, the CS reported searches were well presented and easily reproducible. Searches were carried out on a good range of databases. Supplementary searches of conference proceedings were undertaken by the company and reference checking was undertaken for most stages of the project.

The main strength of the cost effectiveness submission is the searches conducted. The majority of the cost effectiveness searches in the CS were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. The Embase/Medline update searches referenced recognised study design filters to identify relevant information regarding costs, resource use and HRQL.

Also, the structure of the model developed by the company is in line with other, commonly used models used in oncology. The model includes relevant disease states, adverse events, utilities and costs. The cost calculations were quite detailed. Sensitivity (probabilistic and one-way) analyses were performed on a wide range of the model parameters.

1.6.2 Weaknesses and areas of uncertainty

The ERG had some concerns about the language bias of restricting searches to English language only as this is not in line with current best practice. The ERG also felt the inclusion of a facet for disease stage may have been overly restrictive, however the broad range of searches and additional reference checking may have mitigated against some loss of recall.

The main weakness of the clinical evidence submitted is that the indirect comparison relies on small numbers of patients from single arm studies with a limited number of variables included in the matching analyses. In addition, in the MAIC the individual patient data from the HMRN were adjusted to match the summary characteristics of idelalisib patients in study 101-09 and the effective sample size of the adjusted population was small ([redacted]) which provides a low amount of statistical power to detect between group differences. This means the results may not be representative of the UK population.

The main weakness of the cost effectiveness section of the company submission is the non-systematic way of synthesising different pieces of clinical evidence, stemming from different studies, without proper statistical adjusting as outlined in analysis guidelines (e.g. NICE TSD 17). As the company provided multiple comparisons, some of which had the same comparators (i.e. idelalisib vs. chemotherapy), the ERG had difficulty selecting the most reliable one. The company's choice for the base-case, comparison A, was not sufficiently motivated. These comparisons differed not only in terms of clinical inputs that populated the model but also in terms of underlying modelling assumptions/structure. Hence, it is intractable and not possible to pinpoint the actual reason of a discrepancy between the outcomes of some of the comparisons.

The health-related quality of life section and the utility input selection of the company submission is also lacking transparency. The main utility source, Wild et al, is just a conference proceeding and dates back to 2004, and the utility values were unverifiable (by the ERG). The choice of different utility inputs seems also to have a significant impact on the cost effectiveness results.

According to the ERG, additional scenarios could have been conducted, given the inherent structural uncertainties in the comparisons provided in the CS. Furthermore, the ERG considers that the reporting of the validation efforts for the CS was clearly inadequate, and that together with the errors identified

in the model and the gap between the model and trial outcomes, these factors have decreased the level of confidence in the economic analysis.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

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 from Study 101-09, while calculating AE cycle probabilities; 4) Implementing wastage costs for idelalisib (i.e. when patients stop the treatment before the package is finished completely, full package costs are incurred); 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); and 6) Implementing age adjusted utility decline from Ara et al. 2010.

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. This produced additional QALYs of 0.72 years for idelalisib and 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 the following additional scenario analyses: 1) 50% price reduction for rituximab (as a proxy for the price reduction due to biosimilar rituximab availability); 2) Using HR=1 for adjusting prior line treatment time-to-event outcomes; 3) Alternative utility inputs from Bec et al. 2014 or GADOLIN trial; 4) Implementing a 100% increase in CMV monitoring frequency; 5) Assuming CHOP regimen costs for the chemotherapy arm drug costs; 6) Applying minimum function instead of maximum to operationalise the logical constraints on time to event extrapolation curves; and 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 less expensive estimates (e.g. CHOP regimen costs) for the 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). Hence the ERG suggests that the results of Comparison B should be interpreted with caution.

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.

2. BACKGROUND

In this section, the ERG provides a review of the evidence submitted by Gilead in support of idelalisib, trade name Zydelig, ® for the treatment of follicular lymphoma (FL) that is refractory to two prior lines of therapy. We outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from Chapter B.1.3 of the company submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem of this appraisal is FL that is refractory to two prior lines of therapy. The company described FL as the most common of the low-grade lymphomas (also referred to as indolent non-Hodgkin's lymphoma [iNHL]) in the UK.[2] Its incidence increases with age, with a median presentation between 60 and 65 years and a slight female:male predominance.[2] FL is typically characterised by an indolent clinical course, with recurrent remissions and relapses and a median survival of 7–10 years in the pre-rituximab era.[3] FL is an incurable disease with a substantial symptom burden, including B symptoms, fatigue and the local mass effects of lymph node enlargement and bone marrow failure.[3]

The course of FL is highly heterogeneous; approximately 10% to 15% of patients have aggressive disease and short survival, whereas others have more prolonged and subdued disease.[4] Approximately 85% of patients have advanced disease at presentation.[5] FL that is rituximab-refractory displays characteristics of "high-risk FL" which is likely to have early progression and associated poor outcomes.[6] Therefore, it is conceivable that FL that is refractory to two previous lines of treatment, hereafter referred to as double-refractory FL, is likely to confer the worst prognosis. There is no treatment consensus or standard of care for these patients and life expectancy typically falls below 24 months.[7-9]

The CS states that the clinical features of double-refractory FL include: B symptoms (such as fatigue, weight loss, fever and night sweats[10]) and local mass effects of lymph node enlargement and bone marrow failure.[3] Patients with FL have multiple sites of lymphadenopathy that can result in restricted movement, disfigurement and pain.[11] Symptoms related to bone marrow dysfunction (such as anaemia, leukopenia and thrombocytopenia) can also be observed in later stages of disease.[12]

The company submission states: the Haematological Malignancy Research Network (HMRN) estimate that 15,232 people are living with FL in the UK.[13] Following diagnosis, [redacted]% of FL patients are estimated to have symptomatic, progressing disease and thus receive active treatment for their disease; of patients receiving active treatment, [redacted]% are treated at third-line or beyond; and of these, [redacted]% are estimated to have disease refractory to chemotherapy and rituximab.[14] The budget impact appraisal states that the number of people living with double-refractory FL in England who are eligible to receive idelalisib is thought to be 342 patients per year[15] and the number of people diagnosed with double-refractory FL in the UK is not thought to exceed 52 patients per year (43 in England).

ERG comment:

The ERG checked the references cited by the company to support the statements made above and considered the company to have provided an appropriate description of the underlying health problem. However, it would be more relevant for the CS to present up-to-date survival rates (in the rituximab era) instead of pre-rituximab era rates. There is evidence that the median survival in the rituximab era is significantly increased over historical pre-rituximab survival rates: from 7-10 years to 18 years, respectively.[16, 17]

The prevalence and incidence data provided in the original company submission was based on a patient dataset (HMRN) from the geographical area of Yorkshire and the Humber and Yorkshire Coast, which may not be representative across England. After requesting that real-world Office of National Statistics prevalence data across England was used in preference to these estimated HMRN datasets, the company re-ran their analysis and concluded that the actual incidence is numerically higher (59 patients instead of 43 patients in England).

2.2 Critique of company's overview of current service provision

Idelalisib is a small molecule PI3K inhibitor that specifically targets p110δ, the delta isoform of the PI3K enzyme. The PI3K signalling pathway is involved in cell growth, proliferation, trafficking and survival. p110δ is mainly expressed on leucocytes, with an important function in B cells, T cells, mast cells and neutrophils.

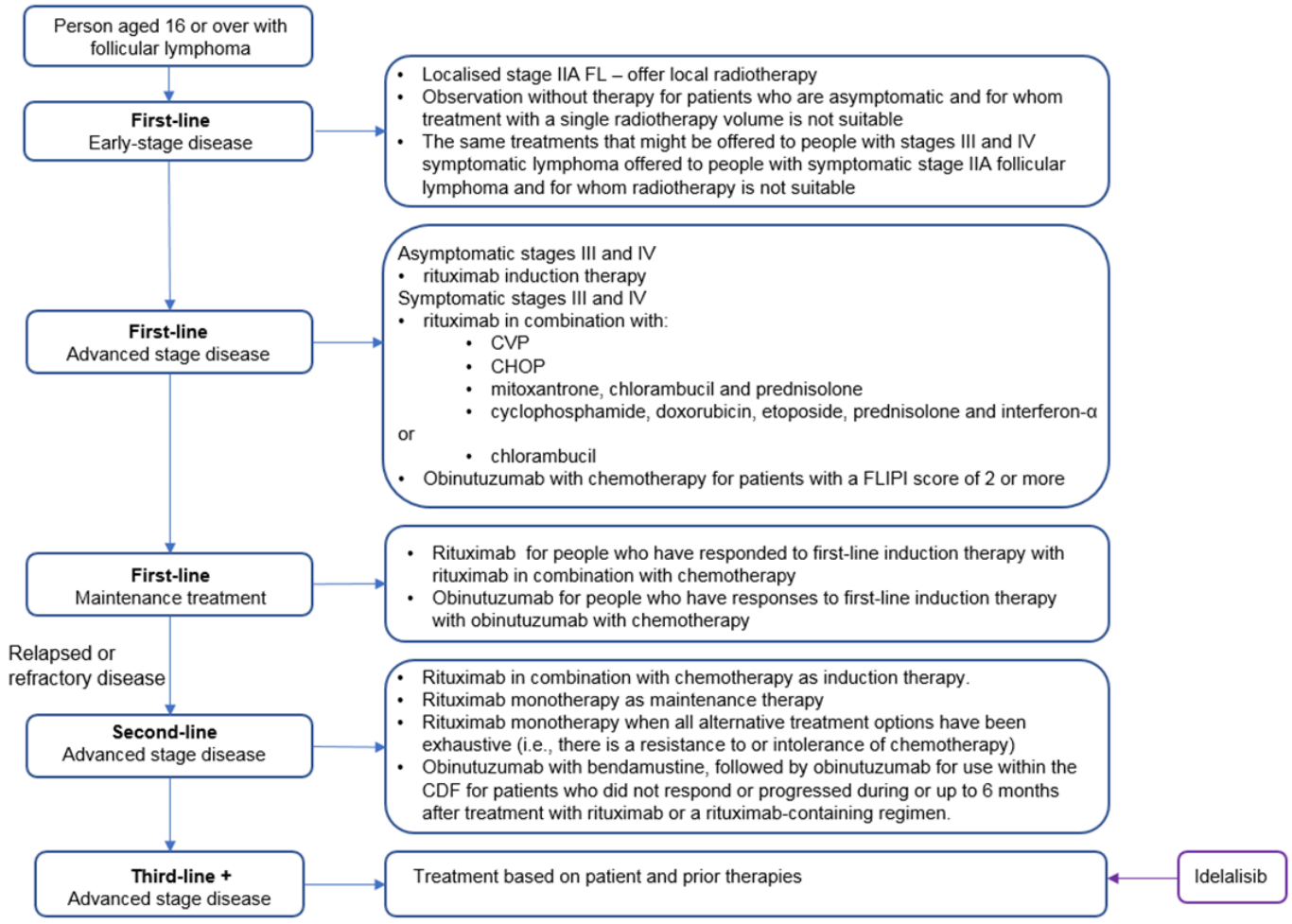
PI3Kδ is hyperactive in B cell malignancies and is central to multiple signalling pathways that drive the growth, differentiation, proliferation, survival, migration and metabolism of malignant cells in lymphoid tissue and bone marrow.[18] As a result, through the inhibition of PI3Kδ, idelalisib induces apoptosis and limits proliferation in cell lines derived from malignant B cells and in primary tumour cells.

The company states that the aim of treatment for FL is to control symptoms and extend remission in order to improve quality of life. Many patients initially experience asymptomatic, slowly progressing disease and will be on a 'watch and wait' policy until treatment becomes necessary. For the 85% of FL patients who present with advanced disease, most undergo first-line induction with rituximab in combination with chemotherapy (R-chemo).[19] This is usually followed by rituximab maintenance therapy. Second-line treatment for FL depends on the timing of relapse following first-line treatment and the chemotherapy agents used at first-line. Patients with FL who do not respond to induction treatment with R-chemo as well as those who initially respond but relapse within six months are considered to have uncontrolled disease and adverse prognosis.[20] These patients are considered to have disease that is refractory to rituximab i.e. "rituximab-refractory" FL. At this point, treatment options are limited for the patient.

The CS states that there is currently no consensus on treatment or standard of care for rituximab-refractory FL patients. Patients who approach third- and later-lines of therapy have markedly diminished treatment options. There is no standard of care (SOC) and treatment tends to be via a 'trial and error' approach. The only regimens and agents available are those used in previous lines, and therefore treatments are either repeated or administered in a different combination according to individual clinician choice. However, there are considerable limitations with such management: reinduction with rituximab and/or chemotherapy often has a short duration of remission, reduced overall survival, limiting toxicity and a negative impact on HRQL.[11, 21] Patients who can no longer tolerate further rituximab or chemotherapy treatment have no alternatives outside of best supportive care (BSC), which involves regular follow-up with a lymphoma specialist and/or palliative care team, blood product support if required, and antibiotics to treat infection.

Figure 2.1 shows the treatment algorithm for FL patients in England based on NICE guidance for treating FL[19] and adapted by the company. In the proposed pathway, the company submission (CS) specified idelalisib as third-line treatment.[1]

Figure 2.1: Treatment algorithm for FL patients in England



Source: CS, Figure 1, page 20.
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; FL = follicular lymphoma

ERG comment:
The company's description of the treatment pathway and options was based on existing NICE guidance (NICE Pathway NG52 2018[19]) which is appropriate and relevant to the decision problem. In particular the third-line treatment options for the management of FL were most relevant for the position of idelalisib in the treatment pathway. The company provided an adapted pathway which appears to be sensible. However, based on recent data from the M7-FLIPI study,[22] and considering that each patient is highly heterogenous in the presentation of their disease, a personalised therapeutic approach based on the genomic and clinical features of a patient's individual disease may represent the preferred approach. Consequently, idelalisib may not be considered the optimal fit for all double-refractory FL patients.

ESMO 2016 treatment guidelines for the treatment of late relapses were highlighted in the CS.[23] These guidelines recommend a return to rituximab monotherapy or palliative radiation for selected cases in patients with low tumour burden; or recommend chemoimmunotherapy plus rituximab maintenance, high-dose consolidation with autologous stem cell transplantation (ASCT), radioimmunotherapy or rituximab monotherapy, idelalisib or allogeneic transplantation for selected cases in patients with high tumour burden.[23]

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	People with follicular lymphoma that is refractory to 2 prior lines of therapy	People with follicular lymphoma that is refractory to 2 prior lines of therapy	N/A	In line with the scope.
Intervention	Idelalisib	Idelalisib	N/A	In line with the scope.
Comparator(s)	• Chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil) In people for whom chemotherapy is unsuitable: • Best supportive care	• Chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil) In patients for whom chemotherapy is unsuitable: • Best supportive care	N/A	No clinical effectiveness evidence is presented for BSC as a comparator.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response/remission • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response/remission • time-to-progression • post-progression survival • time on treatment • adverse effects of treatment • health-related quality of life	The additional outcome measures are necessary for economic analysis.	All outcomes listed in the NICE scope were reported for idelalisib. For the comparator, only overall survival and progression free survival were reported.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of	Incremental cost per QALY gained analysis, with a lifetime NHS and Personal Social Services	N/A	In line with the scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	perspective on costs and health effects on the individual perspective on benefits.		
Subgroup considerations	If the evidence allows, a subgroup of people suitable to receive stem cell transplantation and for whom idelalisib could be used to induce remission before transplantation will be considered.	-	The use of idelalisib to induce remission before transplantation has not been formally investigated. Observations from trials are provided where available but evidence is not sufficient for full consideration of this subgroup.	
Source: CS, Table 1, page 10 N/A = not applicable; PSS = personal social services; QALY = quality-adjusted life years.				

3.1 Population

The population defined in the scope is people with follicular lymphoma (FL) that is refractory to two prior lines of therapy. The population in the submission is in line with the scope.

However, the submission mainly relies on one single arm study, the Phase II study 101-09 which provides data on the use of idelalisib monotherapy for the treatment of double-refractory FL. The population of double-refractory FL patients in this study may not be representative of UK patients in the typical clinical setting. The Canadian Agency for Drugs and Technologies in Health (CADTH) concluded that the majority of patients in the 101-09 trial 'were asymptomatic and somewhat younger than patients in the typical clinical setting' and that the patient population studied in the trial might be 'more favourable than patients in the clinical setting'.[24] Therefore, they concluded that the evidence in the 101-09 trial 'was not sufficient to generalize the efficacy and safety outcomes to the symptomatic clinical population'.[24] This is also illustrated by the differences between the 101-09 trial population and the population in the Haematological Malignancy Research Network (HMRN) data set.[14] The HMRN report included all patients newly diagnosed with follicular lymphoma (ICD-O-3 9690/3, 9698/3) between 1 September 2004 to 31 August 2013 in the HMRN region. The HMRN region covers the former two adjacent UK Cancer Networks with a total population of 3.8 million (Yorkshire and the Humber and Yorkshire Coast Cancer Networks) and collects detailed information about all haematological malignancies diagnosed in the region. Outcomes in patients who had received ≥ 2 prior lines of chemotherapy /immuno-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent, or had a relapse within six months after receipt of those therapies and were subsequently treated were examined in order to perform Matching-adjusted indirect comparisons (MAICs). As such the HMRN data set could be considered a better reflection of double-refractory FL patients in the typical UK clinical setting. Differences between the trial population and the HMRN subgroup of double-refractory FL patients are: percentage of patients aged 62 years or older (50% in the 101-09 trial versus 65% in the HMRN data set), percentage of patients with bulky disease (22% versus 8%), median time since diagnosis in years (4.7 versus 1.8 years), median lines of prior therapy (4 versus 2), and percentage of patients with prior Autologous Stem Cell Transplant (ASCT) (17% versus 4%) (See Table 4.4 in section 4.2.2 of this report for an overview of all baseline characteristics in the two studies).

In addition, the Canadian Agency for Drugs and Technologies in Health (CADTH) noted that it would have been feasible to conduct a randomised controlled trial in this population in order to determine the comparative efficacy of idelalisib in relation to available treatment options or best supportive care (BSC).[24]

The company could have used the MAIC to make the trial population more reflective of UK clinical practice by matching the characteristics of the trial population to the characteristics of HMRN patients as reported in Table 17 (page 33) of the HMRN report. However, the company matched the individual patient data of the HMRN patients to the summary data of the trial population. Thus, making the results of the MAIC applicable to the trial population, but not to the population of patients described in the scope.

3.2 Intervention

The intervention (idelalisib) is in line with the scope. Regulatory approval by the EMA for the treatment of relapsed or refractory patients was granted in 2014. In July 2014 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product idelalisib, 100mg and 150mg, film-coated tablets. The marketing authorisation for the UK was issued on 18 September 2014.

Idelalisib is indicated as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment. The recommended dose of idelalisib is one 150mg tablet to be taken orally twice a day.

Additional tests or investigations include:

- Full blood counts should be monitored in all patients at least every two weeks for the first six months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm^3.
- ALT, AST, and total bilirubin must be monitored in all patients every two weeks for the first three months of treatment, then as clinically indicated.
- Patients with CMV viraemia, without associated clinical signs of CMV infection, should be carefully monitored.
- Regular clinical and laboratory monitoring for CMV infection is recommended in patients with positive CMV serology at the start of treatment with idelalisib or with other evidence of a history of CMV infection.

3.3 Comparators

The description of the comparators in the NICE scope is as follows: chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil); and best supportive care (in people for whom chemotherapy is unsuitable).

For the main comparator (chemotherapy regimens) the company provided data collected via the disease registry for the HMRN to provide real world evidence (RWE) for chemotherapy regimens currently used to treat double-refractory FL in UK practice. These data are subsequently used to perform a matching-adjusted indirect comparison (MAIC), providing an estimate of comparative effectiveness for chemotherapy regimens (HMRN data) versus idelalisib (Study 101-09 data).

No clinical effectiveness evidence was provided for best supportive care in people for whom chemotherapy is unsuitable. In the economic evaluation, Comparison D compares idelalisib with BSC. However, the OS and PFS evidence used in Comparison D is based on idelalisib/chemotherapy effectiveness from Study 101-09, and based on implausible assumptions, hence we do not consider this reliable.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- overall survival
- progression-free survival
- response rates
- duration of response/remission
- adverse effects of treatment
- health-related quality of life.

These were all assessed in Study 101-09 for idelalisib. However, for the comparator only overall survival and progression-free survival were reported. In addition, time to next treatment (TTNT) and relative survival (RS), defined as the interval from the data of the first dose of treatment to death from FL, were reported for patients in the HMRN data set.

3.5 Other relevant factors

The company argues that idelalisib is innovative, because it is 'the first agent to be specifically licensed for use in double-refractory FL and can provide a standard of care (SOC) treatment for these patients,

representing a paradigm change in the management of this difficult to treat disease as it offers a different mode of action for treatment of patients who have disease that has demonstrated a lack of good response to immune-chemotherapy.'[1]

There is an agreed commercial discount of [redacted] to the list price of idelalisib approved by the Department of Health and Social Care that is applicable to this appraisal.

According to the company, idelalisib meets the NICE end of life criteria for the treatment of double-refractory FL (see: CS, Table 22, page 78). The ERG is not sure this is the case (see chapter 7 in this report).

The company states that idelalisib 'is already available to double-refractory FL patients in NHS Wales and NHS Scotland, so availability in NHS England would remove any concerns of inequality across the devolved nations of the UK' (CS, section B1.4, page 22).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify studies reporting the efficacy and safety of idelalisib and potential comparator therapies in adult patients with relapsed and/or refractory indolent non-Hodgkin's lymphoma (iNHL) who had received at least one prior therapy. The patient population upon which systematic searches were based was intentionally broader than the license terms for idelalisib in follicular lymphoma (FL) in order to capture a wide range of evidence. At screening stage, the evidence base was focused to those studies enrolling a comparable patient population to the idelalisib trial, Study 101-09. This section of the ERG report critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis of idelalisib studies.

4.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[25] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[26] The ERG has presented only the major limitations of each search strategy in the report, further limitations are listed in Appendix 1.

The company submission stated that systematic literature review searches designed to identify studies reporting the efficacy and safety of idelalisib and potential comparators were undertaken in February 2014, with an update in February 2018. Search strategies were reported in Appendix D of the CS for the following databases: Embase, MEDLINE, MEDLINE In-Process, Cochrane's CENTRAL, CDSR and DARE databases. Searches contained terms for both RCTs and observational studies and were limited to English language publications and studies published after 1990.

The update also reported supplementary searches of the following conference proceedings for 2016-2017: American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Hematology Association (EHA), European Society for Medical Oncology (ESMO) and an additional search of the International Conference on Malignant Lymphoma (ICML) for 2017.

ERG comments:

- The database searches were clearly structured and documented.
- For all searches the ERG felt that the addition of a facet for disease stage may have been overly restrictive, unfortunately the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit. However, the broad range of searches and additional reference checking reported for the update searches would have mitigated against some loss of recall
- For the 2018 update searches (for all sections including cost effectiveness, HRQL and resource use), the company searched Embase and MEDLINE simultaneously using a single database provider (Embase.com) and search strategy. This approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase.com should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), it is not clear if this is the case for all potentially useful MeSH terms. Given the potential

limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy.

- The ERG was concerned that limiting the clinical effectiveness searches reported in Appendix D to English language only may have introduced potential language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication".[27]
- Best practice outlined in the Cochrane Handbook states that "Reference lists in other reviews, guidelines, included (and excluded) studies and other related articles should be searched for additional studies".[28] The ERG noticed that whilst results from a bibliographic search were recorded in the flow chart for the 2018 update, it was unclear whether reference checking had been undertaken for the 2014 searches. The company responded at clarification that "The clinical SLR report accompanying the 2014 searches does not explicitly state that reference checking took place and therefore we cannot confirm this took place".[29] However given that reference checking was undertaken for the update searches this is unlikely to have greatly affected the overall recall of results.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 4.1.

Table 4.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion criteria	Exclusion criteria
Inclusion criteria		
Population	Adult patients with FL refractory to rituximab and an alkylating agent	• Adolescent or paediatric patients • Non-human • Non-relapsed or refractory FL • Treatment naïve
Interventions	Idelalisib	Any other than those listed
Comparators	• Chemotherapy (single or combination therapy): o Rituximab monotherapy o Rituximab with bortezomib o Fludarabine +/- rituximab o Lenalidomide +/- rituximab o Bortezomib o Interferon or interferon alpha o CVP o CHOP o R-CVP o R-CHOP o R-FMD o R-B o R-FC o FCMR o Mitoxantrone and dexamethasone o R-IEV o R-DHAP o BVR • Radioimmunotherapy • Stem cell transplantation • Watch and wait (including standard of care, best supportive care, and clinical observation)	Any other than those listed
Outcomes	• Response rate • Overall survival • Progression-free survival • Safety	Any other than those listed
Study design	• RCT with active or placebo control using single or combination therapies • Non-RCTs (trials or observational studies where participants were assigned non-randomly to treatment)	• Editorials • Notes • Comments • Letters
Restrictions	• English language only • Publication date 1990-time of search	• Non-English language • Publication date pre-1990

Source: Table 4, Appendix D of the CS
CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone; BVR = bendamustine, bortezomib, and rituximab; FCMR = fludarabine, cyclophosphamide, mitoxantrone, and rituximab; FL = follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; R-B = bendamustine with rituximab; R-CHOP = rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; RCT = randomised controlled trial; R-CVP = rituximab with cyclophosphamide, vincristine, and prednisone; R-DHAP = rituximab with dexamethasone, cytarabine, and cisplatin; R-FC = rituximab with fludarabine and cyclophosphamide; R-FMD = rituximab with fludarabine, mitoxantrone, and dexamethasone; R-IEV = rituximab with ifosfamide, epirubicin, and etoposide.

ERG Comment: Two reviewers were involved in the selection of studies to include in the reviews, which helps to minimise bias. Only English language studies were included. Although this is widely accepted by NICE within STAs, it is not good practice for systematic reviews, since relevant studies may be missed. The exclusion of abstract-only records published prior to 2012 was questionable, particularly given that the four articles that were finally included in the original systematic review were all abstracts. This means that relevant studies may have been missed.

4.1.3 Critique of data extraction

A single reviewer performed the data extraction while a second reviewer checked the extracted data. This approach was adequately designed to minimise error and bias during data extraction.

4.1.4 Quality assessment

No formal, validated quality assessment or risk of bias tools were used to assess the quality of included studies. Instead, a custom tool was presented, which comprised nine questions that were informed by two documents: Drummond and Jefferson[30] and the NICE methodology checklist.[31] However, both of these documents are designed to assess studies that report economic data; therefore, this tool is not appropriate to assess the quality of studies reporting clinical effectiveness and the conclusions regarding study quality must therefore be interpreted with caution.

Out of the nine custom questions, the CUP cohort study scored poorly on selection bias particularly with respect to prior line of therapy analysis. Similarly, for the question, "does the setting reflect UK practice?", three out of four included studies were not conducted in the UK: Study 101-09 was conducted at 41 sites in the USA and Europe (no UK sites); Study 101-2/99 was conducted at eight sites in the USA; and the early access program was performed across Europe (no UK sites) and Australia. Only one study (the compassionate use program) was performed in the UK and Ireland. Thus, while these four studies were considered "generally aligned" with the NICE scope, they could not be considered as specifically aligned with the NICE scope.

Further, it is unclear what threshold is being used to inform the final grade (Yes, No, Not Clear, N/A) associated with each question. Some studies are designated to only partially address a particular question but are still awarded a 'yes' grade to denote high quality in the assessment domain. This appears profoundly inappropriate.

Finally, no information was provided on the number of reviewers involved in the quality assessment, meaning error and bias may be present.

4.1.5 Evidence synthesis

A meta-analysis of idelalisib studies was not performed. The ERG agrees that this was not feasible due to the differences between the idelalisib studies.

The company did attempt to make a comparison of idelalisib versus alternative chemotherapy using a matching-adjusted indirect comparison (MAIC). For idelalisib, data from the 101-09 study were used, while data from the Haematological Malignancy Research Network (HMRN) were used for the comparator. HMRN data are a population-based cohort comprising a total population of 3.8 million people covering the former adjacent UK Cancer Networks of Yorkshire and the Humber and Yorkshire Coast. The HMRN identified patients within their cohort who had received ≥2 prior lines of chemotherapy/immuno-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent; or had a relapse within six months after receipt of those therapies, and who were subsequently treated.

The MAIC is described in section B2.9 of the CS, and in Appendix D of the CS; Appendix D includes the full HMRN report including the MAIC. However, none of these texts provide any details of the methods for the MAIC. For instance, the type of statistical model, the rationale for variable selection, the weighting applied and the statistical software packages used are not described. Therefore, we asked the company to provide these in the clarification letter (See Clarification Letter, Question A20). In the response to the clarification letter, the company explained that the statistical methods were those reported by Signorovitch et al.[32] and analyses conducted using R:

> "Using the Signorovitch methodology, an effective sample size for the re-weighted sample was calculated to assess the impact of the re-weighting process. [redacted] The analysis code and a histogram of MAIC weights were provided in appendix A20 of the response to clarification letter but not the actual data so it was not possible for the ERG to check the analysis.

In addition, the company performed an efficacy comparison of idelalisib to previous line of therapy (CS, B2.6, page 46-47). However, again the CS did not include details of the methods used in the indirect comparison. We asked for these details in question A24 of the clarification letter. The company responded that:

> "details of the statistical analysis methods and how the data for the previous line of therapy were obtained are not reported in full in the published references, but in both studies they are thought to have been derived retrospectively (definitely in the case of the CUP where all data were collected retrospectively). In study 101-09, descriptive statistics were provided to the last regimen patients received prior to study entry. The best response to last therapy (n, %) and duration of response to the last therapy were summarised, primarily based on clinician recall (presumably supported with data collected in routine clinical practice). Duration of response was calculated as the date of response to previous treatment to date of progression; where progression dates were not recorded, the end date of previous treatment was used as the date of progression. Progression-free survival (PFS) to the last therapy were further explored post-hoc. While not reported, it is assumed that this was calculated as the date of initiation of previous treatment to date of progression. Missing data for previous treatment

to date of progression was avoided as it was the end date of previous treatment was taken conservatively as the date of progression. In general, within the study data quality assurance programmes (as per written standard operating procedures generated by INC Research) were used to identify missing data and request for data clarification were forwarded to investigator sites for resolution.

In the CUP, PFS of the prior treatment is reported, though as above this should be considered more reflective of TTP. While no details of the methods around these data were reported in the published reference, this was queried with the primary author who confirmed that this was calculated as the date of initiation of previous treatment to date of progression, and that these data were routinely recorded and well documented on the data collection proforma."

ERG comment: The analysis methods used in the MAIC and indirect comparison will be critiqued in section 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The CS includes four idelalisib studies (see Table 4.2). The main trial is Study 101-09; this is a multi-centre, single arm study investigating the efficacy and safety of idelalisib in patients with iNHL refractory to rituximab and an alkylating agent. Study 101-09 enrolled patients with different types of iNHL, but the FL population was the largest population (72 of 125).

Data collected via the disease registry for the HMRN was included to provide evidence for the comparator: chemotherapy regimens currently used to treat double-refractory FL in UK practice.

Table 4.2: Clinical effectiveness evidence for idelalisib in refractory or relapsed FL

Study	101-09[33]	101-02/99[34]	Compassionate use programme: UK[35]	Early access programme: Europe/Australia[36]
Study design	Phase II, open label, single arm study of idelalisib	Phase Ib dose escalation and extension study	Retrospective data collection from real world patients	Retrospective data collection from real world patients
Population	Patients with relapsed iNHL refractory to rituximab and chemotherapy containing an alkylating agent. Histological subtypes included FL.	Patients with relapsed iNHL, refractory to or relapsed after at least one prior chemotherapy regimen and rituximab. Histological subtypes included FL.	Patients with refractory or relapsed FL	Patients with refractory FL
Intervention(s)	Idelalisib 150mg (or reduced to 75/100mg) BID, taken orally	Idelalisib Doses: 50mg, 100mg, 200mg and 350mg BID. Regimens of idelalisib: 150mg BID, 150mg or 300mg QD, and 150mg BID taken 2 weeks on and 1 week off subsequently added. Dose escalation: 3+3 design in sequential cohorts.	Idelalisib 150mg BID	Idelalisib Presume 150mg BID
Comparator(s)	None	None	None	None
Trial used in the economic model	Yes, pivotal trial	No, small scale, dose escalation study	Yes, provides additional data from real world evidence with relevant endpoints	No, safety data limited, no efficacy data
Reported outcomes specified in the decision problem: those marked in bold are incorporated in the economic model	• Overall survival • Progression-free survival • Response rates • Duration of response/ remission • Adverse effects of treatment • Health-related quality of life	• Adverse effects of treatment • Response rate • Progression-free survival	• Overall response rate • Progression-free survival • Overall survival • Adverse effects of treatment	• Adverse effects of treatment

Study	101-09[33]	101-02/99[34]	Compassionate use programme: UK[35]	Early access programme: Europe/Australia[36]
All other reported outcomes	• Time to progression • Post-progression survival • Time on treatment • Laboratory abnormalities	• Pharmacokinetics		• Patient characteristics
Source: CS, Table 6, pages 25-26 BID = twice a day; CR = complete response; iNHL = indolent non-Hodgkin lymphoma; PD = progressive disease; PR = partial response.				

Study 101-09

Study 101-09 is a multi-centre, single arm, open label, Phase II study that enrolled iNHL patients to receive 150mg idelalisib twice daily. Patients had received at least two prior treatments for iNHL and were refractory to both rituximab and an alkylating agent; all patients with FL had double-refractory disease. The primary outcome of study 101-09 was overall response rate (ORR), assessed by an independent review committee (IRC).

Study 101-02/99

Study 101-02/99 is a Phase Ib dose escalation study and its extension that enrolled iNHL patients to receive various doses of idelalisib. Patients had received at least one prior chemotherapy and prior rituximab, to which they were refractory to or had relapsed after. The primary outcome of Study 101-02 was to determine dose-limiting toxicity (DLT) for patients with haematological malignancies. Patients permitted to enter the extension study were identified as benefiting from continued idelalisib treatment. The primary outcome of Study 101-99 was ORR. Only 10 of the 64 patients included were treated with idelalisib at the recommended 150mg twice daily dose level, and 38 out of 64 patients had FL. It is unclear how many patients had FL and were treated at the recommended dose. The company could not provide subject disposition data for the 10 patients treated with idelalisib at the recommended 150mg twice daily dose level when requested to do so at the clarification letter stage (see clarification letter question, A12). Consequently, the applicability of this study to the decision problem is unclear.

UK and Ireland CUP

In the UK and Ireland Compassionate Use Programme (CUP) patients with refractory or relapsed FL were treated with 150mg idelalisib twice daily until progressive disease, toxicity or death as per license terms. Data were retrospectively collected and analysed to determine ORR, PFS and OS. Information on adverse events (AEs) was also collected but grading of AEs was not routine.

Early Access Programme

The Europe and Australia Early Access Programme (EAP) is a retrospective data collection from real world patients, included to provide further safety data for idelalisib monotherapy. Efficacy data are not available from this non-UK programme, and data have only been presented at conferences to date.

Comparator study: HMRN data

The Haematological Malignancy Research Network (HMRN) data set is a population-based cohort comprising a total population of 3.8 million people covering the former adjacent UK Cancer Networks of Yorkshire and the Humber and Yorkshire Coast. The HMRN was set up in 2004 to provide robust, generalisable data to inform clinical practice and research and collects detailed information about all haematological malignancies in the region. The HMRN identified patients within their cohort who had received ≥2 prior lines of chemotherapy/immuno-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent; or had a relapse within six months after receipt of those therapies, and who were subsequently treated.

4.2.2 Methodology of included studies

The methodology of the three idelalisib studies that provided effectiveness data is described in Table 4.3.

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

Study	101-09[33]	101-02/99[34]	Compassionate use programme[35]
	squamous cell carcinoma of the skin, cervical carcinoma *in situ*, superficial bladder cancer, localised prostate cancer, other adequately treated Stage I or II cancer currently in complete remission, or any other cancer that had been in complete remission for ≥5 years • Evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment		
Trial drugs	Idelalisib 150mg BID	Dose escalation trial Idelalisib x 28 days: 50, 75, 100, 150, 200, 350mg BID; 150, 300mg daily Idelalisib x 21 days, 7 days off: 150mg BID	Idelalisib 150mg BID
Concomitant medication	No restriction on concomitant medication		
Primary outcomes (including scoring methods and timings of assessments)	ORR, defined as the proportion of patients who achieved CR or PR during treatment with idelalisib Response rates were assessed by an independent review committee (IRC) Patients were evaluated at 2 week intervals during the first 12 weeks of treatment, at 4 week intervals from Week 12 to Week 24 of treatment, at 6 week intervals from Week 24 to Week 48 of treatment, and at 12 week intervals thereafter	Study 101-02: Safety and dose-limiting toxicity Study 101-99: ORR (defined as proportion of patients who achieve CR, PR or minor response (for WM only) Safety, as assessed by incidence of Grade ≥3 AEs	ORR, including CR/unconfirmed CR and PR
Other outcomes used in the economic	• ORR assessed by an investigator • PFS, defined as the interval from the start of treatment to the earlier of the first documentation of PD or death from any cause	Study 101-02: • Clinical response rate Study 101-99:	• PFS • OS • AE

Study	101-09[33]	101-02/99[34]	Compassionate use programme[35]
model/specified in the scope	• OS, defined as the interval from the date of first treatment to death from any cause • TTP, defined as the interval from the start of treatment until objective tumour progression, but does not include deaths • ToT, time on treatment • Change in HRQL as assessed through the FACT-Lym questionnaire • AEs, defined as any untoward medical occurrence in a patient who began or worsened in the period from administration of the first dose of the study drug to 30 days after administration of the last dose	• DOR (from onset of response to disease progression) • PFS (from enrolment to disease progression or death) • OS (from start of treatment to death) • TTR (from first dose to first documentation of CR or PR)	
Pre-planned subgroups	• Age (<65 or 65+ years) • Sex • Lymphoma subtype • Presence/absence of bulky disease • Number of previous therapies (<4 or 4+) • Previous bendamustine use (yes/no) • Refractoriness to bendamustine (yes/no) • Refractoriness to last therapy (yes/no)		

Source: CS, Table 7, pages 29-32

AE = adverse event; BID = twice daily; CR = complete response; DOR = duration of response; FL = follicular lymphoma; HRQL = health-related quality of life; iNHL = indolent non-Hodgkin's lymphoma; LPL = lymphoplasmacytic lymphoma; N/A = not applicable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; TTP = time to progression; TTR = time to response; WM = Waldenström's macroglobulinaemia.

4.2.3 Baseline characteristics

The baseline characteristics of patients included in the three idelalisib studies that provided effectiveness data and in the comparator study (HMRN patients) are described in Table 4.4.

As can be seen from Table 4.4, when compared to Study 101-09, patients in the comparator study (HMRN patients) had a shorter median time since diagnosis ([redacted] years for HMRN vs 4.7 years for 101-09), less often bulky disease ([redacted] vs 22.2%), less often prior SCT ([redacted] vs 16.7%) and fewer prior regimens (median: [redacted] (range: [redacted]) vs 4 (2-12).

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, 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%)	NR	NR
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%)	NR
Alkylating agent	125 (100)	72 (100)	58 (91%)	78 (99%)	NR
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	NR
Alkylating agent	124/125 (99)[a]	72/72 (100)	NR	NR	NR
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

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)			
Source: CS, Table 8, pages 34-35; Table 40, Appendix M of the CS; and CS, Table 9, pages 36-37. ANC = absolute neutrophil count; ECOG = European Cooperative Oncology Group; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; NR = not reported; R-bendamustine = rituximab with bendamustine; R-CHOP = rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP = rituximab with cyclophosphamide, vincristine and prednisone. **Notes:** [a], Refractoriness to two cycles was required to meet the criteria for alkylator-refractory disease. One patient received only one cycle, with no response after this cycle. Refractory defined as lack of response or progression within 6 months from completion of prior therapy; [b], All patients refractory to rituximab and 99% refractory to an alkylating agent; [c], Missing data for four patients.					

4.2.4 Statistical analyses

Study 101-09

The objective of Study 101-09 was to characterise the clinical activity and safety of idelalisib. The data presented in the CS were taken from the latest database lock (DBL), of 30 June 2015, which provide a minimum of 31.5 months follow-up in the majority. Data for the FL population from the published DBL of 11 June 2014 (20 months minimum follow-up), were used in the MAIC. Health-related quality of life (HRQL) data were not updated in the latest DBL and therefore were presented from June 2014 analyses. At the latest DBL (30 June 2015), four FL patients (5.6%) were continuing to receive idelalisib. Of those no longer on treatment, the most common reason for discontinuation was progressive disease (55.6%). Of note, three patients discontinued at the request of the investigator as they were referred to undergo SCT.

Study 101-02/99

The primary analysis in Study 101-02/99 was conducted on the ITT population. Response rates, exact binomial 95% confidence intervals, and p-values were calculated for the primary efficacy outcome of ORR. Time to response (TTR) and DOR were summarised using the Kaplan–Meier (KM) method.

Participant flow data show that 19 patients completed the planned 48-week duration of Study 101-02 and were enrolled in Study 101-99. Of the 45 patients who discontinued before 48 weeks, the majority was due to progressive disease (51.1%), and half of all patients enrolled in Study 101-99 (n=19) also discontinued treatment for this reason.

UK and Ireland CUP

Data were collected between January 2015 and August 2016 from 46 of 51 approached centres in the UK and Ireland. The median follow-up at the time of analysis was 6.1 months (0.1–18.8 months).

PFS and OS were calculated in standard fashion with follow-up censored at most recent visit or death. Cox regression determined univariate predictors of PFS.

Participant flow data are not fully reported but 24 patients received treatment post-idelalisib. Of the remaining 55 patients, 18 died without further therapy because of progressive disease (n=17) or toxicity (n=1), 35 remained on idelalisib without progression, and two stopped treatment due to toxicity without progression.

4.2.5 Results

4.2.5.1 Study 101-09

Results from Study 101-09 based on the June 2014 database lock were used in the HMRN matching-adjusted indirect comparison and in the economic analyses. Results based on the June 2015 database lock were presented in the main submission. Where possible we have presented both data sets.

A summary of OS and PFS for the FL population is presented in Table 4.5. Median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks.

Median PFS was 11.0 months in the FL population for both data-sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 data-set, this was not reported for the June 2014 data-set.

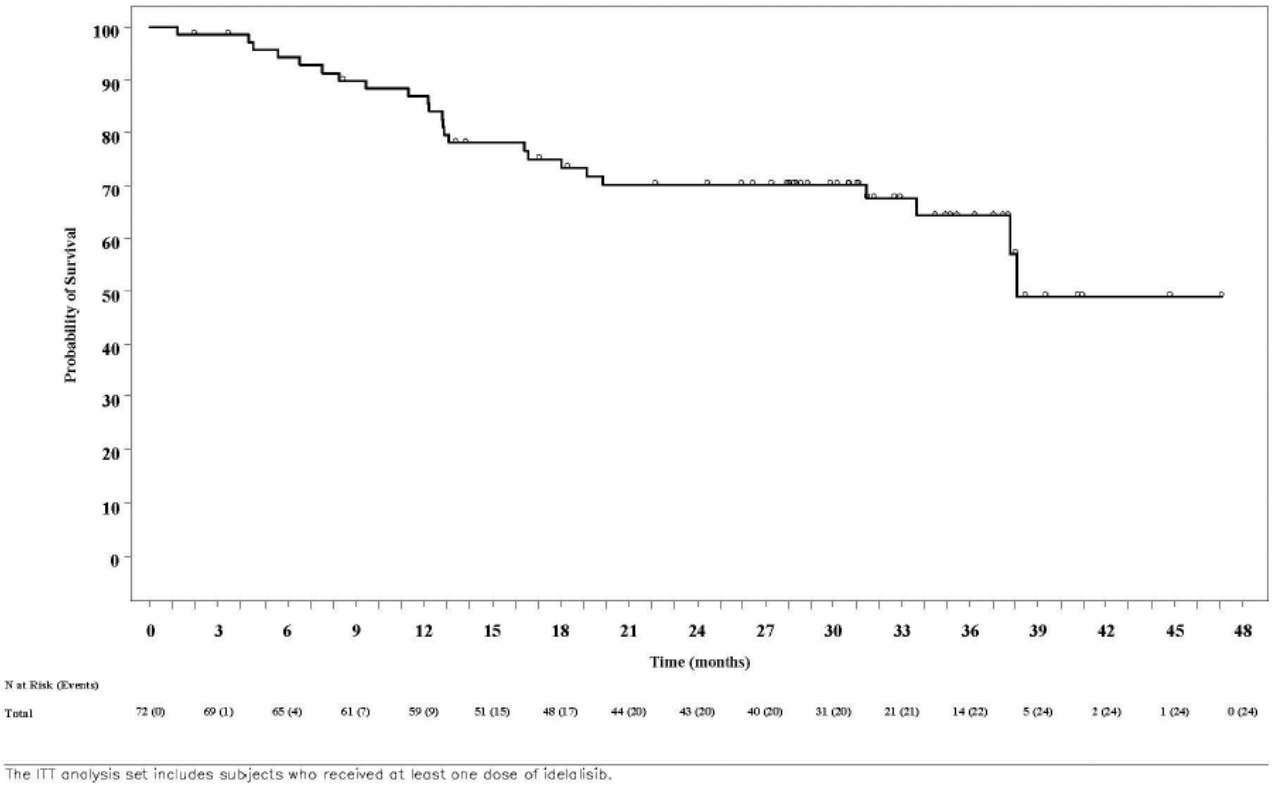
Table 4.5: Summary of OS and PFS, Study 101-09

	FL population (N=72) June 2014		FL population (N=72) June 2015	
	IRC assessment	**Investigator assessment**	**IRC assessment**	**Investigator assessment**
Overall survival				
Died, n (%)	NR		24 (33.3)	
Median OS (95% CI)	Not reached		38.1 (37.8, not reached)	
KM estimate of proportion of survival, % (95% CI)				
24 weeks	NR		95.7 (91.0, 100.5)	
36 weeks	NR		89.9 (82.8, 97.0)	
48 weeks	NR		88.4 (80.9, 96.0)	
2 years	69.8% (NR, NR)		NR	
Progression-free survival				
Patients with event, n (%)	NR	NR	40 (55.6)	47 (65.3)
PD	NR	NR	36 (50.0)	43 (59.7)
Death	NR	NR	4 (5.6)	4 (5.6)
Median PFS (95% CI)	11.0 (8.0, 14.0)	NR	11.0 (8.0, 14.2)	10.8 (5.7, 14.2)
KM estimate of proportion progression-free, % (95% CI)				
24 weeks	NR	NR	66.8 (55.1, 78.5)	68.5 (57.0, 80.0)
36 weeks	NR	NR	57.5 (44.9, 70.1)	56.1 (43.6, 68.7)
48 weeks	NR	NR	47.2 (34.1, 60.4)	44.7 (31.8, 57.6)

Source: CS, Table 12, page 44-45 and Appendix N, Table 42.
CI = confidence interval; FL = follicular lymphoma; IRC = independent review committee; KM = Kaplan–Meier; OS = overall survival; PD = progressive disease; PFS = progression-free survival.

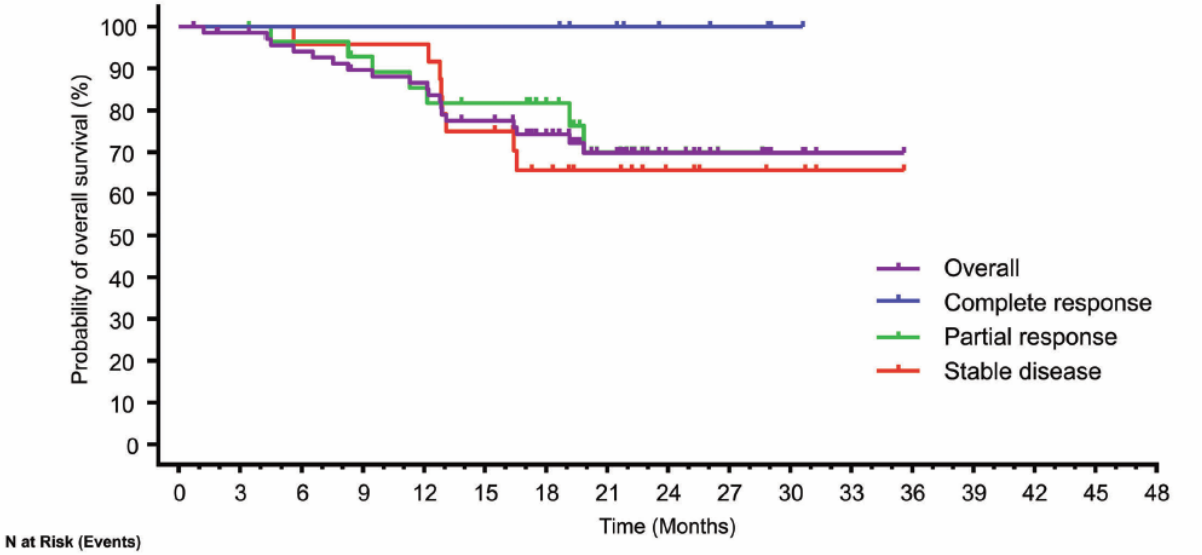
The KM plot for OS in the FL population based on June 2015 data is provided in Figure 4.1 and the same KM plot based on June 2014 data is provided in Figure 4.2. In Figure 4.2, the purple line represents the KM -plot for OS in the total FL population.

Figure 4.1: KM plot of OS, Study 101-09, FL population, June 2015 data-cut



Source: CS, Figure 3, page 45.
FL = follicular lymphoma; KM = Kaplan–Meier; OS = overall survival.

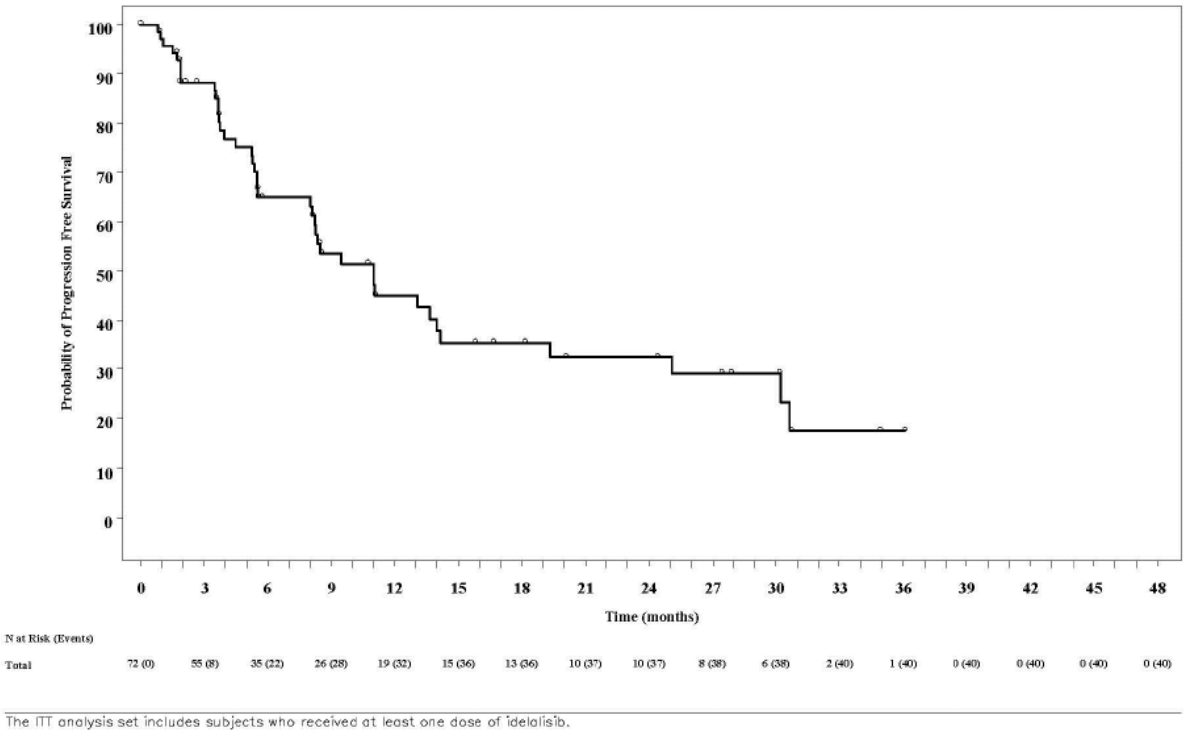
Figure 4.2: Kaplan–Meier plot of OS, Study 101-09, FL population, June 2014 data-cut



Source: CS, Figure 13, Appendix N.
FL = follicular lymphoma; OS = overall survival.

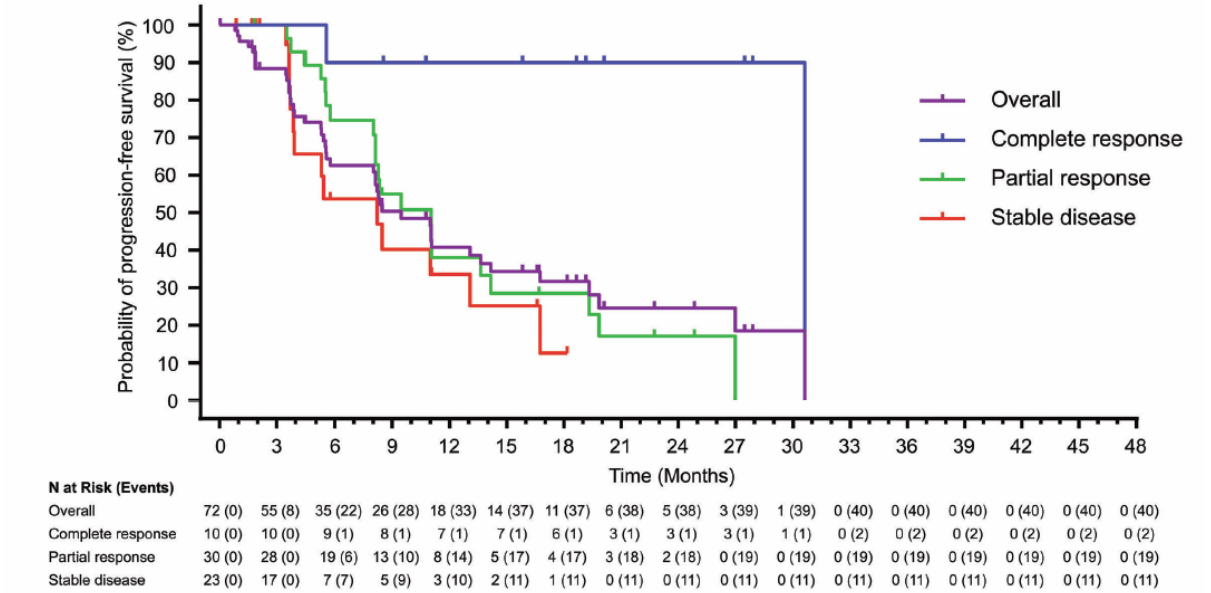
The KM plot for PFS in the FL population based on June 2015 data is provided in Figure 4.3 and the same KM plot based on June 2014 data is provided in Figure 4.4. In Figure 4.4, the purple line represents the KM -plot for PFS in the total FL population.

Figure 4.3: KM plot of PFS by IRC assessment, Study 101-09, FL population, June 2015 data-cut



Source: CS, Figure 3, page 45.
FL = follicular lymphoma; IRC = independent review committee; KM = Kaplan–Meier; PFS = progression-free survival.

Figure 4.4: KM plot of PFS by IRC assessment, Study 101-09, FL population, June 2014 data-cut



Source: CS, Figure 13, Appendix N.
FL = follicular lymphoma; IRC = independent review committee; KM = Kaplan–Meier; PFS = progression-free survival.

Clinical response outcomes are summarised in Table 4.6. In the FL population, the overall response rate (ORR, 95% CI) was 55.6% (43.4, 67.3) as assessed by the independent review committee (IRC), comprising 10 complete responses (CRs, 13.9%) and 30 partial responses (PRs, 41.7%) in the June 2015 data-cut. Response data from June 2014 are similar using IRC assessment, but were not reported for investigator assessment.

Table 4.6: Summary of clinical response outcomes, Study 101-09

	FL population (N=72) June 2014		FL population (N=72) June 2015	
	IRC assessment	**Investigator assessment**	**IRC assessment**	**Investigator assessment**
Overall response rate				
n (%)	40 (55.6)	NR	40 (55.6)	44 (61.1)
95% CI	43.4, 67.3	NR	43.4, 67.3	48.9, 72.4
Best overall response, rate (%)				
CR	10 (13.9)	NR	10 (13.9)	6 (8.3)
PR	30 (41.7)	NR	30 (41.7)	38 (52.8)
MR	0	NR	0	0
SD	23 (31.9)	NR	23 (31.9)	19 (26.4)
PD	8 (11.1)	NR	8 (11.1)	8 (11.1)
Not evaluable	1 (1.4)	NR		
Duration of response				
Events, n (%)	NR	NR	20 (50.0)	29 (65.9)
PD	NR	NR	17 (42.5)	27 (61.4)
Death	NR	NR	3 (7.5)	2 (4.5)
Median DOR, months (95% CI)	10.8 (0, 26.9)	NR	11.8 (6.4, 26.9)	9.2 (5.9, 14.9)
Median TTR, months (range)	2.6 (1.6, 11.0)	NR	NR	NR

Source: CS, Table 11, page 42 and Appendix N, Table 41.
Notes: [a], Patient with Waldenström's macroglobulinemia
CI = confidence interval; CR = complete response; DOR = duration of response; FL = follicular lymphoma; IRC = independent review committee; MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease; TTR = time to response.

Overall health related quality of life (HRQL) was reported to be stable or improved for patients treated with idelalisib in Study 101-09 (up to 20 months minimum follow-up).

Among the FL population, the median Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) Total score was 126.8 at baseline and 126.0 at Week 72. Median best change from baseline in FACT-Lym total score was 7.5 (95% CI: -39.0 to 47.0). The confidence interval was quite wide and the median did not exceed the minimally important difference threshold of 10-11, as shown in Table 4.7.

In the CS, the company only presented 'best change from baseline' (defined as the highest change score at post-baseline) for FACT-Lym scores, rather than actual mean change scores. Therefore, we asked the company in the clarification letter to provide mean or median changes for HRQL (FACT-Lym) over the whole follow-up period or the area-under-the curve values for FL patients in this study. However,

the company declined to provide these, without giving a reason (see Response to Clarification Letter, question A10b). Therefore, there is currently insufficient data provided to understand the impact of idelalisib on HRQL in the double-refractory FL patient population.

Table 4.7: FACT-Lym scores, Study 101-09, FL population, June 2014 data-cut

Median FACT-Lym score	Patients with FL treated with idelalisib 150mg BID, orally (N=72)		
	Best change from baseline	Median time to improvement, months	Minimally important difference
Physical well-being	1.0 (-12.0 to 11.0)	NR (0.0 to 30.6)	2–3
Social/family wellbeing	1.0 (-4.7 to 11.0)	NR (0.0 to 30.6)	2–3
Emotional wellbeing	3.0 (-9.0 to 12.0)	NR (0.0 to 30.6)	2–3
Functional wellbeing	2.0 (-10.0 to 14.0)	NR (0.0 to 30.6)	2–3
Additional concerns	5.0 (-17.0 to 19.0)	4.2 (0.0 to 27.9)	3–5
Total Outcome Index	6.0 (-34.0 to 35.0)	2.8 (0.0 to 30.6)	7–8
FACT-G total score	4.0 (-29.7 to 31.0)	6.9 (0.0 to 30.6)	3–7
FACT-Lym total score	7.5 (-39.0 to 47.0)	1.9 (0.0 to 30.6)	10–11

Source: CS, Table 13, page 48.
BID = twice daily; FACT-G = Functional Assessment of Cancer Therapy-General; FACT-Lym = Functional Assessment of Cancer Therapy-Lymphoma; FL = follicular lymphoma; NR = not reported.

4.2.5.2 Study 101-02/99

Most results for Study 101-02/99 are presented for the total population (N=64) rather than the FL population (N=38). The only result specifically for the FL population was ORR, which was 45%.

In addition, patients in this study received different doses. According to the response to the clarification letter (Question A12), only 10 of the 64 patients included were treated with idelalisib at the recommended 150mg twice daily dose level. It is unclear how many patients had both FL and were treated at the recommended dose. Therefore, results from this study are both less important and less appropriate for the decision problem.

4.2.5.3 UK and Ireland CUP

Median OS was not reached, but median follow-up for the CUP was only 6.1 months (range 0.1–18.8 months). Median PFS was 7.1 months (95% CI 5.0, 9.1 months) in the total population.

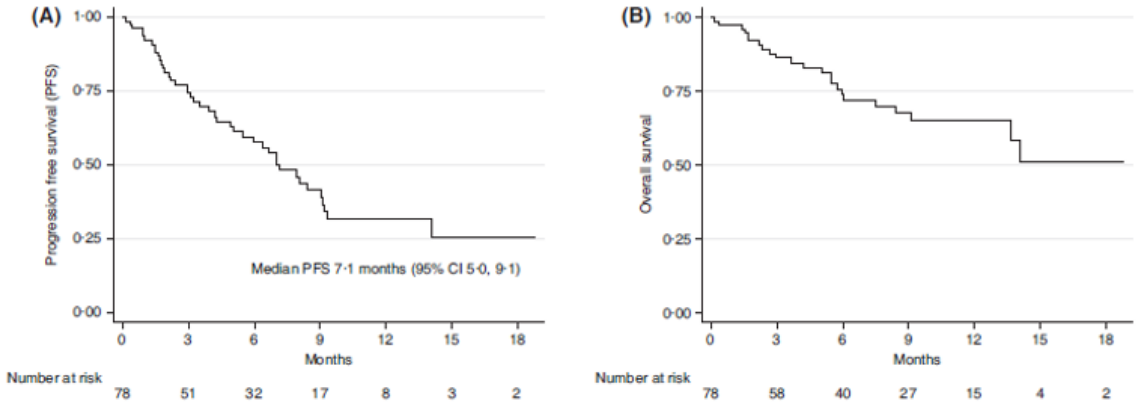
The median PFS for the total population was lower than that observed in Study 101-09 (see Table 4.8). The company suggests that this "may reflect the differences in the quality of study designs and rigour of progression assessment methods across trials. In standard clinical practice there is no objective, uniform approach to disease progression assessment, and thus, there are inherent errors when assessing PFS in a real-world, retrospective setting. More definitive endpoints such as OS and ORR are more reliable but due to an immaturity of follow-up in the CUP and a relatively short average duration of treatment, OS data also have to be interpreted with caution. The higher proportion of patients who had high-risk FLIPI score, and an ECOG performance status score of two or more is also a factor, suggesting some patients may have been treated through the CUP as a 'last resort' but with little expectation of long-term benefit. If routinely available, it is expected that patients with double-refractory FL would be immediately treated and therefore would have a better chance of longer-term benefit on receipt of idelalisib in clinical practice." (CS, section B.2.6.3, page 52).

Of note, only unconfirmed complete responses were provided for the CUP study, but these could not be further confirmed by the company when requested (see clarification letter, question A14). Therefore, there is some uncertainty around the reliability of the comparison between complete responses for Study 101-09 vs. CUP.

Table 4.8: Summary of results, CUP compared to Study 101-09

	Study 101-09 FL population (N=72)	CUP retrospective cohort (N=65)
Overall response rate, n (%)	40 (55.6)	37 (57)
CR/CRu, n (%)	10 (13.9)	10 (15)
PR	30 (41.7)	27 (42)
Median PFS, months (95% CI)	11.0 (8.0, 14.2)	7.1 (5.0, 9.1)
Median OS, months (95% CI)	38.1 (37.8, not reached)	Not reached (13.7, not reached)
Source: CS, Table 15, page 52. CR = complete response; Cru = unconfirmed complete response; CUP = compassionate use programme; PR = partial response.		

Figure 4.5: KM plots for (A) PFS and (B) OS, CUP cohort



Source: CS, Figure 9, page 53.
CI = confidence interval; CUP = compassionate use programme; KM = Kaplan–Meier; OS = overall survival; PFS = progression-free survival.

4.2.6 Adverse events

The majority of patients enrolled in study 101-09 experienced at least one AE, many of which were deemed to be treatment-related, as summarised in Table 4.9; 25% of FL patients discontinued treatment due to an AE.

Table 4.9: Overall summary of safety, Study 101-09, June 2015 data-cut

Adverse event	Total population (N=125)	FL population (N=72)
Any AE, n (%)	123 (98.4)	71 (98.6)
Grade ≥3 AE, n (%)	94 (75.2)	48 (66.7)
Treatment-related AE	107 (85.6)	61 (84.7)
Treatment-related Grade ≥3 AE, n (%)	74 (59.2)	41 (56.9)
Any SAE, n (%)	72 (57.6)	36 (50.0)

Adverse event	Total population (N=125)	FL population (N=72)
Treatment-related SAE, n (%)	45 (36.0)	24 (33.3)
AE leading to dose reduction, n (%)	40 (32.0)	22 (30.6)
AE leading to study drug discontinuation, n (%)	36 (28.8)	18 (25.0)
AE leading to death, n (%)	13 (10.4)	6 (8.3)
Death on study drug or within 30 days of last study drug dose, n (%)	13 (10.4)	7 (9.7)
All deaths, n (%)	49 (39.2)	24 (33.3)
Source: CS, Table 19, page 65. AE = adverse events; ITT = intent-to-treat; SAE = serious adverse event.		

AEs were manageable and reversible in the majority of cases. The most frequently reported Grade ≥3 AEs such as neutropenia, diarrhoea, pneumonia and elevated aminotransferase were anticipated *a priori* in light of common risks associated with idelalisib and in the context of an extensively pre-treated population.

The most frequently reported AEs of Grade ≥3 are reported in Table 4.10. In both the total population and the FL population, the most common Grade ≥3 AE was neutropenia, occurring in 27 (21.6%) and 16 (22.2%) patients, respectively. Other common Grade ≥3 AEs included diarrhoea and pneumonia, both reported by more than 10% of patients.

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).

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

Table 4.10: Grade ≥3 AEs reported for ≥2% of patients, Study 101-09, June 2015 data-cut

Adverse event	Total population (N=125)	FL population (N=72)
Patients with any Grade ≥3 AE	94 (75.2)	60 (83.3)
Neutropenia	27 (21.6)	16 (22.2)
Diarrhoea	21 (16.8)	14 (19.4)
Pneumonia	15 (12.0)	8 (11.1)
Alanine aminotransferase increase	11 (8.8)	9 (12.5)
Aspartate aminotransferase increased	8 (6.4)	7(9.7)
Hypokalaemia	9 (7.2)	5 (6.9)
Thrombocytopenia	8 (6.4)	7 (9.7)
Anaemia	7 (5.6)	5 (6.9)
Dehydration	6 (4.8)	6 (8.3)
Dyspnoea	6 (4.8)	3 (4.2)
Colitis	4 (3.2)	1 (1.4)

Adverse event	Total population (N=125)	FL population (N=72)
Febrile neutropenia	5 (4.0)	2 (2.8)
Asthenia	4 (3.2)	4 (5.6)
Hypotension	4 (3.2)	3 (4.2)
Pyrexia	4 (3.2)	1 (1.4)
Renal failure acute	4 (3.2)	2 (2.8)
Abdominal pain	3 (2.4)	1 (1.4)
Confusional state	3 (2.4)	2 (2.8)
Deep vein thrombosis	3 (2.4)	1 (1.4)
Hepatic enzyme increased	3 (2.4)	2 (2.8)
Hypercalcaemia	3 (2.4)	2 (2.8)
Hyponatraemia	3 (2.4)	2 (2.8)
Pleural effusion	3 (2.4)	3(4.2)
Pneumonitis	3 (2.4)	2 (2.8)
Sepsis	3 (2.4)	2 (2.8)
Vomiting	3 (2.4)	3 (4.2)

Source: CS, Table 20, page 66.
AE = adverse event; FL = follicular lymphoma.

In total, 13 (10.4%) patients had an AE that resulted in death. The most common of these was pneumonia in three patients (2.4%) and multi-organ failure in two patients (1.6%). In the FL population, six (8.3%) patients had an AE that resulted in death; fatal AEs were multi-organ failure, acute abdomen, cardiac arrest, cardiac failure, pneumonitis and splenic infarction.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Two types of indirect comparisons were performed:

1) a matching-adjusted indirect comparison (MAIC), comparing idelalisib with alternative chemotherapy, using data from the 101-09 study for idelalisib and HMRN data for the comparator.
2) an indirect comparison, comparing idelalisib with previous line of therapy, using data from Study 101-09 and the compassionate use programme in the UK and Ireland (CUP-cohort).

The methods for both types of indirect comparison are described in Section 4.1.5 of this report. The results and the critique will be described below.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 MAIC – idelalisib vs alternative chemotherapy

The MAIC included 72 patients with FL from study 101-09 and [redacted]

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].

[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 (n=[redacted])
Male, n (%)	39 (54.2)	[redacted]	[redacted]
Median age, years (range)	62 (33–84)	[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)	4.7 (0.8–18.4)	[redacted]	[redacted]
Median lines of prior therapy (range)	4 (2–12)	[redacted]	[redacted]
Prior ASCT, n (%)	12 (16.7)	[redacted]	[redacted]

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 (n=[redacted])*	Adjusted HMRN excluding time to diagnosis (n=[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.

ERG comment: The ERG had several problems with the way the company performed the MAIC. First of all, it seems counter-intuitive to try to match the HMRN data to the baseline characteristics of Study 101-09 patients. The HMRN population includes all relevant patients who have been prescribed idelalisib in a real-world UK setting; as such the HMRN population seems more representative of the population defined in the NICE scope than the 101-09 study population. Study 101-09 had specific inclusion criteria, such as, 'Karnofsky performance score of 60 or higher (on a scale of 0=death and 100=complete absence of symptoms)' and 'radiographically measurable disease (defined as ≥1 lymph node with perpendicular dimensions measuring ≥2.0 x ≥1.0cm)', which were not present in the HMRN data and makes Study 101-09 a more selected population. When performing a MAIC it is beneficial to have similar patient inclusion/exclusion criteria in those studies with and without IPD, or to be able to adjust the IPD to match the included study population without IPD. Therefore, the ERG considers that it would have been preferable to match IPD from Study101-09 to the HMRN population. Particularly as the effective sample size from the adjusted HMRN population was only seven and that " the occurrence of a small effective sample size can indicate that some patients are receiving extreme weights, and there may be little statistical power to detect differences between treatments" Signorovitch et al.[32]

Secondly, the ERG did not agree with the exclusion of variables from the MAIC. [redacted] However, given the small sample sizes, excluding a few patients may similarly give too much weight to the characteristics of the remaining patients. [redacted] However, even though variables may be correlated, these variables might still be important in the MAIC to produce two datasets which are balanced for all important prognostic variables. As this analysis is an unanchored MAIC (there is no common comparator arm in each study) it assumes that outcomes can be predicted from the included variables and "all effect modifiers and prognostic factors are accounted for".[38] As only those variables included in both studies can be included in the MAIC this is a strong assumption which cannot be verified. Therefore, excluding additional variables from the model when there are only a limited number to start with is a further source of bias. NICE TSD18 also recommends that "submissions using unanchored forms of population adjustment must provide evidence on the likely extent of error due to unaccounted for covariates, in relation to the observed relative treatment effect".

A further issue relating to the choice of variables is that in their response to the clarification letter the company provided an updated version of the HMRN analysis (Version 2.1 dated 21 March 2018) which contained an additional MAIC analysis which excluded time from diagnosis. This was because the two study populations were considered to differ in this variable with the HMRN patients having a poorer prognosis. When time from diagnosis was excluded from the MAIC the effective sample size for the adjusted HMRN dataset increased from seven to 19 patients, estimated two-year OS from 19.8 to 39.9% and estimated one-year PFS from 24.7 to 49.9%. Both survival estimates increased by approximately 20% indicating improved survival with chemotherapy which indicates that the MAIC results are very sensitive to the choice of variables in the model.

The ERG asked the company to repeat the MAIC by using Study 101-09 data as the source of IPD and matching it to summary HMRN data, using the most recent data for Study 101-09; and to provide also MAIC results including all possible variables (see Clarification letter questions A19b and A23). However, they declined to repeat the MAIC using Study 101-09 as the source of IPD. When the MAIC

included all possible variables the effective sample size was very small at 3.8 patients and the OS and PFS estimates were less than 1% and considered to lack face validity.

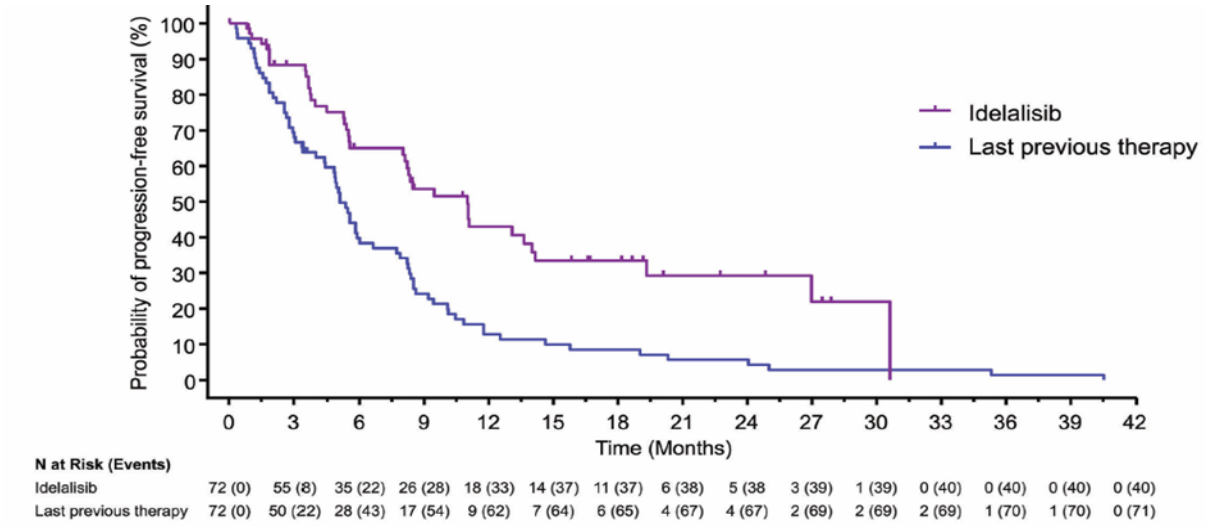
As acknowledged by the company, there is uncertainty associated with these analyses, primarily stemming from the small sample of FL patients with disease refractory to rituximab and an alkylating agent identified in the HMRN cohort and because some variables were excluded from the MAIC, such that potentially meaningful differences in treatment history could not be adjusted for (CS, B2.9.5, page 63). The use of MAIC analysis is in itself a major limitation as it was an unanchored comparison and used single arm data only. There was no comparative RCT data available for idelalisib or alternative chemotherapy. The sample size of the HMRN IPD data was small and the MAIC results appeared to be sensitive to the choice of variables in the model. The company provided survival estimates for each treatment but not any effect sizes for comparisons between the treatments. The MAIC results are potentially biased and should be treated with caution.

4.4.2 IC – idelalisib vs previous line of therapy

The company states that: "While direct comparative efficacy data are not available from the relevant clinical effectiveness evidence, assessment of clinical efficacy associated with previous lines of treatment are available from study 101-09 and the CUP. These data allow a crude estimate of indirect comparative efficacy (in the absence of trial data for comparator treatments), but do not reflect true PFS (as patients could not have died prior to study enrolment) and are at high risk of selection bias; in the case of study 101-09, these data are also primarily based on clinician recall. In the case of the CUP, analyses are based on subjective, non-uniform assessment of disease progression. Both analyses should therefore be treated with the necessary caution." (CS, B2.5, page 41)

The results of this indirect comparison show a benefit for idelalisib in terms of overall response rate (ORR), duration of response (DOR) and progression-free survival (PFS, see Figure 4.1) based on June 2014 data from study 101-09 (CS, B2.6, pages 46-47). The company points out "that these data are a conservative estimate of the treatment effect that may be expected with chemotherapy regimens at the next line of therapy (where the idelalisib arm is being assessed), given that with each relapse in FL, the disease becomes more resistant and/or refractory to treatment" (CS, page 47).

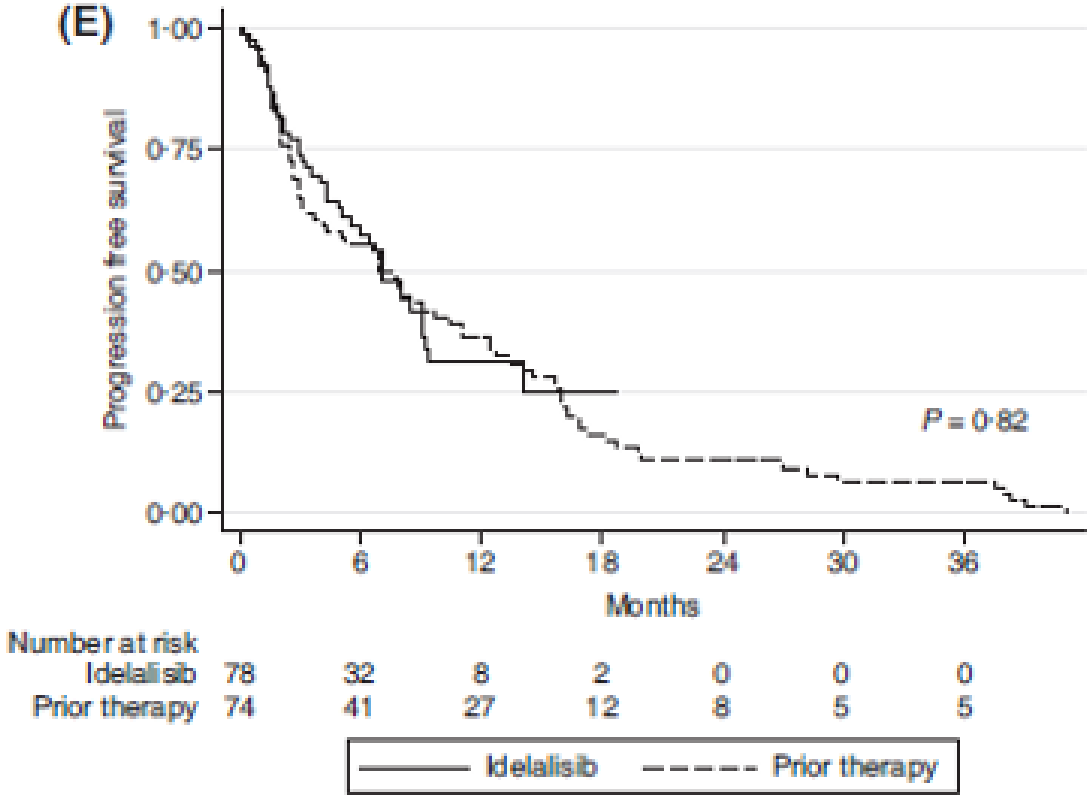
Figure 4.6: PFS for on study idelalisib versus last prior therapy, FL population, June 2014 data-cut Study 101-09



Source: Cs, Figure 9E, page 53. FL = follicular lymphoma; PFS = progression-free survival.

Using data from the CUP cohort, the comparison of PFS for idelalisib versus prior treatment showed no difference (See Figure 4.2, p=0.82).

Figure 4.7: Kaplan-Meier plot for PFS comparison idelalisib versus prior line of therapy, CUP cohort



Source: Cs, Figure 9E, page 53.
CUP = compassionate use programme; PFS = progression-free survival.

Possible reasons for the difference of results between Study 101-90 and the CUP cohort are the differences in the quality of study designs and rigour of progression assessment methods across trials. In standard clinical practice there is no objective, uniform approach to disease progression assessment, and thus, there are inherent errors when assessing PFS in a real-world, retrospective setting. The higher proportion of patients who had high-risk FLIPI score, and an ECOG performance status score of two or more is also a factor, suggesting some patients may have been treated through the CUP as a 'last resort' but with little expectation of long-term benefit (CS, pages 51-52).

ERG comment: The ERG requested details of the statistical analysis methods used for the indirect comparisons between idelalisib and prior therapy but they were not provided by the company (clarification response A24). Full details of the data collection methods were also not available and for Study 101-09, the company states in their response to clarification letter (question A.24) that these data were "primarily based on clinician recall (presumably supported with data collected in routine clinical practice)". This suggests that these data were retrospectively collected and may have been subject to selection bias and error. As the data were retrospective and from the same study the estimates for idelalisib and chemotherapy were based on the same patients but different time periods for the two treatments. This means that survival cannot be accurately measured and should not be statistically compared between the two groups. Without knowing whether the analysis was a simple statistical test

between the groups or a more complex survival model adjusting for other factors, or how censoring was performed, it is not possible to judge whether this analysis was reliable.

As the company themselves highlight in their response to clarification letter (Question B.9b), the inability to differentiate the effect of idelalisib versus chemotherapy upon patient outcomes from the effect of an additional line of therapy on patient outcomes using study 101-09 data [highlights] the difficulty of answering the decision problem generally. The ERG considers that comparisons between idelalisib and last prior therapy using the same patient population from the same study is highly unreliable and should be interpreted with extreme caution.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The NICE scope describes the decision problem as the clinical and cost effectiveness of idelalisib within its marketing authorisation for people with follicular lymphoma (FL) that is refractory to two prior lines of therapy. The population in the submission is in line with the scope. However, the submission mainly relies on one single arm study, the Phase II study 101-09 which provides data on the use of idelalisib monotherapy for the treatment of double-refractory FL. The population of double-refractory FL patients in this study may not be representative of UK patients in the typical clinical setting (see section 3.1).

The comparators listed in the NICE scope are: chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil); and, in people for whom chemo-therapy is unsuitable: best supportive care (BSC). For the main comparator (chemotherapy regimens) the company provided data collected via the disease registry for the HMRN to provide real world evidence (RWE) for chemotherapy regimens currently used to treat double-refractory FL in UK practice. These data are subsequently used to perform a matching-adjusted indirect comparison (MAIC), providing an estimate of comparative effectiveness for chemotherapy regimens (HMRN data) versus idelalisib (Study 101-09 data). No evidence was provided for best supportive care in people for whom chemotherapy is unsuitable.

The company presented evidence from four idelalisib studies. The main trial is Study 101-09, this is a multi-centre, single arm study investigating the efficacy and safety of idelalisib in patients with iNHL refractory to rituximab and an alkylating agent. Study 101-09 enrolled patients with different types of iNHL, but the FL population was the largest population (72 of 125).

Data collected via the disease registry for the HMRN ([redacted]) was included to provide evidence for the comparator: chemotherapy regimens currently used to treat double-refractory FL in UK practice.

Results from Study 101-09 based on the June 2014 database lock were used in the HMRN matching-adjusted indirect comparison and in the economic analyses. Results based on the June 2015 database lock were presented in the main submission. Where possible we have presented both data sets. Median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks. Median PFS was 11.0 months in the FL population for both data-sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 data-set, this was not reported for the June 2014 data-set.

In the FL population, the overall response rate (ORR, 95% CI) was 55.6% (43.4, 67.3) as assessed by the independent review committee (IRC), comprising 10 complete responses (CRs, 13.9%) and 30 partial responses (PRs, 41.7%) in the June 2015 data-cut. Response data from June 2014 are similar using IRC assessment, but were not reported for investigator assessment.

Health-related quality of life (HRQL) was assessed with the Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) scale. Median best change from baseline in FACT-Lym total score was 7.5 (95% CI: -39.0 to 47.0). The confidence interval was quite wide and the median did not exceed the minimally important difference threshold of 10-11.

The company performed a matching-adjusted indirect comparison (MAIC), comparing idelalisib with alternative chemotherapy, using data from the 101-09 study for idelalisib and HMRN data for the comparator. The MAIC included 72 patients with FL from study 101-09 and [redacted] Variables for matching included in the MAIC were [redacted] The respective two-year OS rate of FL patients treated with idelalisib in Study 101-09 trial was 69.8% and the one-year PFS rate was 43.0%, in the data-cut used for MAIC (11 June 2014 DBL).

The majority of patients enrolled in Study 101-09 experienced at least one AE, many of which were deemed to be treatment-related; 25% of FL patients discontinued treatment due to an AE. In both the total population and the FL population, the most common Grade ≥3 AE was neutropenia, occurring in 27 (21.6%) and 16 (22.2%) patients, respectively. Other common Grade ≥3 AEs included diarrhoea and pneumonia, both reported by more than 10% of patients.

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 ERG had several problems with the way the company performed the MAIC. First of all, it seems counter-intuitive to try to match the HMRN data to the baseline characteristics of Study 101-09 patients. The HMRN population includes all relevant patients who have been prescribed idelalisib in a real-world UK setting; as such the HMRN population seems more representative of the population defined in the NICE scope than the 101-09 study population. Study 101-09 had specific inclusion criteria, such as, 'Karnofsky performance score of 60 or higher (on a scale of 0=death and 100=complete absence of symptoms)' and 'radiographically measurable disease (defined as ≥1 lymph node with perpendicular dimensions measuring ≥2.0 x ≥1.0cm)', that may have influenced patient characteristics. Therefore, the ERG would have preferred to match the 101-09 study population to the characteristics of the HMRN population. That way, the resulting adjusted population might have been larger than the resulting adjusted HMRN sample size of [redacted] Secondly, the ERG did not agree with the exclusion of variables from the MAIC. [redacted]

[redacted] However, given the small sample sizes, not taking characteristics from one or a few patients into account in the analyses may similarly give too much weight to the characteristics of the remaining patients. [redacted] However, even though variables may be correlated, these variables might still be important for matching the populations in the MAIC. Therefore, we asked the company to repeat the MAIC by using the Study 101-09 data as the source of IPD and matching it to summary HMRN data, using the most recent data for Study 101-09; and to provide MAIC results including all variables (see Clarification letter questions A19b and A23). However, the company declined to repeat the MAIC by using the Study 101-09 data as the source of IPD and matching it to summary HMRN data. The analysis including all variables in the MAIC model [redacted]. These differences illustrate the concerns about the reliability of the MAIC analyses.

Overall, there is substantial uncertainty associated with these analyses, primarily stemming from the small sample of FL patients with disease refractory to rituximab and an alkylating agent identified in the HMRN cohort, the use of an unanchored MAIC in the absence of comparative trial data, and the MAIC results were sensitive to the inclusion and exclusion of important variables in the model which meant that potentially meaningful differences in treatment history could not be adjusted for.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission (e.g. searches for the measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation).

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Objectives of cost effectiveness analysis search and review

The CS reported that searches were carried out in February 2014. Searches were limited to studies published after 2004 and in the English language. Searches were carried out on the following databases: Embase, MEDLINE, MEDLINE In-Process, NHS EED via The Cochrane Library and EconLit. Where appropriate searches contained facets to identify relevant studies regarding the costs, HRQL and resource use identification of refractory FL. Individual update searches for costs, HRQL and resource use were conducted in February 2018 on Embase/MEDLINE using recognised study design filters, additional joint update searches were reported for all other databases in Appendix G.2. Searches were carried out in line with the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[39] Supplementary searches of the HTA database and the following conference proceedings were reported for 2016-2017: American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), the European Society for Medical Oncology (ESMO), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and an additional search of the International Conference on Malignant Lymphoma (ICML) for 2017. The CS also reported that the reference lists of key articles were checked to ensure that all relevant economic studies were captured.

ERG comments:

- The ERG queried missing information regarding the hosts for the database searches, the Company provided full details ensuring that all searches were clear and reproducible.
- For all searches the ERG felt that the addition of a facet for disease stage may have been overly restrictive. Unfortunately the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit. However the broad range of searches and additional reference checking may have mitigated against some loss of recall
- For the 2018 update searches (for all sections), the company searched Embase and MEDLINE simultaneously using a single database provider (Embase.com) and search strategy. Please see section 4.1.1 for potential limitations of this approach
- The original 2014 search contained a clear and comprehensive facet for resource use terms. The ERG queried its whereabouts in the update searches reported in Appendices G and H, the company apologised for the omission and provided a full strategy in their response to clarification.[29]

5.1.2 Inclusion/exclusion criteria used in the study selection

The eligibility criteria for the original cost effectiveness systematic literature review of 2014 were summarised in Table 17 from the Appendix G of the company submission.[40] The in- and exclusion criteria were categorised into six different groups as below:

- Population: studies with adult patients with relapsed or refractory iNHL who have received at least one previous therapy are included. As subpopulation, studies with adult patients with relapsed or refractory indolent FL, indolent MZL, indolent Waldenström's or lymphoplasmacytic lymphoma, or indolent mantle cell lymphoma who have received at least one previous therapy were considered.
- Outcomes: resource use and cost parameters associated with iNHL medications and iNHL complications.
- Study design: cost benefit analysis, cost effectiveness analysis, cost minimisation analysis, cost utility analysis, costing analysis, and cost consequence analysis were included. Review studies, editorials, notes, comments, and letters were excluded.
- Language: only studies in English language were included.
- Publication year: studies published between 2004 and 2014 were included.
- Countries: no restriction based on the country/jurisdiction of the study.

For the cost effectiveness systematic literature review update of 2018, the eligibility criteria for in- or exclusion were summarised in Table 18 from the Appendix G of the company submission.[40] The eligibility criteria of the updated 2018 search were classified into seven main categories as below:

- Population: studies with adult patients with relapsed or refractory FL and who were refractory to rituximab and an alkylating agent, i.e. double refractory were included.
- Interventions: no exclusion based on interventions.
- Outcomes: studies with the following outcomes were included: incremental costs, LYs gained and QALYs, and any other measure of effectiveness reported together with costs; model inputs; sensitivity analysis; and resource use and cost parameters.
- Study design: cost benefit analysis, cost effectiveness analysis, cost minimisation analysis, cost utility analysis, cost consequence analysis, budget impact analysis, costing analysis, cost of illness, and systematic reviews were included. Review studies, letters, and comment articles were excluded.
- Language: only studies in English language were included.
- Publication year: studies published from 1 January 2014 onwards were included.
- Countries: no restriction based on the country/jurisdiction of the study.

ERG comments: Although the company stated that the updated review was conducted in line with the original SLR, the ERG noticed a few discrepancies between the original and the updated SLR. First, in the updated review, additional conference proceedings were also searched in addition to the databases in the original SLR. Secondly, the eligible patient population in the in-/exclusion criteria was slightly different in the updated review in comparison to the original review. Furthermore, there were differences in the screening procedure. The primary and secondary screening of the original review was done by only one reviewer and a second independent reviewer was consulted when there was uncertainty or disagreement about inclusion of publications. For the updated review, primary and secondary screening was performed by two independent reviewers who reviewed each reference and decided whether to in- or exclude the study. A third reviewer was consulted when there was uncertainty regarding the inclusion of studies. Finally, for the quality assessment in the original review, the

Drummond and Jefferson and the NICE checklists were used.[30, 31] In the updated review, only the Drummond and Jefferson checklist was used.[30] The ERG thought that the differences between the original and the updated SLR and the potential effect of the differences should have been highlighted in the CS. Additionally, the company could have searched some of the primary HTA databases (e.g. NICE, CADTH, etc.) to check previous appraisals/relevant HTA submissions for refractory FL patients.

5.1.3 Included/excluded studies in the cost effectiveness review

Eight studies were identified for the economic database and conference proceeding abstract search from 2014. The updated search from 2018 identified three additional studies. The number of excluded studies and their reasons of exclusion were summarised in the PRISMA diagram given in Figure 7 for the original review of 2014 and Figure 8 (Appendix G of the CS) for the updated review from 2018.

The summary of the eight studies of the original search from 2014 were provided in Table 23. The three studies identified from the updated search from 2018 were summarised in Table 29 (Appendix G of the CS). Results of the quality assessment of these included studies were not presented. None of the identified studies evaluated the cost effectiveness of idelalisib in double-refractory FL patients.

Even though they were not identified in the SLR, the company revealed three economic evaluations underpinning dossier submissions to the Scottish Medicines Consortium (SMC), the National Centre for Pharmacoeconomics (NCPE) in Ireland, and the All Wales Medicines Strategy Group (AWMSG) for idelalisib monotherapy to treat FL patients.[41-43] In the CS, it was mentioned that these dossier submissions guided the company in development of the model structure and selection of inputs.

ERG comments: Table 23 and 29 in Appendix G provide a summary of the extracted data from the included studies from the SLR (e.g. type of study, population, health states included, and outcomes). However, it would have been useful to extract some additional information from these identified studies (e.g. the data sources used for clinical effectiveness, utility values, resource use etc.).

The quality assessment of the identified studies was missing in the CS. Due to the time and resource limitation, the quality assessment of these studies could not be conducted by the ERG.

In the CS, the NICE submission TA472 (obinutuzumab with bendamustine for refractory FL) was mentioned in later sections, however this TA was not identified in the company's SLR, similar to the other three submissions to Scotland, Ireland, and Wales HTA agencies mentioned above.[44] The ERG considered that the selection of previous HTA appraisals were rather arbitrary in the CS and this should have been conducted systematically.

5.1.4 Conclusions of the cost effectiveness review

The literature review cannot provide useful information for the cost effectiveness of idelalisib monotherapy for refractory FL, and a de novo economic analysis appeared to be necessary.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.1 presents a summary of the de novo economic model developed by the company.

Table 5.1: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in ERG report)
Model	A cohort-level discrete-time state transition model with a cycle length of 1 week was used. Earlier versions of the same model were used in submissions to the SMC, NCPE and AWMSG of idelalisib for the same patient population. The time horizon of the analysis was 39 years. Half cycle correction was not applied.	The CS stated that after 38 years in the simulation the age of the cohort population would be 100 years old and over 99% of patients would have been dead. Half cycle correction was not deemed necessary due to the short cycle length.	Section 5.2.2
States and events	The model consisted of the following health states: pre-progression on treatment, pre-progression off treatment, post-progression, palliative care, and death. The simulation cohort enters the model in the 'pre-progression on treatment' state. Patients are at risk of death in each state, but transition to the death state is only possible through a transitory "palliative care" state. From the pre-progression on treatment state (starting state), patients can either stop treatment or experience disease progression or die. Patients in the pre-progression off treatment phase remain in that state until progression occurs or die.	The distinction between on and off treatment was included as patients can withdraw from active treatment before disease progression.	Section 5.2.2
Comparators	The model is used in four different comparisons. Comparison A: Idelalisib vs. chemotherapy regimens as used in the previous line of treatment (as observed in Study 101-09) Comparison B: Idelalisib vs. chemotherapy regimens as observed in the HMRN database Comparison C: Idelalisib vs. chemotherapy regimens as used in the previous line of treatment (as observed in the UK & Ireland compassionate use programme) Comparison D: Idelalisib vs. best supportive care	Chemotherapy and best supportive care were listed as comparators in the final scope.	Section 5.2.3 and 5.2.4
Natural history	Advanced stage FL is a progressive condition. Patients are usually considered incurable and therefore standard therapeutic approaches attempt to control the condition. Median life expectancy ranges from 8–12 years after diagnosis,		Section 2

	Approach	Source/Justification	Signpost (location in ERG report)
	although this has extended to around 15 years in the post-rituximab era.[3, 45] Advanced stage FL is typified by a chronic course of repeated relapses, treatment and progression, and is associated with a number of physical and psychological symptoms that affect patients' HRQoL. With each relapse in FL, the disease becomes more resistant and/or refractory to treatment and each remission becomes shorter than the preceding one.[46]		
Treatment effectiveness	In Comparisons A, C and D no difference in terms of post-progression survival between treatment alternatives was assumed. The treatment alternatives in these comparisons differ with respect to progression free survival or time to treatment progression. In Comparison B the treatment alternatives differed both on progression free survival and overall survival. Parametric survival models or other statistical methods were used to provide the estimates for each of the transitions in the model. Each comparison used different data sources and different underlying assumptions for these survival inputs.	Study 101-09, HMRN database, UK & Ireland compassionate use programme studies were the only studies that the company had full/partial access to the patient level data for the safety/efficacy of chemotherapy or idelalisib in double refractory FL patients.	Section 5.2.6
Adverse events	The model included the following Grade 3 and 4 adverse events in the economic model: acute kidney injury, increased alanine aminotransferase, anaemia, increased aspartate aminotransferase, asthenia, colitis, dehydration, diarrhoea, dyspnoea, febrile neutropenia, hypokalaemia, hypotension, neutropenia, pneumonia, pyrexia, and thrombocytopenia. The effect of adverse events on HrQoL was incorporated by applying a utility decrement to the health state utility for the duration of the adverse event. The effect of adverse events on costs was included by applying a management cost for each adverse event that occurred in a cycle. Utility decrements and unit management costs were sourced through a targeted literature search. The probability of experiencing an adverse event was taken from Study 101-09 and assumed same for both idelalisib and chemotherapy arms.	The company had patient-level data from the Study 101-09 for patients receiving idelalisib, and argued that using idelalisib adverse event rates for chemotherapy would be conservative for the cost-effectiveness estimate for idelalisib vs. chemotherapy comparison as they expected more adverse events for chemotherapy.	Section 5.2.7
Health related QoL	Pre-progressive disease and post-progressive disease state utilities were sourced from literature. Previously published research using the EQ-5D questionnaire in FL patients was used to inform the model (Wild et al. 2006[47]). Adverse event specific utility decrements from the literature were also applied.	In Study 101-09, HRQoL was assessed using FACT-Lym instrument. Since the company did not find a mapping algorithm to map FACT-Lym scores to EQ-5D values,	Section 5.2.8

	Approach	Source/Justification	Signpost (location in ERG report)
		EQ-5D values from the literature were used.	
Resource utilisation and costs	The model includes the costs of treatment (idelalisib and chemotherapy regimens), drug administration costs, costs for monitoring and prophylaxis (pneumonia in idelalisib users), costs for healthcare use in the form of visits, tests, and procedures (haematologist visits, blood testing, etc.), and costs for the treatment of adverse events. Separate estimates of healthcare utilization for pre- and post-progressive disease are used. A separate palliative care cost estimate for the last 8 weeks of life is used.	Clinical sources (healthcare utilization), literature, expert opinion and NHS reference costs.	Section 5.2.9
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case.	Section 5.2.5
Sensitivity analysis	Both probabilistic and deterministic sensitivity analyses were included. Deterministic sensitivity analysis was done using both the confidence intervals of the input parameters and predefined scenarios.		Section 5.2.11

AIC = Akaike information criterion; AWMSG = All Wales Medicines Strategy Group; BIC = Bayesian information criterion; CS = company submission; HMRN = Haematological Malignancy Research Network; HrQoL = health related quality of life; NCPE = National Centre for Pharmacoeconomics; PFS = progression-free survival; SMC = Scottish Medicines Consortium

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: Comparison of the CS model with the NICE reference case

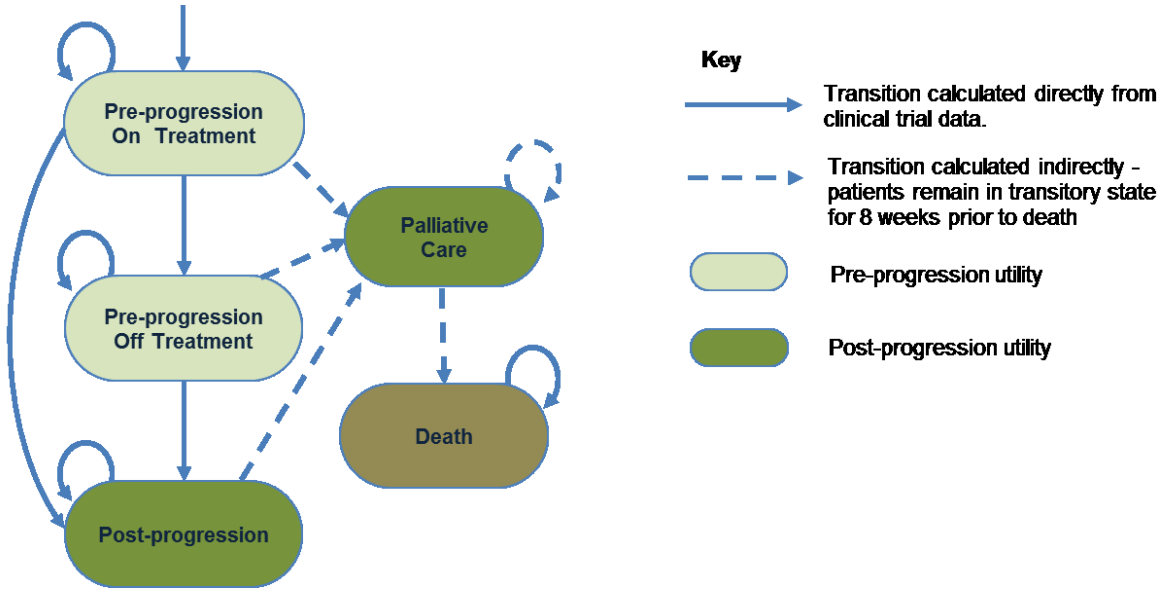
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	Chemotherapy and best supportive care were considered as the relevant comparators in the CS. Not clear if the chemotherapy options used in the CS reflect UK clinical practice.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon can be considered lifetime.
Synthesis of evidence in outcomes	Systematic review	Yes	Systematic literature reviews were conducted for relevant cost-effectiveness studies, and studies on HRQOL, cost and resource utilization in the target population.
Measure of health effects	QALYs Life-years	Yes	
Source of data for measurement HRQOL	Reported directly by patients and/or carers.	Yes	Utilities were taken from a previously published study that administered the EQ-5D in a group of follicular lymphoma patients.[47]
Source of preference data for valuation of changes in HRQOL	Sample of public	Not clear	In the CS, it was not mentioned which tariff was used.
Discount rate	Annual rate of 3.5% on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	In addition, univariate sensitivity and scenario analyses were performed.
NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year			

5.2.2 Model structure

The company developed a cohort-level state transition decision analytical model to capture the comparative cost effectiveness analyses described in the CS. In the model, for each of the treatment

arms, simulated patients move through the health states until death as depicted in Figure 5.1, starting from the "pre-progression on-treatment" state.

Figure 5.1 Model structure used in the economic evaluation



Source: CS, Figure 14, page 86

The health states in the economic model were categorised into dead and alive states. The alive states were further divided into pre-progression and post-progression states. The company also differentiated the pre-progression states according to the active treatment receiving status (i.e. pre-progression on-treatment and pre-progression off-treatment states), as the patients can withdraw the active treatment before disease progression. The company can move to post-progression state from both pre-progression on-treatment and pre-progression off-treatment states. It is also possible to have a transition to death state `from all states, via a transitory "palliative care" health state, which reflects the heightened cost of palliative care for cancer patients in the weeks preceding death. In the electronic model, the "palliative care" transitory state is actually not a separate state, but rather a virtual state to incur additional costs during the last eight weeks of a patient before his/her death. Hence, a patient is still in either pre-progression or post-progression state, while receiving palliative care in the model. This was not clear from description in the CS and the model structure depicted in Figure 5.1.

The transitions in the economic model in between different states can be listed as below:

- Transition 1: From pre-progression on treatment to pre-progression off treatment
- Transition 2: From pre-progression on treatment to post-progression
- Transition 3: From pre-progression on treatment to death
- Transition 4: From pre-progression off treatment to post-progression
- Transition 5: From pre-progression off treatment to death
- Transition 6: From post-progression to death

Calculation of these transition rates from time to event data in different comparisons will be explained in Section 5.2.6.

The company uses a one-week cycle length in the model and did not implement half cycle correction to clinical and cost outcomes, due to the short cycle lengths. In the base-case, the OS was modelled as the sum of the time spent in pre-progression and post-progression states.

The above model structure was used in four different comparisons by the company. The first three comparisons (A, B, C) were analysing the cost effectiveness of idelalisib vs. chemotherapy and the last Comparison (D) was analysing the cost effectiveness of idelalisib vs. best supportive care for chemotherapy ineligible patients. Each comparison used different clinical inputs or followed different approaches for deriving the model transition probabilities, and therefore each comparison providing different cost effectiveness estimates of idelalisib treatment in follicular lymphoma patients that are refractory to two prior lines of therapy. The list of the comparisons are as follows:

- Comparison A: idelalisib vs. chemotherapy, using time-to-event data from Study 101-09 for both idelalisib and chemotherapy treatments (NB: the prior line of therapy before idelalisib in Study 101-09 was considered as a proxy for chemotherapy)[33]
- Comparison B: idelalisib vs. chemotherapy, using time-to-event data from Study 101-09 for idelalisib arm and using data from MAIC adjusted time-to-event data from HMRN database for chemotherapy arm.[14]
- Comparison C: idelalisib vs. chemotherapy, using data from Eyre et al. 2017 study, which presented the results from the Compassionate Use Program (CUP) in UK & Ireland for pre-progression related transition probabilities for both idelalisib and chemotherapy. (NB: the prior line of therapy before idelalisib in CUP UK and Ireland study was considered as a proxy for chemotherapy)[35]
- Comparison D: idelalisib vs. best supportive care, for patients who are ineligible for chemotherapy, using data from Study 101-09 for both treatment arms (but assuming immediate progression and assuming only post-progression survival after idelalisib from Study 101-09 for the best supportive care arm).

The details of each comparison, including how the transition rates for each of the comparisons were derived for the economic model will be described in Section 5.2.6.

ERG comments: The model structure in the CS can be considered in line with other, commonly used, Markov models used in oncology. Except for Comparison B, the transitions between health states were modelled explicitly from the time to event data from the trials and the overall survival was calculated by summing the time spent at each alive health state, in that sense the approach was slightly different from the other area under the curve approaches often employed in partitioned survival models.

The company provided a comparison of the key features of their analysis with that of NICE TA472 (obinutuzumab with bendamustine for treating refractory follicular lymphoma) in Table 27 of the CS. This comparison of the company is summarised and critiqued in Section 5.2.12 of the ERG report.

5.2.3 Population

The patient population considered in the company's economic analyses was adults with follicular lymphoma that is refractory to two prior lines of therapy. The scope also requested that, if the evidence would allow, a subgroup of people suitable to receive stem cell transplantation and for whom idelalisib could be used to induce remission before transplantation would be considered. The company has indicated that there is not sufficient evidence for such a subgroup analysis, but in section B2.6.3 of the CS observations from trial regarding such patients were discussed.

ERG comments: The population considered in the company's economic analyses is in line with the NICE scope. The three clinical studies that were used in the model, in different comparisons, formed the non-randomised evidence base, involving a total of 177 patients (72 double-refractory FL patients in US and Europe from Study 101-09, 26 double-refractory FL patients in UK from HMRN database and 79 double refractory FL patients in UK and Ireland). 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.

5.2.4 Interventions and comparators

The intervention considered in the company's economic model is idelalisib and is implemented as per its marketing authorisation: as a monotherapy, 150mg orally, twice daily.

The comparators are various chemotherapy regimens (such as cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil) in chemotherapy-suitable patients. In people for whom chemotherapy is unsuitable, best supportive care (BSC) is assumed as comparator

In the company submission, it is explained that the comparator chemotherapy regimens are represented by the basket of chemotherapies received immediately prior to idelalisib by FL patients in Study 101-09. These comprise 16 different treatment strategies across 72 patients. Table 5 in the CS shows the list of comparators with the rationale for inclusion, whereas Table 43 in the CS shows for each comparator the number of patients receiving each treatment in Study 101-09 FL patients, and the recommended treatment duration in weeks.

An exact definition of BSC was not provided in the CS, but on page 19 of the CS, it was mentioned that BSC *"involves regular follow-up with a lymphoma specialist and/or palliative care team, blood product support if required and antibiotics to treat infection"*.

ERG comments: The comparators included in the cost effectiveness analyses were in line with the final scope. In the clarification letter, the ERG asked why recently approved treatment options for refractory FL, such as obinutuzumab with bendamustine, were not included and requested the company to explain to what extent the chemotherapy regimens used in the various included studies were reflective of the UK clinical practice. The company indicated in their response that the clinical expert had suggested that obinutuzumab with bendamustine would be typically used before idelalisib monotherapy and also added that "*it is challenging to fully define the relevant comparator treatments for NHS England outside of 'chemotherapy regimens', as there is no standard of care for double refractory FL patients and treatments are either repeated (from first- or second-line) or administered in a different combination according to individual clinician choice*".[9]

The ERG doubts if obinutuzumab and bendamustine would be always used before idelalisib monotherapy, as this statement was based on only one clinical expert, without any trial evidence or justification from the current clinical care. Hence, excluding this potential comparator based on a single expert opinion appears to be risky and might be an important omission. Clinical expert input can be a valuable source of evidence if there are no other alternatives, but the ERG would have preferred a more structured approach for elicitation of expert opinion and validation for the model and its inputs, not from a single but from multiple experts.

5.2.5 Perspective, time horizon and discounting

The cost effectiveness analyses performed by the company adopted the perspective of the NHS/PSS. A discount rate of 3.5% was applied for both costs and utilities. A 38-year time horizon with a cycle length of one week was assumed in the cost effectiveness model. After 38 years, patients had reached the age

of 100, at which point in time >99% of patients had died in both treatment arms. Half cycle correction was not applied due to the short cycle length (one week).

ERG comments: The choice of the time horizon seems appropriate since after 38 years, the patients in the cohort are 100 years old, and less than 1% of the patients in either arm of the model simulation are still alive.

The ERG considers that half cycle correction would be necessary to be able to consistently apply the total costs and QALY calculations. Therefore, the half cycle correction is applied in the exploratory analyses in Section 5.3.

In the economic model, while discounting was being applied, the ERG realised that a discounting was incorporated discretely, and a discounting interval of one year was used.

5.2.6 Treatment effectiveness and extrapolation

As explained in Section 5.2.2, the company presented the results of four different comparisons, each comparison uses different combinations of data from different studies. The Comparison A results were presented as the base-case and the other comparisons were presented as scenario (Comparison B and C) or subgroup (Comparison D) analysis.

In Table 5.3, the overview of the datasets used in deriving the time-to-event outcomes for each of the comparisons are provided.

Table 5.3: The overview of the datasets used in deriving the time-to-event outcomes for each of the four comparisons

Comparison A (Base-case)	
Idelalisib	**Chemotherapy regimens**
Dataset used: Study 101-09 • Idelalisib TTP • Idelalisib ToT • Idelalisib PrePS • Idelalisib PPS	Dataset used: Study 101-09 (prior line of treatment) • Prior treatment TTP^{+} • Prior treatment ToT^{+} • Idelalisib PrePS • Idelalisib PPS
Comparison B*	
Idelalisib	**Chemotherapy regimens**
Dataset used: Study 101-09 • Idelalisib OS • Idelalisib PFS • Idelalisib ToT	Dataset used: HMRN • MAIC adjusted “chemotherapy” OS • MAIC adjusted “chemotherapy” PFS Dataset used: Study 101-09 • Prior treatment ToT
Comparison C	
Idelalisib	**Chemotherapy regimens**
Dataset used: Eyre et al. 2017 (CUP) • Idelalisib TTP Dataset used: Study 101-09	Dataset used: Eyre et al. 2017 (CUP) • Prior treatment TTP^{+} Dataset used: Study 101-09

• Idelalisib ToT • Idelalisib PrePS • Idelalisib PPS	• Prior treatment ToT+ • Idelalisib PrePS • Idelalisib PPS
Comparison D (Chemotherapy ineligible)	
Idelalisib	**Best supportive care**
Dataset used: Study 101-09 • Idelalisib TTP • Idelalisib ToT • Idelalisib PrePS • Idelalisib PPS	• No treatment costs since instant disease progression is assumed. Dataset used: Study 101-09 • Idelalisib PPS
CUP = compassionate use programme; HMRN = Haematological Malignancy Research Network; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression free survival; PPS = post-progression survival; PrePS = pre-progression survival; ToT = time on treatment; TTP = time to progression * Diffferent from other comparisons, in Comparison B, the model uses area under the curve approach and OS, PFS and ToT curves directly determine the number of patients in each health state + Time-to-event outcomes from the prior line therapy before idelalisib (such as TTP and ToT) were adjusted with an HR=0.75 to account for the additional line of therapy the patients received at the start of the idelalisib treatment.	

ERG comments: The company generated comparative clinical effectiveness inputs for the economic model (e.g. time-to-event outcomes such as TTP, ToT, PPS, PrePS, PFS and OS) from non-randomised evidence. This non-randomised evidence was obtained either from different single arm studies as in Comparison B (e.g. TTP for idelalisib from Study 101-09 vs. TTP for chemotherapy from MAIC adjusted HMRN data) or obtained from the same study but using data from different time points as in Comparison A (e.g. TTP for idelalisib from Study 101-09 after idelalisib initiation vs. TTP for chemotherapy from Study 101-09, but from the previous line therapy, before idelalisib initiation).

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[48]. Firstly, the method selection algorithm sketched in Figures 2 and 3 in TSD 17 was not used. The methods that were employed to obtain clinical effectiveness estimates in each comparison seemed to be chosen arbitrarily. In Comparisons A and C, survival parametric functions fitted to the TTP and ToT outcomes from the previous line treatment were used as a proxy for chemotherapy comparator, after they were adjusted by a HR=0.75. The company mentioned that this HR was reflecting the expected worsening prognosis of FL at each successive treatment line, since the patients initialising idelalisib (or its comparator) would have one additional line of therapy in comparison to the previous line treatment.[22] In Comparison B, MAIC method was used to match the TTP data from the HMRN double refractory FL patient dataset with the idelalisib TTP data from Study 101-09. No explanation was given why specifically these methods were chosen, without consideration of the plausibility of other potential methods.

The ERG considered that a covariate adjusted survival analysis as specified in question B8 in the clarification letter might have provided a less biased and confounder-adjusted treatment effect of idelalisib for the relevant time-to-event endpoints. However, this analysis was not conducted by the company, arguing that they did not have access to the patient level data from CUP UK and Ireland studies and the HMRN dataset, and also in Study 101-09, data from the prior line therapy was available

only for the TTP (and not for PFS, OS, PPS and PrePS). The company also added that there was an intractable correlation between treatment currently received and the number of prior line of therapies.[29]

The ERG disagrees with the company on the last two points. Firstly, the suspected correlation between the "number of prior line therapies" and "the treatment received after the last progression" is not a reason to dismiss covariate adjustment analysis, but on the contrary, it suggests that "the number of prior line therapies" is either a confounding or an intermediate factor, and therefore the analysis should be adjusted for, together with other possibly confounding/intermediate factors. Secondly, the PFS, OS, PPS and PrePS data associated with the previous line treatment in Study 101-09 should be available to the company. Basically, the PFS of the previous line treatment is the same as the TTP of the previous line treatment, since there is no pre-progression death. Therefore, PrePS would be equal to 1. If idelalisib was initiated immediately after the previous line treatment progression, the PPS associated with the previous line treatment would be the OS after idelalisib initiation, and finally the OS related with previous line treatment would be the sum of the TTP (of previous line) and the OS after idelalisib initiation. This would lead to a situation that OS of the prior line therapy is always higher than the OS of idelalisib, and this might be attributable to the study design, and the fact that no deaths occurred during prior line therapy. However, given the uncertainties of the clinical effectiveness, the ERG would have liked to see an area under the curve approach based analysis, using the PFS and OS from idelalisib and prior line therapy as discussed above.

The ERG had some concerns regarding the HR=0.75 estimate used for the chemotherapy arm, to adjust for the additional number of prior treatments received. Actually, in the Scottish, Welsh and Irish HTA submissions for idelalisib, a hazard ratio (HR) of 0.9 was applied, but this estimate was changed to 0.75, based on the feedback from the company's clinical expert, who stated that the latter estimate was based on M7 FLIPI study.[22] The ERG could not verify and trace back this suggested HR from the publications mentioned in the CS. Furthermore, it is not clear to the ERG why the same HR value of 0.75 was applied to adjust for both TTP and ToT, without any evidence showing that the impact of "the number of prior line therapies" on these different clinical endpoints would be the same. The ERG would have preferred a separate HR for each of the corresponding time-to-event outcome, each derived from the relevant covariate adjustment survival analysis on Study 101-09 data as discussed above. To demonstrate the impact of the uncertainty of this HR on the cost effectiveness results, exploratory scenario analysis results with different HR values will be explored in Section 5.3.

After these general issues, the ERG will summarise its critique specific to each comparison below.

Comparison A

In Comparison A, for the chemotherapy arm, it was not clear why PrePS and PPS data associated with idelalisib from Study 101-09 were used. For the sake of consistency, in the chemotherapy arm, the ERG would have preferred to see the estimates based on the PrePS and PPS data associated with the previous line treatment before idelalisib.

Related to the Comparison A, the ERG identified three programming errors in the economic model.

Firstly, in calculating the transition probabilities from pre-progression to other alive health states, the ERG realised that the conditional probability that the cohort survived the previous cycle was not incorporated at all, or incorporated incorrectly.

The second problem is related to the implementation of PPS in the economic model. In the model, at cycle t, PPS value of cycle t was applied to all patients in the post-progression state in the model. However, this is incorrect, since not all patients who are in the post-progression state at cycle t were in

the post-progression state from the beginning, and some of them would have only recently progressed. This error did not lead to a problem in the base-case, because, as will be summarised in the next subsection, the PPS in Comparison A was extrapolated using an exponential distribution in the base-case, which has a constant hazard rate and therefore probability of death from the post-progression state is not affected by the time spent in the post-progression state. However, in scenario analyses in which different distributions were chosen to model PPS, this approach would result in wrong transitions.

Finally, at any given time t, the model uses the maximum of the TTP and ToT extrapolations, in order to calculate the probability of progression at time t. Even though this approach was followed to ensure that the number of patients non-progressed is always larger than the number of patients still on treatment, another plausible approach could be followed by using the minimum of the TTP and ToT extrapolations, to calculate the probability of being on treatment at time t.

In Section 5.3, the ERG will correct the first two programming errors mentioned above and will also provide the results of the exploratory analysis to show the cost effectiveness impact of following an alternative approach of using the minimum of TTP and ToT extrapolations, to calculate the probability of being on treatment at time t.

Comparison B

Since only PFS and OS endpoints were available from the HMRN dataset, the company followed a different, area under the curve approach, in this comparison. It was unclear to the ERG why area under the curve approach was not explored as a modelling option in other comparisons, as well.

In Comparison B, for the chemotherapy arm, PFS and OS values from the MAIC adjusted data from the HMRN dataset were used, whereas the ToT data for chemotherapy was sourced from the previous line treatment data (before idelalisib), from Study 101-09, since it was not available from the HMRN. The ERG could understand the limitations of the data from the HMRN dataset, but considered using inputs from different sources without any adjustment in the same model would be susceptible to bias. In this specific example, it is unclear to what extent the ToT data from the previous treatment line of Study 101-09 would be reflective of the ToT from the patients in the adjusted HMRN dataset.

Also, we noticed that the ToT from the previous line treatment before idelalisib from Study 101-09 was not adjusted for the additional number of therapy (i.e. HR=0.75 was not applied). The ERG considered that this is an important omission. Hence the ERG implements this HR to the ToT in its exploratory analyses in Section 5.3.

Similar to Comparison A, in Comparison B at any given time t, the model uses the maximum of the actual PFS and ToT values at time t, in order to calculate the probability of staying progression free (and alive) at time t. Likewise, at any given time t, the model uses the maximum of the actual OS and the probability of being progression free and alive, in order to calculate the probability of staying alive at time t. The ERG will also provide the results of the exploratory analyses to show the cost effectiveness impacts of following an alternative approach, using the minimum of ToT and PFS extrapolations, to calculate the probability of being on treatment at time t; and using the minimum of OS and PFS extrapolations, to calculate the probability of being progression free at time t.

Comparison C

Comparison C is identical to Comparison A, except for the source of the TTP data for idelalisib and chemotherapy, both of which were derived from the Eyre et al. 2017 (CUP) study. Using data from different sources without adjustment might be susceptible to bias, and all the issues related to Comparison A are relevant for Comparison C, as well. However, the TTP data from Eyre et al. 2017

study might be more reflective of the UK clinical practice, since the study reports the findings of a compassionate use program conducted in UK and Ireland.

In Section 5.3, the ERG will correct the first two programming errors mentioned for Comparison A above and will also provide the results of the exploratory analysis for Comparison C to show the cost effectiveness impact of following an alternative approach of using the minimum of TTP and ToT extrapolations, to calculate the probability of being on treatment at time t.

Comparison D
In Comparison D, it was assumed that the patients who are receiving palliative care progresses immediately, therefore TTP, PrePS and ToT values are always zero.

The ERG considers that this assumption was too strong. In the literature it was suggested that some patients may respond well to the palliative care, and thus these patients receiving palliative care do not necessarily progress immediately (e.g. Heinzelman et al. 2010[49]). Furthermore, it was not clear to the ERG why idelalisib PPS from Study 101-09 would be reflective of the PPS of the patients who progressed after palliative care. The ERG thought better estimates from the literature might have been found by the company. Due to the limited timelines, the ERG could not search for a plausible estimate.

The ERG considers that since the evidence underlying each comparison has different problems, the decision should be based on the cost effectiveness estimates considering all comparisons, hence the cost effectiveness threshold should be satisfied in all comparisons.

In the next subsections, the specifics of the analysis (survival analysis) of the time to event data from Study 101-09, HMRN study and Eyre et al. 2017 (CUP UK/Ireland study) will be summarised and critiqued.

5.2.6.1 Study 101-09

The company generated Kaplan Meier curves from the patient level data from the 30 June 2015 cut-off point of the Study 101-09 dataset for TTP, ToT, PrePS, PPS, OS and PFS of idelalisib and for TTP and ToT of the previous treatment before idelalisib, the latter curves as a proxy of the chemotherapy. Parametric curves (exponential, Weibull, Gompertz, lognormal, log-logistic and generalised gamma) were then fitted to these KM curves. The company mentioned that the recommendations in the NICE TSD 14[50] were followed, and the most plausible parametric curve was chosen based on the statistical goodness of fit (AIC and BIC), visual fit as well as the clinical plausibility (based on face to face meeting with Dr. Robert Marcus, an expert haematologist from the UK).

A hazard ratio of 0.75 was applied in the economic model to the previous treatment time-to-event extrapolations from Study 101-09, to adjust for the mismatch of the number of prior lines of therapy with the idelalisib time-to-event extrapolations.

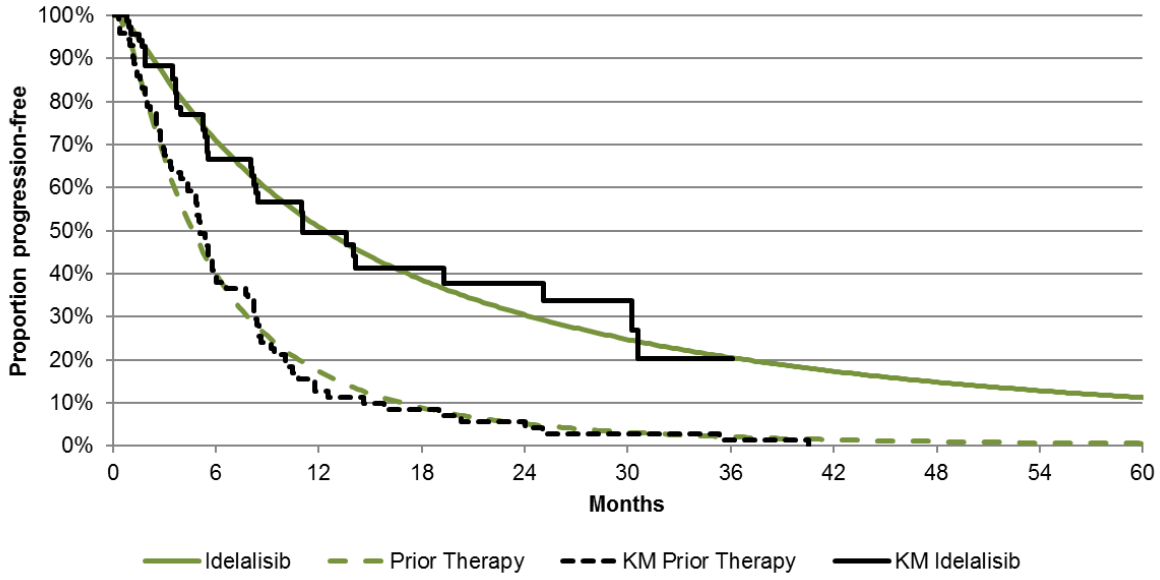
Time to Progression (TTP)
The parametric curves that were fitted to the idelalisib TTP KM data are shown in Figure 15 of the CS, and the AIC/BIC statistics for these model fits were provided in Table 28 of the CS. The lognormal distribution provided the best fit to the observed idelalisib TTP KM data based on the goodness of fit statistics.

Similarly, parametric curves were fitted to the prior therapy TTP KM data separately. The goodness of fit results were provided in Table 29 of the CS and the fitted parametric curves with the prior line TTP

KM were depicted in Figure 16 of the CS. The generalised gamma distribution provided the best fit to the observed prior therapy TTP KM data based on the goodness of fit statistics.

In line with the recommendations in the TSD 14, the company decided to use the same parametric 'type' of model, for both arms, and chose lognormal distribution to extrapolate the idelalisib and prior therapy TTP from the Study 101-09 in the cost-effectiveness analysis, which are depicted in Figure 5.2 below alongside with the TTP KM data.

Figure 5.2: KM data and lognormal parametric model fits for the TTP data from Study 101-09

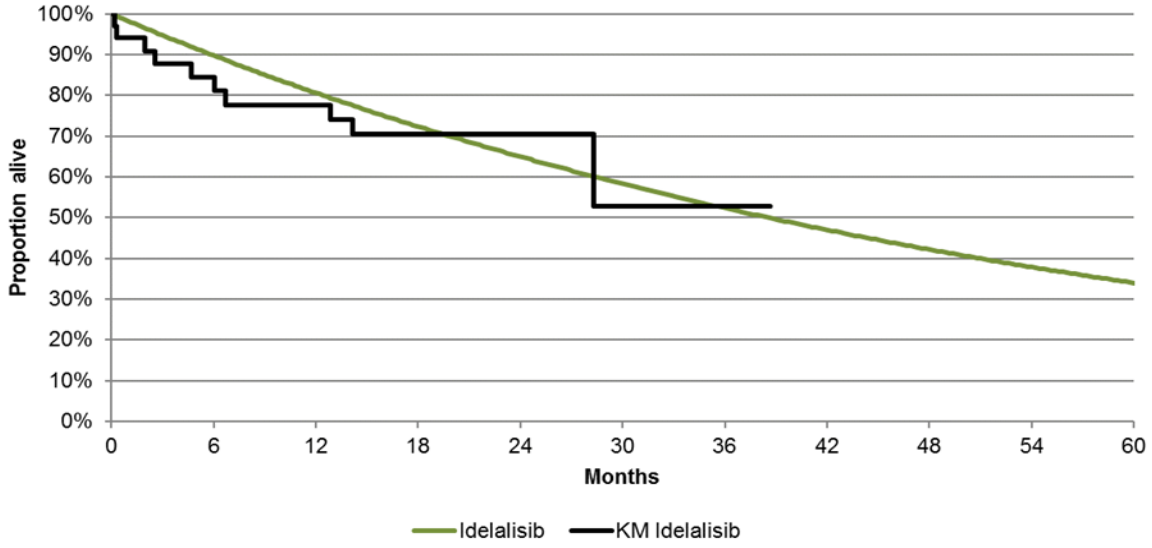


Source: CS, Figure 17, page 93
KM = Kaplan-Meier; TTP = time to progression

Post-progression survival (PPS)

PPS KM data was generated for the 36 patients from the Study 101-09 that were treated with idelalisib, who progressed before a death event. Afterwards, parametric survival curves were fitted to the KM data. The goodness of fit results were provided in Table 30 of the CS and the fitted parametric curves with the PPS KM were depicted in Figure 18 of the CS. The lognormal distribution provided the best fit to the PPS KM data based on the goodness of fit statistics, however exponential distribution was chosen for the extrapolation based on the clinical expert opinion in the cost effectiveness analysis. The exponential parametric model extrapolation together with the idelalisib PPS KM from the Study 101-09 is depicted in Figure 5.3 below.

Figure 5.3: KM data and exponential parametric model fit for the PPS data from Study 101-09



Source: CS, Figure 19, page 96
KM = Kaplan-Meier; PPS = post progression survival

The company did not provide the PPS data associated with the prior treatment before idelalisib from the Study-101, and in the model it was assumed that the PPS after idelalisib would be reflective of the PPS after previous line therapy.

Time on Treatment (ToT)
The parametric curves that were fitted to the idelalisib ToT KM data were shown in Figure 20 of the CS, and the AIC/BIC statistics for these model fits were provided in Table 31 of the CS. The exponential distribution provided the best fit to the observed idelalisib ToT KM data based on the goodness of fit statistics.

Similarly, parametric curves were fitted to the prior therapy ToT KM data separately. The goodness of fit results were provided in Table 32 of the CS and the fitted parametric curves with the ToT KM were depicted in Figure 21 of the CS. The Gompertz distribution provided the best fit and exponential distribution provided the second best fit to the observed prior therapy ToT KM data based on the goodness of fit statistics.

In line with the recommendations in the TSD 14, the company decided to use the same parametric 'type' of model, for both arms, and chose exponential distribution to model the idelalisib and prior chemotherapy TTP extrapolations for the Study 101-09 in the cost effectiveness analysis, which are depicted in Figure 5.4 below, alongside with the corresponding TTP KM data.

Figure 5.4: [redacted]

Figure redacted – commercial in confidence

Source: CS, Figure 22, page 99
KM = Kaplan-Meier; ToT = time on treatment

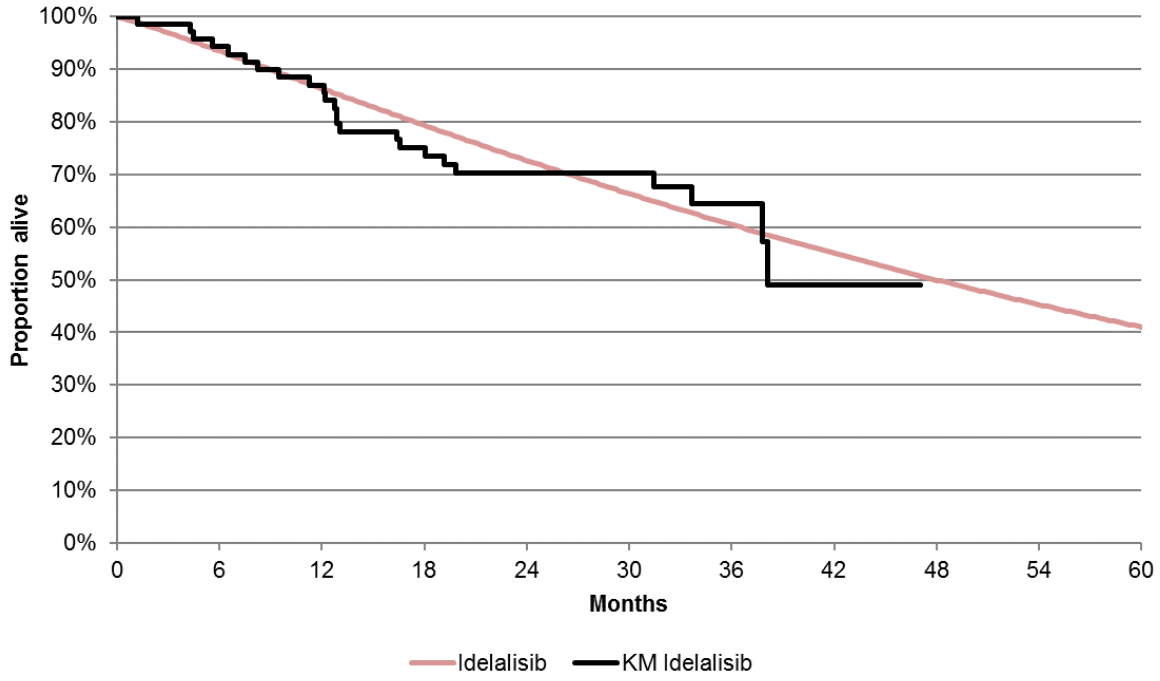
Pre-progression survival (PrePS)
In the CS, it was mentioned that only four pre-progression deaths were recorded in the Study 101-09. The KM curve for the pre-progression survival of idelalisib patients in Study 101-09 was given in Figure 23 of the CS. A hazard ratio (HR) of 5.71 for double-refractory follicular lymphoma pre-progression survival (versus age and gender adjusted general population survival) was estimated from the KM curve in Figure 23 from the CS and from the age and gender adjusted Office for National Statistics (ONS) life tables. This HR and age /gender adjusted ONS life tables were then used in the economic model.

Overall survival (OS)
Overall survival KM data for Study 101-09 idelalisib patients and parametric survival model fits to these data are shown in Figure 24 in the CS, and the AIC and BIC statistics of these parametric survival models are presented in Table 33 in the CS. The lognormal (AIC) and the exponential (BIC) distributions provided the best and second-best fits to the observed OS idelalisib data from the Study 101-09.

Even though the Weibull model did not provide the best statistical fit to the KM data, it was chosen for the OS extrapolation in the cost-effectiveness analyses due to its clinical plausibility, as the company mentioned that it was the only distribution that predicted less than 5% survival after 15 years.

The Weibull parametric model extrapolation together with the idelalisib OS KM from the Study 101-09 is depicted in Figure 5.5 below.

Figure 5.5: KM data and Weibull parametric model fit for the OS data from Study 101-09 idelalisib patients



Source: CS, Figure 25, page 103

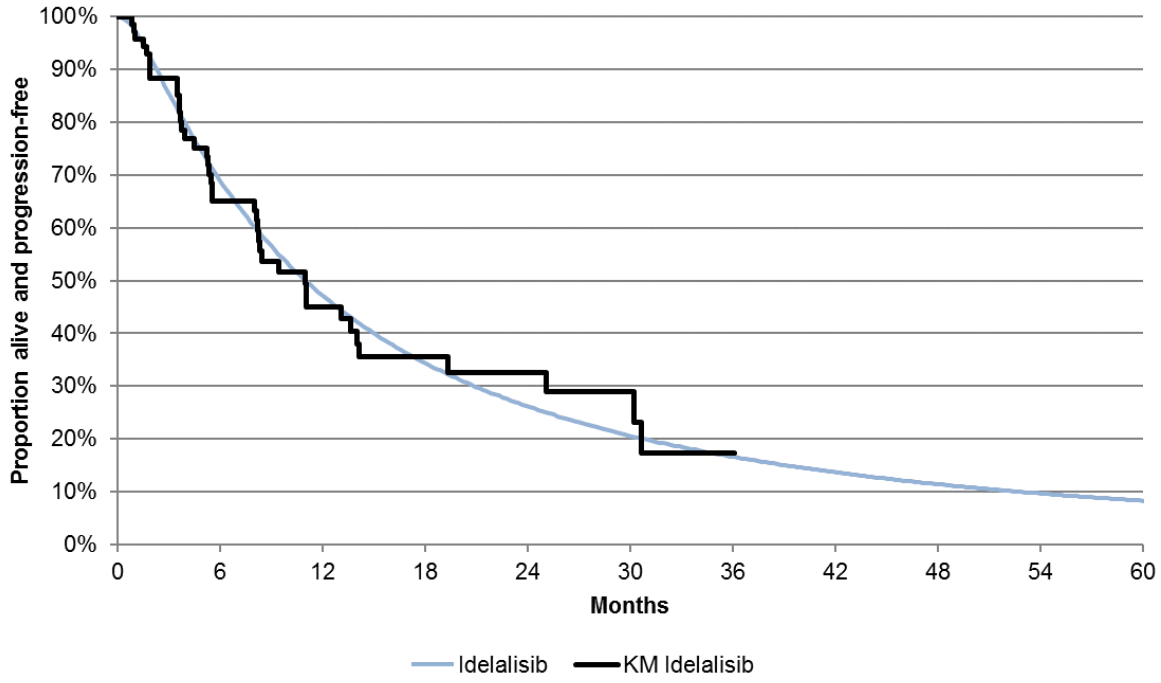
Progression free survival

Progression free survival KM data for Study 101-09 idelalisib patients and parametric survival model fits to these data are shown in Figure 26 in the CS, and the AIC and BIC statistics of these parametric survival models are presented in Table 34 in the CS.

The lognormal distribution was the distribution with the best statistical fit and was chosen to extrapolate the PFS in the cost effectiveness analysis.

The lognormal parametric model extrapolation together with the idelalisib PFS KM from Study 101-09 is depicted in Figure 5.6 below.

Figure 5.6: KM data and lognormal parametric model fit for the PFS data from Study 101-09 idelalisib patients



Source: CS, Figure 27, page 105

ERG comments: In the CS, it was not clear which type of progression event definition (i.e. IRC or investigator assessed) was used in the economic model. The ERG asked for clarification on this and asked the company to provide cost-effectiveness analyses based on both definitions. The company confirmed that the analyses were based on IRC assessed progressions and did not provide the cost-effectiveness analyses based on investigator assessed progression events, arguing the similarity of the results (from Table 12 of the CS). The ERG considers that this justification of not conducting this analysis is wrong. The similarity of the figures in the summary table does not necessarily show that the underlying time-to-event patient level data are alike. The investigator assessed progression might reflect the clinical practice better and the ERG would like to see the analyses based on investigator assessed progression events, as well.

In the CS, it was mentioned that the survival analyses followed the recommendations in TSD 14, however, the log-cumulative hazard plots of the analysed time-to-event data, which play a key role in the TSD 14 recommendations were not provided in the CS.[50]

Upon the request from the ERG, the company provided the log-cumulative hazard plots for the TTP, PPS, ToT, PrePS, OS and PFS associated with the idelalisib treatment. However, the log-cumulative hazard plots associated with the chemotherapy were not provided, arguing that testing for proportional hazards assumption would be unnecessary since the parametric extrapolations were conducted on data that were not from a randomised trial and the provided log-cumulative hazard plots for each outcome except PrePS appeared to be reasonably straight and hence did not provide evidence to suggest that more flexible models than the standard parametric survival models were required.

Also, the ERG considers that the parametric distributions in survival modelling do not appear to have been chosen systematically (e.g. sometimes the parametric distribution of choice was justified as being "conservative" whereas in other cases the selection was based on the best statistical fit only). In addition,

even though in NICE TSD14 there was a recommendation of using the same distribution 'type' for the intervention and control, TSD14 did not dismiss modelling the arms with different distribution 'types', in case an explanation was provided for the biological/clinical plausibility. The ERG thought that different distribution possibilities could have been explored by the company. While the fit of the parametric curves should be assessed based on statistical, visual and clinical plausibility, not all these assessments were reported in detail.

In their response to the clarification letter, the company also stated that the approach for model selection was systematic and sufficiently reported, mentioning that for the outcomes with mature data, statistical goodness of fit was relatively more important, whereas for outcomes with immature data, clinical plausibility gained more importance in model selection. The ERG was rather unconvinced, as it was not clear how the company assessed the maturity of the data and also considered that the level of detail in the clinical expert meeting document and the number of experts involved (n=1) were insufficient. Furthermore, from the minutes of the clinical expert meeting, the ERG noted that the parametric extrapolation model was already selected before the clinical expert meeting, and the clinical expert was not asked to discuss "which parametric model would provide the most plausible extrapolation" but asked to comment only on the a priori chosen extrapolations. The ERG cannot assess how these questions were formulated and how the expert opinion was elucidated, therefore cannot judge if the model input decisions based on clinical expert were sufficiently reliable.

In Section 5.3, the impact of choosing different distributions for extrapolations will be assessed in different exploratory analyses.

5.2.6.2 HMRN dataset

In Comparison B, parametric survival models were fitted to the matched OS and PFS data from the HMRN dataset. The details of the MAIC method were explained previously in Section 4.1.5 of the ERG report.

The KM survival curves pertaining to the MAIC adjusted OS and PFS data were digitised and pseudo patient level data were created using the algorithm given in Guyot et al.[51] An iterative sample-inflation process based on analyst judgement was used to increase the number at risk at time zero from n=6.9 to n=90 in OS and to n=80 for PFS. Six parametric curves than were fitted to the OS and PFS pseudo patient-level data.

The KM curve pertaining to the MAIC-adjusted inflated sample OS for double-refractory FL patients and the parametric survival models fitted to the data are shown in Figure 28 of the CS. The goodness of fit results for the fitted survival models are given in Table 35 of the CS. Lognormal distribution provided the smallest AIC and BIC statistics for the OS chemotherapy data, however the company chose Weibull distribution, to have a single 'type' distribution for both idelalisib and chemotherapy extrapolations in Comparison B, since Weibull was chosen as for extrapolating the idelalisib OS from Study 101-09 as discussed in Section 5.2.6.1. The OS KM and the fitted extrapolation curves for the chemotherapy are depicted in Figure 5.7 below.

Figure 5.7: [redacted]

Figure redacted – academic in confidence

Source: Response to the clarification letter, supplementary files for B8

The KM curve pertaining to the MAIC-adjusted inflated sample PFS for double-refractory FL patients and the parametric extrapolations are shown in Figure 29 of the CS. The goodness of fit results for the fitted survival models are given in Table 36 of the CS. Generalised gamma distribution provided the smallest AIC and BIC statistics for the PFS data, however the company chose lognormal distribution to extrapolate for the chemotherapy PFS in the cost effectiveness analysis in Comparison B, as it was chosen as the distribution with the best-fit for the idelalisib PFS from Study 101-09 as discussed in Section 5.2.6.1. The PFS KM and the fitted extrapolations are given in Figure 5.8 below.

Figure 5.8: [redacted]

Figure redacted – academic in confidence

Source: Response to the clarification letter, supplementary files for B8

ERG comments: The ERG critique on MAIC methods applied in the CS was already summarised in Section 4.1.5. Besides those MAIC related issues, the ERG identified a number of additional points in the extrapolation of the time-to-event outcomes from the HMRN dataset.

In the CS, it was mentioned that "*analyst judgement was used to increase the number-at-risk at time zero iteratively until the recreated KM curves provided a visually good fit to the original KM curves.*" (CS, p106). Although the company was asked to provide all relevant details of the statistical analyses, the codes used in sample inflation approach, and particularly the specifics of the "*analyst judgement*", were not reported sufficiently. Also, it was not clear to the ERG how "*visually good fit*" was determined by the company. Therefore, the ERG deemed that the inflated sample size of PFS and OS (n=90 and n=80) appeared to be determined rather arbitrarily.

The ERG considers that even though the KM curves from the inflated sample and from the MAIC adjusted HMRN database looked similar, the underlying (pseudo) patient-level time to event data should be quite different from each other. For instance, the size of the inflated sample dataset was substantially larger, involving multiple simultaneous death/progression events and possibly with different censoring events/times. This sample inflation approach seemed to underestimate the parametric uncertainty of the survival regression coefficient estimates due to artificially decreased variance. Also, it might have led to different survival regression coefficients in comparison to the coefficients that would have been obtained if the patient-level data from the HMRN database were available. The last claim is something that the ERG cannot verify, but just deduced due to the differences between the datasets.

Finally, the log-cumulative hazard plots of the analysed time-to-event data were provided only after the request from the ERG. These provided log cumulative hazard plots did not necessarily indicate that

standard parametric distributions would be sufficient. Furthermore, the ERG considers that the parametric distribution choice for the OS and PFS modelling were not made systematically, for instance the parametric distribution choice for OS and PFS were not based on statistical/clinical plausibility but instead, these choices were based on the prior decisions made for the extrapolation of idelalisib OS/PFS from Study 101-09.

In Section 5.3, the impact of choosing different distributions for extrapolations will be assessed in different exploratory analyses.

5.2.6.3 Eyre et al. 2017: UK and Ireland Compassionate Use Program (CUP)

The PFS and OS time-to-event data for idelalisib and for the previous treatment before idelalisib (as a proxy for chemotherapy) from the Eyre et al. 2017 study were analysed and the corresponding TTP curves were generated to be used in the cost effectiveness analysis in Comparison C.

The PFS of the prior therapy before idelalisib from the Eyre et al. 2017 study was identical to the TTP of the prior therapy, since no death events were recorded during the prior therapy. The PFS/TTP curve pertaining to the prior therapy patients before idelalisib were digitised and pseudo patient-level data were created using the algorithm given in Guyot et al. 2012.[51]

To obtain the idelalisib TTP, first the OS and PFS KM curves for the CUP idelalisib patients were digitised and pseudo patient-level data were created using the algorithm given in Guyot et al. 2012.[51] Afterwards, the analyst compared the idelalisib PFS and OS curves from Eyre et al. 2017 study and classified the PFS events into death and progression. This classification was used while generating the TTP KM curve for idelalisib from the pseudo patient-level OS and PFS data from Eyre et al. 2017.

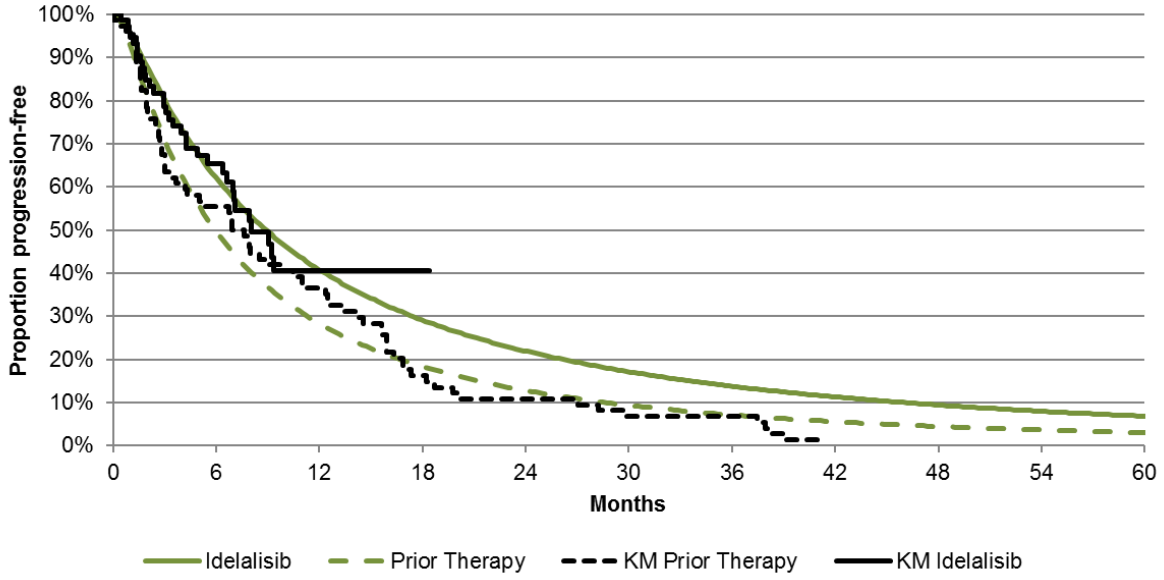
Six parametric curves were than fitted to the TTP KM for idelalisib and for the prior line therapy (as a proxy for chemotherapy). Note that the survival results for the prior line therapy were adjusted using the HR=0.75, to adjust for the additional line of therapy idelalisib patients received in comparison to the prior line therapy patients, as discussed in Section 5.2.6.1.

The KM curve pertaining to the idelalisib receiving patients' TTP, from Eyre et al. 2017 and the parametric extrapolations are shown in Figure 30 of the CS. The goodness of fit results for the fitted survival models are given in Table 37 of the CS. Lognormal distribution provided the smallest AIC and BIC statistics.

The KM curve pertaining to the prior therapy TTP, as a proxy for chemotherapy, from Eyre et al. 2017 and the parametric extrapolations are shown in Figure 31 of the CS. The goodness of fit results for the fitted survival models are given in Table 38 of the CS. Exponential distribution provided the smallest AIC and BIC statistics.

In line with the recommendations in the TSD 14, the company decided to use the same parametric 'type' of model, for both arms, and chose the lognormal distribution to model the idelalisib and prior therapy TTP extrapolations from CUP UK & Ireland, for the cost-effectiveness analysis in Comparison C. The chosen extrapolations are depicted in Figure 5.9 below alongside the TTP KM data.

Figure 5.9: KM data and lognormal parametric model fits for the TTP data from Eyre et al. 2017



Source: CS, Figure 32, page 113
KM = Kaplan-Meier; TTP = time to progression

ERG comments: It was unclear to the ERG how the analyst classified the idelalisib progression and death events from the OS and PFS idelalisib KM curves from Eyre et al. 2017. The details of this classification process were not provided despite the ERG's request.

Similar to the survival extrapolations conducted for Study 101-09 and HMRN database, the log-cumulative hazard plots of the analysed time-to-event data were provided only after the request from the ERG. These provided log cumulative hazard plots did not necessarily indicate that standard parametric distributions would be sufficient.

Furthermore, the ERG considers that the parametric distribution choice for the TTP modelling were not made systematically, and lognormal distribution (generated the second worst AIC and BIC for prior line therapy) was chosen for the prior line therapy, just because it provided the smallest AIC and BIC values for idelalisib. The ERG considers that this decision approach might be biased and considers that the chosen distribution should be plausible enough for both arms, not only for the interventional arm.

In Section 5.3, the impact of choosing different distributions for extrapolations will be assessed in different exploratory analyses.

5.2.7 Adverse events

Adverse events (AEs) for patients receiving idelalisib were included in the cost effectiveness model in the form of costs and disutilities. The operationalisation of these adverse events in the model are further described in Section 5.2.8.2 and Section 5.2.9.3 of this report. The AEs considered in the model were those treatment-emergent Grade 3 or 4 AEs reported by the investigator in Study 101-09 occurring in ≥3% of subjects. For each of the considered AEs, the number of observed AEs was divided by the mean number of patient weeks on treatment from Study 101-09, which generated cycle rates for that AE. That cycle rate was converted to AE cycle probability, which were then used in cost and disutility calculations.

For the chemotherapy regimens in the comparator arm, AE incidence probabilities were assumed to be equivalent to those for idelalisib.

ERG comments: In the company submission, a incidence based threshold of 3% was applied to grade 3 or 4 adverse events to create a shortlist of the most frequent ones from Study 101-09. It was not clear to the ERG why an arbitrary 3% threshold was chosen, as the justification for this was not given in the company submission. Furthermore, a threshold based on incidence only might overlook the most relevant AEs, hypothetically, an adverse event might have an incidence less than 3% but might have a substantial disutility, so that in terms of cumulative disutility, might be considered as relevant.

In the original CS, the mean ToT time (used in AE probability calculations) was based on June 2013 cut-off date from Study 101-09. This value will be updated with the mean ToT value based on June 2015 (latest) data cut-off date, [redacted] months, which was provided in company's response to the clarification letter, in the ERG exploratory analyses in Section 5.3.

The company uses the same AE incidences for idelalisib and chemotherapy and stating that this would be a conservative approach since they expected that AEs were likely to be more in the chemotherapy arm than in the idelalisib arm. Under this approach, the company implicitly assumed that there is no difference in terms of AE disutilities and costs between the treatment arms. The ERG cannot comment on the plausibility of this assumption and whether this would be conservative without comparative safety evidence between idelalisib and chemotherapy.

All other commentaries on the adverse events-related costs and disutilities form adverse events can be found in Section 5.2.8.2 and Section 5.2.9.3.

5.2.8 Health-related quality of life

In Study 101-09, HRQL in the target population was measured using the FACT-Lym instrument. The company stated that there was no mapping algorithm for this instrument to EQ-5D utilities available, and therefore this source of evidence on HRQL could not be used in the cost effectiveness analysis.

5.2.8.1 HRQL evidence used in the economic model

The company conducted a systematic literature review to identify previously published studies on HRQL in the target population (Appendix H of the CS). One study identified in the systematic review was used as input for the HRQL parameters in the model.[47] This study collected data on 222 patients with FL in eight UK centres. Utilities were elicited from patients using the EQ-5D questionnaire and clinical data collected allowed allocation of patients to five utility health states: active disease - newly diagnosed, active disease – relapsed, partial response to therapy, complete response to therapy/remission and disease free. Two patient groups were formed from these five utility health states to incorporate them in the health economic model. Patients classified as 'partial response to therapy', 'complete response to therapy/remission' or 'disease free' were grouped together as 'pre-progression. The mean reported EQ-5D utility of this group was used as the utility for the 'pre-progression on treatment' and 'pre-progression off treatment' health states in the health economic model. Patients classified as 'active disease - newly diagnosed' or 'active disease – relapsed' were grouped together as 'post-progression'. The mean reported EQ-5D utility of this group was used as the utility for the 'post-progression' and 'palliative care' health states in the model.

Table 5.4: Health state utilities, as used in the base-case of the health economic model

Health state	Mean estimate	Standard error	Source
Pre-progression on treatment	0.805	0.018	Wild et al. 2006[47]
Pre-progression off treatment	0.805	0.018	Wild et al. 2006[47]
Post-progression	0.618	0.056	Wild et al. 2006[47]
Palliative care	0.618	0.056	Wild et al. 2006[47]
Source: CS, page 120			

ERG comments: The ERG's main concerns regarding the assumptions made for the utilities used in the company's model are explained in detail below.

In the CS, it was stated that change in HRQL in Study 101-09 was assessed using the FACT-Lym instrument. However, no studies mapping FACT-Lym patient data to EQ-5D values in the specific FL population were identified by the company. Therefore, the company stated that mapping from Study 101-09 data to UK EQ-5D utility values was not possible.

The ERG noted that the FACT-Lym questionnaire is an extended version of FACT-G, with additional 15 questions. Hence, the ERG requested the company to explain why published mapping algorithms based on FACT-G, (e.g. Yost et al., Cheung et al. 2009 and Teckle et al. 2013)[52-54] were not used to derive utility estimates. In their response, the company stated the following limitations associated with the use of the mapping algorithms reported by Cheung et al. 2009 or Teckle et al. 2013[53, 54] to derive utility estimates from Study 101-09 quality of life data:

- Ignorance of the elements of quality of life captured by the additional 15 questions specified for lymphoma patients to create FACT-Lym.
- The limitations of Teckle et al. 2013 and Cheung et al. 2009 mapping algorithms in their ability to predict EQ-5D utility from FACT-G response within their patient samples.
- Key differences between the samples in Cheung et al. 2009 (n=367 cancer patients, none of whom were lymphoma patients, let alone refractory FL patients) and Teckle et al. 2013 (n=558 cancer patients, 4.1% of whom were lymphoma patients but the number of FL patients were not reported) and the Study 101-09 FL sample, and ultimately the FL patients who stand to benefit from NHS England availability of idelalisib monotherapy.

Despite these limitations, the ERG considers that EQ-5D estimates using these mapping algorithms would have provided valuable insights, especially considering that the utility estimate that the company use is dating back to 2006 and not published.

In the CS, the study by Wild et al. 2006[47], identified through a systematic review, was used for the utility estimates in their model. Wild et al. 2006 considered a relatively large sample of FL patients from UK (n=222)[47], however, the corresponding publication submitted in the reference pack was just a poster abstract, and none of the EQ-5D values from the CS were reported in that abstract. A further search conducted by the ERG to retrieve the full publication was unsuccessful. Therefore, the reported utilities in the CS could not be verified by the ERG. Furthermore, neither the CS nor the publication mention which tariff was used to calculate utilities from the EQ-5D responses.

The ERG considers that the derivation and choice of EQ-5D utility values for the health states in the CS were non-transparent and non-replicable. Therefore, the utility values reported in the pre-meeting

briefing of the obinutuzumab and bendamustine appraisal consultation document (TA472), from different sources, are provided below in Table 5.5.[44]

Table 5.5: Literature-based mean and sources for utilities

Health state	Wild et al. 2006[47]	Bec et al. 2014[55] UK Sample	GADOLIN[44]
PFS (on treatment)	0.81	0.71	0.82
PFS (off treatment)			0.81
PD	0.62	0.51	0.76
Key: PD, progressed disease; PFS, progression free survival			

It was unclear to the ERG why these utility estimates were not identified by the company in their systematic literature review. In TA472, utilities from Wild et al. 2006 were used in both CS and ERG base-case. Considering these uncertainties, in Section 5.3, the ERG will provide additional scenarios by using different utility values from different sources in Table 5.5.

The company was requested to incorporate age-adjusted decline in the utilities to the economic model. The company stated that: "*Understanding of how patient utility changes over time, beyond typical trial endpoints and particularly in late-stage cancer patients, remains low, as a recent review of evidence in this area attests. Assuming that utility for the patient group under consideration at hand will change over time in the fashion observed in general population samples is in itself an untested and unevidenced assumption*".[56] Despite the concerns from the company, the ERG considers that the inclusion of age-related decline from Ara et al. 2010[57] would be more plausible than assuming constant health state utility values in the model, since due to the indolent nature of the disease and the immature data available from the trial, a patient can stay in the same health state for multiple years and assuming a constant utility would overestimate the total number of QALYs estimated. Age-adjusted utility decline will be incorporated in the exploratory analyses in Section 5.3.

5.2.8.2 Disutility from adverse events

The health economic model incorporated the impact of Grade 3 and 4 adverse events on HRQL. In total, 16 adverse events were included. Targeted literature searches were used to inform the specific utility decrement for each adverse event. The disutility estimates for 10 of the included 16 adverse events and their expected duration estimates were taken from a phase-III trial in patients with relapsed non-Hodgkin's lymphoma (PIX301 trial).[58] Since no estimate for the duration of the remaining six adverse events was found in the literature review, the duration for these remaining adverse events was assumed to be the same as the duration of the longest persisting adverse event in the PIX301 trial, which was asthenia with a duration of 35.33 days. The disutility and duration estimates of the adverse events included in the health economic model are shown in Table 5.6.

Table 5.6: Disutility and duration of adverse events

Grade 3/4 adverse event	Dis-utility	SE	Source	Incidence per cycle[b]	Duration of adverse event (days)	Source
Acute kidney injury	-0.060	0.012[a]	[59]	0.001	35.33	Assumed to be the maximum of all Grade 3/4 AEs
Alanine aminotransferase increased	0.000	0.000	Assumption	0.002	35.33	Assumed to be the maximum of all Grade 3/4 AEs
Anaemia	-0.119	0.020	[60]	0.002	16.07	[58]
Aspartate aminotransferase increased	0.000	0.000	Assumption	0.002	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Asthenia	-0.115	0.023[a]	[61]	0.001	35.33	[58]
Colitis	-0.047	0.016	Assumed equivalent to diarrhoea	0.001	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Dehydration	-0.100	0.020[a]	[61]	0.001	8.00	[58]
Diarrhoea	-0.047	0.016	[62]	0.005	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Dyspnoea	-0.050	0.012	[63]	0.001	12.72	[58]
Febrile neutropenia	-0.150	0.030[a]	[61]	0.001	7.14	[58]
Hypokalaemia	-0.124	0.018	[64]	0.002	35.33	Assumed to be the maximum of all Grade 3/4 adverse events
Hypotension	-0.057	0.011[a]	[65]	0.001	8.00	[58]
Neutropenia	-0.090	0.015	[62]	0.006	15.09	[58]
Pneumonia	-0.200	0.020	[66]	0.003	14.00	[58]
Pyrexia	-0.110	0.022[a]	[66]	0.001	12.30	[58]
Thrombocytopenia	-0.108	0.022[a]	[67]	0.002	23.23	[58]

Source: Tables 39 and 40 in the CS, p.117 & p.118

SE = standard error.

[a], in the absence of reported SE information, SE is assumed to be 20% of the mean estimate; [b], cycle length = 1 week, source: Study 101-09.

The disutilities from these adverse events were implemented in the model by subtracting the total disutility incurred from all adverse events in each model cycle from the utility assigned to pre-progression on-treatment health state in the health economic model.

In Comparisons A, B, and C, where the comparator treatment is a chemotherapy regime, the incidence of adverse events is assumed to be the same for both treatment alternatives. In Comparison D, where the comparator treatment is best supportive care it is assumed that no adverse events occur in the comparator arm.

ERG comment:
Using same AE incidences for both arms would lead to same disutilities per cycle. The critique on the equivalence assumption for the AE incidence rates between idelalisib and chemotherapy arms have already been discussed in Section 5.2.7.

In the CS, the duration of six out of 16 AEs was assumed to be same as the duration of the longest persisting AE in the PIX301 trial (35.33 days). However, the reason behind this assumption is not mentioned.

5.2.9 Resources and costs

The company conducted a systematic search for relevant healthcare resource use and cost data. Details were reported in Appendix I of the CS.[40] This search was a modified update of a previous search conducted in 2014. None of these searches identified any relevant evidence to be included in the company's analyses. The cost categories considered by the company in their economic analyses are described in the remaining of this section.

5.2.9.1 Intervention and comparator acquisition and administration costs

Idelalisib

Idelalisib list price is £3,114.75 per pack of 60 tablets. The total acquisition costs per week is estimated as £681.35 under the following assumptions: using two tablets per day, mean dose-intensity of 93.75%, based on physician-prescribed reductions, escalations and interruptions that occurred in Study 101-09 (June 2015 DBL, ITT [iNHL] analysis set). After the application of the agreed confidential commercial discount (CCD), the NHS England acquisition cost for one patient per week is [redacted].

Chemotherapy regimens

Chemotherapy costs are calculated assuming the distribution of chemotherapy treatments received prior to idelalisib by FL patients as observed in Study 101-09. This included 16 different treatment strategies across 72 patients as summarised in Table 43 of the CS.

In Table 44 of the CS, average weekly doses per patient for each chemotherapy regimen in Table 43 of the CS is shown. Average doses were calculated assuming the dose and treatment duration in Table 43 of the CS.

A mean body surface area (BSA) of 1.91m^2 (the mean baseline BSA from Study 101-09) was used to calculate the weekly dose for those regimens whose dose was determined by a patient's BSA.[68] Drug unit, measure in mg, pack size, and cost per mg for component elements of each chemotherapy regimen are summarised in Table 45 of the CS.

Administration costs for intravenous therapies can be seen in Table 46 of the CS.

Finally, the weekly drug acquisition and administration costs associated with each chemotherapy regimen in the cost effectiveness model are shown in Table 47 of the CS. This summary table is reproduced here in Table 5.7 below. In order to get an average chemotherapy cost per model cycle, the total cost of each prior therapy regimen in Study 101-09 was weighed according to the proportion of FL patients who received it, as indicated in Table 43 of the CS. The four patients who received "investigative therapy" in Table 43 of the CS were not included in the calculation.

Treatment duration for chemotherapy regimens are based on Table 43 of the CS under the assumption that the recommended maximum treatment durations were used in clinical practice in England. Given the distribution and duration of prior chemotherapy regimens in Study 101-09 and the weekly estimated drug acquisition costs in Table 5.7, the weekly treatment and administration costs per model cycle are summarised in Table 5.8.

Table 5.7: Summary of drug and administration costs for each modelled chemotherapy regimen

Regimen	Drug	Active weekly drug costs		Active weekly administration costs
		Each component	Total	
R-CHOP	Rituximab	£417.82	£434.35	£118.51
	Cyclophosphamide	£7.36		
	Doxorubicin	£3.09		
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
R	Rituximab	£1,253.45	£1,253.45	£355.54
R-B	Bendamustine	£23.76	£337.12	£163.81
	Rituximab	£313.36		
R-CVP	Rituximab	£417.82	£431.26	£118.51
	Cyclophosphamide	£7.36		
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
CHOP	Cyclophosphamide	£7.36	£16.54	£99.89
	Doxorubicin	£3.09		
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
R-P	Rituximab	£417.82	£421.01	£118.51
	Prednisolone (oral)	£3.19		
R-CHO	Rituximab	£417.82	£431.16	£118.51
	Cyclophosphamide	£7.36		
	Doxorubicin	£3.09		
	Vincristine	£2.90		
CVP	Cyclophosphamide	£7.36	£13.45	£99.89

Regimen	Drug	Active weekly drug costs		Active weekly administration costs
		Each component	Total	
	Vincristine	£2.90		
	Prednisolone (oral)	£3.19		
FR	Fludarabine	£22.57	£335.93	£88.89
	Rituximab	£313.36		
CHEP	Cyclophosphamide	£5.89	£9.25	£99.89
	Doxorubicin	£1.55		
	Etoposide	£0.54		
	Prednisolone (oral)	£1.28		
R-Ch	Rituximab	£313.36	£354.39	£88.89
	Chlorambucil	£41.03		
CHOEP	Cyclophosphamide	£7.36	£20.59	£299.68
	Doxorubicin	£3.09		
	Vincristine	£2.90		
	Etoposide	£4.05		
	Prednisolone (oral)	£3.19		
CHEPi	Cyclophosphamide	£5.89	£75.43	£899.04
	Doxorubicin	£1.55		
	Etoposide	£0.54		
	Prednisolone (oral)	£1.28		
	Interferon	£66.18		
ChP	Chlorambucil	£57.44	£60.12	£74.92
	Prednisolone (oral)	£2.68		
FM	Fludarabine	£27.09	£45.73	£74.92
	Mitoxantrone	£18.65		
Source: Table 47 in the CS.[1]				

Table 5.8: Weekly prior therapy treatment costs across model cycles

Model weeks	Weekly drug cost	Weekly administration cost	Weekly total cost
1–4	£463.29	£167.56	£630.85
5–16	£278.96	£115.27	£394.23
17–18	£273.35	£112.86	£386.21
19–24	£272.10	£98.17	£370.28
25–32	£6.10	£2.41	£8.50
Source: Table 48 in the CS.[1]			

Monitoring patients treated with idelalisib
Patients treated with idelalisib are assumed to receive prophylaxis for PJP and to be screened for CMV infections, as described in Section 2.10 of this report.

PJP prophylaxis consists of a continuous treatment with co-trimoxazole (480mg daily), while the patient is on idelalisib treatment and between two and six months after treatment when treatment with idelalisib is finished. The model assumed that PJP prophylaxis is continued until six months after finishing idelalisib treatment. The cost per pack of co-trimoxazole (28 tablets) is £2.29,[69] resulting in a weekly cost of £0.57 per patient.

CMV monitoring consisted of a polymerase chain reaction (PCR) test. The cost of a PCR test is £7.50 assuming the NHS reference costs estimate for a microbiology test, or £56.00 assuming the Medtech innovation briefing cost [MIB24], NICE (2015).[69] In the base-case the Medtech innovation briefing cost was used. Based on the clinical expert opinion, following frequency of PCR tests per year for idelalisib patients was assumed: 1) months 0-6: one test every month, 2) months 6-12: one test every two months, and 3) months 12+: one test every three months.

ERG comments: The ERG is doubtful if the treatment frequencies observed in prior line therapy from Study 101-09 would be reflective of the treatment frequencies in the UK clinical practice for double refractory FL patients. The ERG considers that these prior line treatment percentages would be different for the next line, and that the UK practice might be different than what is observed in the trial. Since the unit drug acquisition costs differ between chemotherapy options substantially, the ERG will conduct some additional scenario analyses based on the chemotherapy acquisition costs in its exploratory analyses in Section 5.3.

In the CS, the company did not incorporate drug wastage costs and applied mean dose intensity only for idelalisib but not for chemotherapy. However, drug wastage would occur if a patient stops the treatment before the package is consumed completely. Concerning mean dose intensity: dose reductions, escalations or interruptions might also occur in chemotherapy patients. The company, in its response to the clarification letter, acknowledged the presence of drug wastage possibility and dose deviations for chemotherapy, however added that there was a lack of data for the chemotherapy mean dose intensity and suggesting to use the idelalisib mean dose intensity from Study 101-09. The ERG found some published data suggesting that the real-life proportion of patients experiencing dose reductions or interruptions on chemotherapy may be slightly lower (~85-90% in FL patients).[70] The ERG considers that not applying mean dose intensity for chemotherapy patients would overestimate the chemotherapy arm costs and therefore, will incorporate mean dose intensity in the explorative analyses in Section 5.3.

In the CS, the biosimilar price for rituximab was not used while calculating chemotherapy drug acquisition costs. These assumptions would lead to an overestimation of chemotherapy arm drug acquisition costs. The ERG will conduct some additional scenario analyses based on the rituximab biosimilar prices.

Finally, the idelalisib related monitoring frequencies were all based on a single clinical expert opinion, and might be subject to uncertainty. The ERG will conduct explorative scenario analyses on these monitoring frequencies in Section 5.3.

5.2.9.2 Health-state unit costs and resource use

Unit costs per resource use associated with disease management included in the economic model are presented in Table 5.9.

Table 5.9: Unit costs for resource use

Resource	Unit cost	Source
Haematologist/outpatient visit	£167.83	NHS Reference Costs 2016/17 CL WF01A: 303 (Clinical Haematology)[71]
Specialist nurse	£110.00	PSSRU 2017[72]
Blood test or haematology/blood count or Serum chemistry	£3.06	NHS Reference Costs 2016/17 Directly Accessed Pathology Services; DAPS05[71]
Radiological/CT assessment	£85.56	NHS Reference Costs 2016/17 Computerised Tomography Scan of one area, without contrast, 19 years and over; RD20A[71]
Biopsy	£512.59	NHS Reference Costs 2016/17 SA33Z Diagnostic Bone Marrow Extraction Day Case[71]
Radiotherapy/Palliative Care	£145.12	NHS Reference Costs 2016/17 weighted average of RAD DCRDN[71]
Allogeneic stem cell transplantation	£35,180	NHS Reference Costs 2016/17 Total HRGs: weighted average of SA38A, SA39A and SA40Z[71]
Autologous stem cell transplantation	£17,174	NHS Reference Costs 2016/17 Total HRGs: SA26A[71]
Other chemotherapy	£10,316	Average prior therapy treatment cost

Source: Table 49 in the CS.[1]
CT = computed tomography; NHS = National Health Service; PSSRU = Personal Social Services Research Unit.

Disease management costs per health state (i.e. pre-progression and post-progression) are reported in Table 50 to Table 53 of the CS. Note that costs in Table 51 of the CS **Error! Reference source not found.**are one-off costs associated with disease progression, which were applied in the cycle where progression took place. Post-progression costs are divided into disease management and relapse management costs. These are shown in Table 52 and Table 53 of the CS, respectively. Subsequent chemotherapy costs were assumed to be applicable to the 15% of the progressed patients for both idelalisib and its comparator, and they were assumed to be equal to the mean cost of the prior line chemotherapy in Study 101-09, as reported in Table 48 of the CS.

The frequency estimates for the healthcare provider visits were taken from a Swedish economic evaluation for rituximab maintenance in refractory FL patients, which was identified by the company in the review of economic evidence.[73] The frequency of tests and procedures and other resource use estimates were based on clinical expert opinion as well as the European Society for Medical Oncology (ESMO) guidelines for the diagnosis, treatment and follow-up of FL.[23]

ERG comments: The ERG considered that the choice of the inputs for the health care resource use frequency estimates was rather arbitrary. It was not clear why a particular Swedish study, which was

not mentioned in the cost effectiveness SLR conducted by the company, was used in informing the economic model.[73] Also, most of the inputs were based on a single clinical expert opinion, and therefore subject to substantial uncertainty.

Furthermore, it was not obvious how the proportion of subsequent chemotherapy after progression estimate (15%) was derived, as well as the reasons of the underlying assumption that this proportion would be the same for idelalisib and its comparator.

5.2.9.3 Adverse event unit costs and resource use

The company, in the economic model, included the costs associated to treatment-emergent adverse events of Grade 3 or 4 as reported by the investigator in Study 101-09 occurring in at least 3% of subjects. The unit costs associated with the management of these adverse events are presented in Table 54 of the CS.

Applying the adverse event probabilities to the unit AE costs would yield the model cycle costs as shown in Table 5.10, which resulted in a total cost per cycle of £49.95. Note that the same total adverse event cost was assumed for the chemotherapy arms in Comparisons A, B and C. For the comparison with BSC, Comparison D, no adverse event costs were applied.

Table 5.10: Cycle cost attributable to treatment-related AEs for active treatments

Grade 3/4 AE	Cycle probability	Cost per cycle
Acute kidney injury	0.001	£2.38
Alanine aminotransferase increased	0.002	£0.29
Anaemia	0.002	£3.78
Aspartate aminotransferase increased	0.002	£0.21
Asthenia	0.001	£0.15
Colitis	0.001	£1.29
Dehydration	0.001	£1.94
Diarrhoea	0.005	£6.76
Dyspnoea	0.001	£1.18
Febrile neutropenia	0.001	£7.29
Hypokalaemia	0.002	£0.68
Hypotension	0.001	£1.94
Neutropenia	0.006	£11.31
Pneumonia	0.003	£8.49
Pyrexia	0.001	£1.36
Thrombocytopenia	0.002	£0.91
Total cycle cost		£49.95

Source: Table 55 in the CS.[1]
AE = adverse event.

5.2.9.4 Miscellaneous unit costs and resource use

The company, in the economic model, included the costs associated with care prior to death. These costs were sourced from a King's Fund report on improving choice at the end of life,[74] which represent the average costs of community and acute care for UK patients with cancer in the last eight weeks of their life, inflated to 2017 levels.[72] The costs for eight weeks of care are estimated as £6,262.43. Assuming that these are spread evenly across the last eight weeks of a patient's life, resulted in £782.80 per week, which were applied to the proportion of patients in the "Palliative care" health state.

5.2.10 Base-case incremental cost effectiveness analysis results

The base-case analysis selected by the company was based on Comparison A (intervention and comparator arms' effectiveness inputs are from Study 101-09). The cost effectiveness results are summarised in Table 5.11. All results included the agreed confidential price discount of [redacted] to the list price for idelalisib and discounting. Results in Table 5.11 indicated that idelalisib provided additional 0.91 QALYs at an additional cost of £23,762 when compared to the chemotherapy regimens representing the current standard of care. The estimated incremental cost effectiveness ratio for idelalisib was thus £26,076 per QALY gained.

Table 5.11: Base-case (Comparison A) cost effectiveness results, including idelalisib CCD

Technologies	Total costs	Total LYG*	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Chemotherapy Regimens	[redacted]	5.01	2.80	-	-	-	-
Idelalisib	[redacted]	6.34	3.71	£23,762	1.33	0.91	£26,076

Source: Table 58 in the CS.[1]
CCD = confidential commercial discount; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.
*Note that all the LYG results provided are undiscounted

5.2.10.1 Disaggregated results of the base-case incremental cost effectiveness analysis

Disaggregated results of idelalisib versus chemotherapy are presented below for QALYs. For cost breakdown for health states and cost items, we refer the reader to Table 37 and Table 38 from the Appendix J of the CS.[1]

From Table 5.12 below, it can be seen that both on-treatment and off-treatment pre-progression states contributed the most to the incremental QALY gains for idelalisib. From the tables in Appendix J, drug acquisition costs in the pre-progression state contributed the most to the incremental costs for idelalisib.

Table 5.12: Summary of QALY gain by health states

Health state	Idelalisib	Chemotherapy	Increment	Absolute increment	% absolute increment
Pre-progression (on-treatment)	0.71	0.18	0.52	0.52	32%
Pre-progression (off-treatment)	0.95	0.19	0.76	0.76	46%
Post-progression	2.05	2.43	-0.38	0.38	23%
Total	3.71	2.80	0.91	1.66	100%

Source: Table 36 in the CS Appendix J.[1]

5.2.11 Sensitivity analyses

5.2.11.1 Probabilistic sensitivity analysis (PSA)

The model input parameters which were included in the PSA, with their corresponding probability distribution, are presented in Table 56 of the CS. If possible, the uncertainty was characterised statistically, by a standard error or a covariance matrix. Otherwise, an error of 20% from the mean was assumed. Idelalisib drug acquisition and administration costs were kept fixed and therefore not included in the PSA.

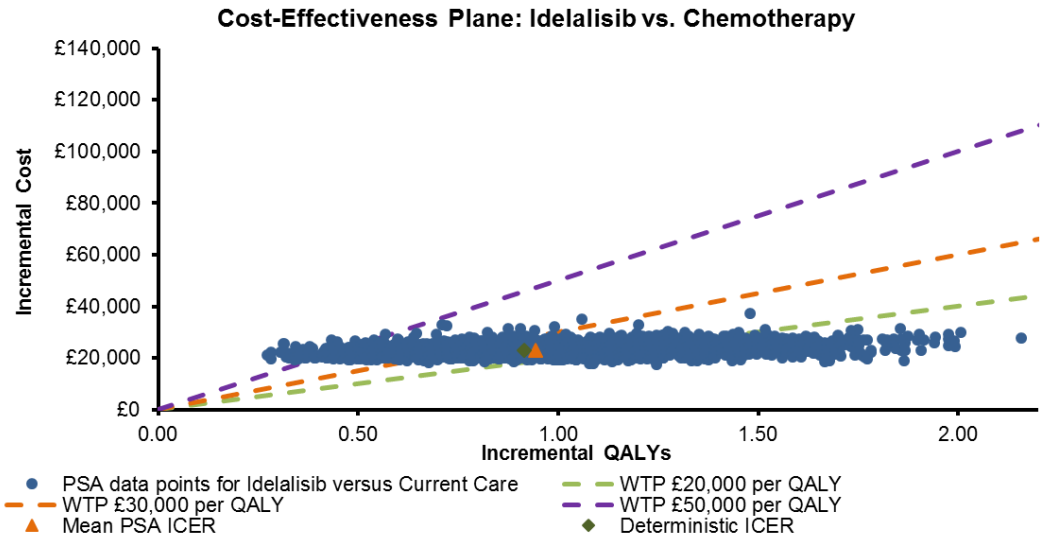
The company presented PSA results for the base-case analysis only (Comparison A) based on 4,000 PSA iterations. Results are presented in Table 5.13. It was observed that the mean probabilistic results are close to the deterministic results in Table 5.11. Figure 5.10 and Figure 5.11 show the scatter plot of the PSA outcomes on the CE plane and the associated cost effectiveness acceptability curve, respectively. All the 4,000 outcomes were located on the NE quadrant of the CE plane. The estimated probability that idelalisib is cost effective compared to current chemotherapy treatment is 17% at a willingness to pay threshold of £20,000, 68% at a threshold of £30,000, and 97% at a threshold of £50,000 (see Figure 5.11).

Table 5.13: PSA base-case (Comparison A) results, including idelalisib CCD

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Probabilistic ICER
Chemotherapy Regimens	[redacted]	2.81	-	-	-
Idelalisib	[redacted]	3.75	£23,821	0.94	£25,364

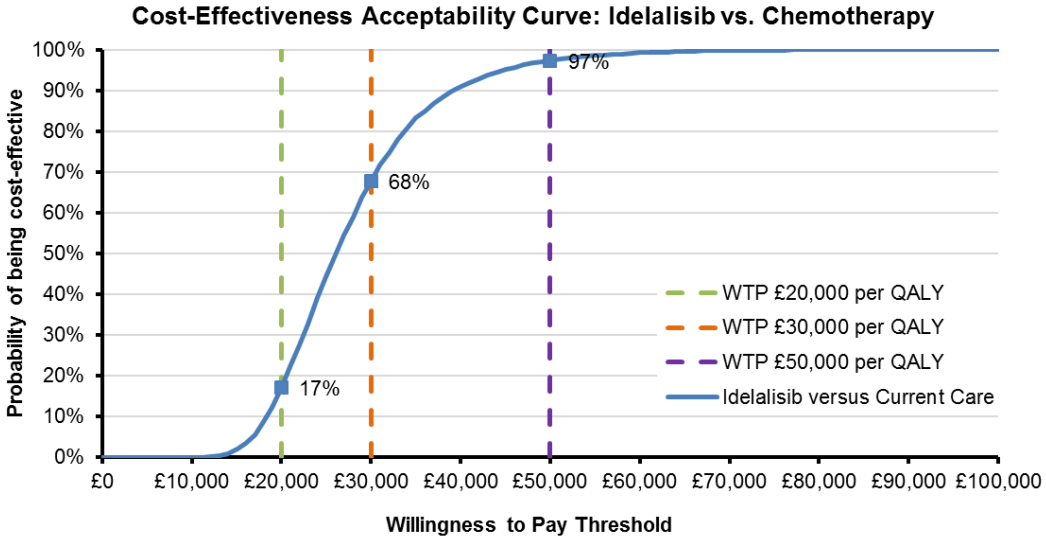
Source: Table 59 in the CS.[1]
CCD = confidential commercial discount; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 5.10: PSA Scatterplot, from base-case (Comparison A) probabilistic results, idelalisib versus chemotherapy regimens, including idelalisib CCD



Source: Figure 34 in the CS.[1] CCD = confidential commercial discount; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years; WTP = willingness to pay.

Figure 5.11: Cost effectiveness acceptability curve, from base-case (Comparison A) probabilistic results, including idelalisib CCD



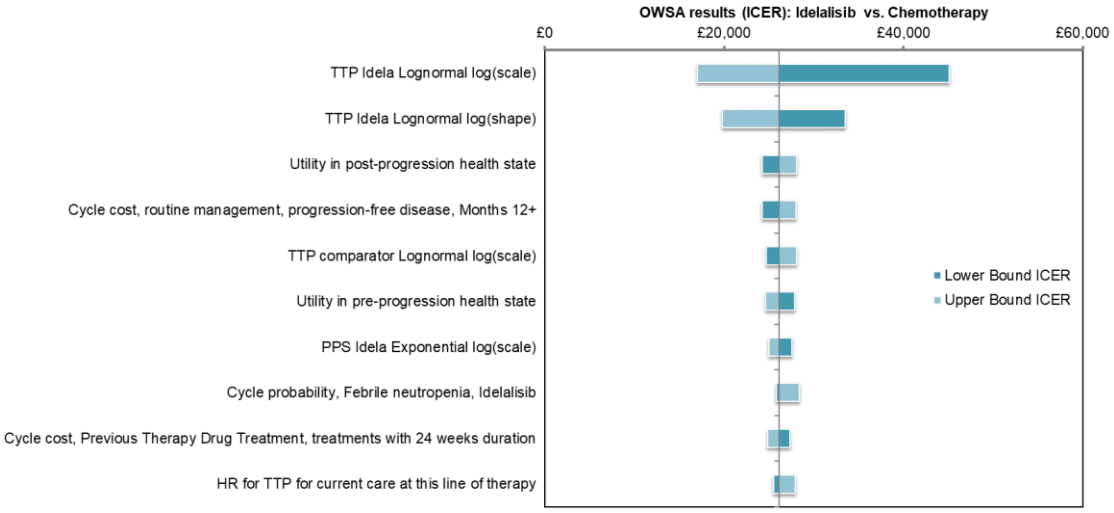
Source: Figure 33 in the CS.[1]
CCD = confidential commercial discount; QALY = quality-adjusted life year; WTP = willingness-to-pay.

5.2.11.2 Deterministic sensitivity analysis (DSA)

A deterministic sensitivity analysis (DSA) was carried out by the company. The same parameters as in the PSA and additionally cohort age was varied using the 2.5 and 97.5%-percentile values obtained from the PSA (except for the HR=0.75, used for prior line adjustment, lower and upper bounds of 0.6 and 1 were used respectively). The company presented DSA results for the base-case analysis only (Comparison A). Results are depicted graphically in a tornado diagram showing the 10 parameters that

have the greatest influence on the ICER in Figure 5.12. From the DSA results, it was observed that the ICERs remained below £50,000 and were close to the base-case value in most cases. The most influential parameters seem to be the shape and scale parameters of the lognormal distribution used to model idelalisib TTP.

Figure 5.12: Tornado diagram showing OWSA results, base-case (Comparison A) cost effectiveness analysis, including idelalisib CCD



Source: Figure 35 in the CS.[1]
CCD = confidential commercial discount; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; PPS = post-progression survival; QALYs = quality-adjusted life years; ToT = time on treatment; TTP = time to progression.

5.2.11.3 Scenario analyses

Additional scenario analyses were conducted by the company to explore the impact on the cost effectiveness results of several of the structural uncertainties present in the economic analyses. Besides the scenarios described in Section B 3.2 of the CS (Comparison B, C and D),[1] the company considered modifications of their base-case (Comparison A) by assuming alternative 1) hazard ratio adjustment for expected drop in TTP, 2) discount rates, 3) time horizon, 4) pre-progression survival, 5) parametric distribution for TTP, 6) parametric distribution for PPS and 7) parametric distribution for ToT.

Table 5.14 below summarises the different scenarios explored by the company and shows the impact on the ICER compared to the base-case.

Table 5.14: Scenario analyses summary

Scenario	Scenario description	Rationale	Impact on base-case ICER	
Base-case			£26,076	-

Scenario	Scenario description	Rationale	Impact on base-case ICER	
Comparison B	Haematological Malignancy Research Network (HMRN) chemotherapy KM data digitised and used to create pseudo-IPD after matching adjusted indirect comparison with Study 101-09, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering HMRN chemotherapy clinical effectiveness estimates, where possible	-£6,204	-23.8%
Comparison C	Published UK & Ireland idelalisib CUP KM data digitised and used to create pseudo-IPD, to which parametric survival models were fitted, and incorporated into the economic analysis	Exploration of the impact upon CE conclusions of considering published CUP idelalisib clinical effectiveness estimates, where possible	£20,935	80.3%
Comparison D	Best supportive care (BSC) is considered as a comparator, for the patients who are not eligible for chemotherapy, under the assumptions that patients would progress instantly in the absence of an active treatment.	Exploration of the impact upon CE conclusions of considering best supportive care (BSC) as a comparator	-£804	-3.1%
Comparison A, Hazard ratio adjustment for expected drop in time to progression in the next line of treatment	Hazard ratio set to 1 implying no drop in time to progression in the next line of treatment for chemotherapy.	Exploration of alternative assumption that all patients will respond same in this line of therapy as they have in the previous line of therapy	£1,817	7.0%
Comparison A, alternative discount rate preferences	Costs and benefits are discounted at 6%.	Discounting the benefits and costs in the future at a higher rate	£2,800	10.7%
Comparison A, alternative discount rate preferences	Costs and benefits are not discounted.	Undiscounted results	-£4,119	-15.8%
Comparison A, alternative time horizon	Costs and benefits are accumulated for 10 years.	Shorter time horizon	£5,462	20.9%

Scenario	Scenario description	Rationale	Impact on base-case ICER	
Comparison A, alternative pre-progression survival assumptions	Mortality hazard is assumed to be equal to that of a general population to model no risk of higher mortality in the pre-progression population.	Exploration of impact of no higher pre-progression mortality risk assumptions on the CE model conclusions	-£3,208	-12.3%
Comparison A, alternative parametric model choice for TTP	A Generalised Gamma parametric survival model fitted to the time to progression data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time to progression data	-£7,117	-27.3%
Comparison A, alternative parametric model choice for PPS	A Lognormal parametric survival model fitted to the post-progression survival data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of post-progression survival data	£3,785	14.5%
Comparison A, alternative parametric model choice for ToT	A Lognormal parametric survival model fitted to the time on treatment data.	Exploration of the impact upon CE conclusions of considering alternative extrapolation of time on treatment data	£2,023	7.8%

Source: Table 60 in the CS.[1]
BSC = best supportive care; CCD = confidential commercial discount; CE = cost-effectiveness; CUP = Compassionate Use Programme; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; IPD = individual patient data; KM = Kaplan-Meier; UK = United Kingdom.

Results from these scenario analyses will be explained in the subsections below.

Comparison B

In Comparison B, PFS and OS data for idelalisib were derived from Study 101-09 whereas for chemotherapy PFS and OS, MAIC adjusted HMRN database was used. Details of this comparison were already described in Section 5.2.6. Results from Comparison B are presented in Table 5.15. These results indicate that Comparison B leads to poorer health outcomes both for chemotherapy and idelalisib and lower total costs for chemotherapy, compared to the base-case (Comparison A). The decline of QALYs for the chemotherapy was bigger, this resulted in an amplified incremental QALYs and together with decreased chemotherapy costs, these resulted in a lower ICER.

Table 5.15: Comparison B: Study 101-09 vs. HMRN (chemotherapy) results, including idelalisib CCD

	Costs	QALYs	Life years*	Incremental			ICER
				Costs	QALYs	Life years	
Chemotherapy Regimens	[redacted]	1.44	2.29	-	-	-	£19,872
Idelalisib	[redacted]	3.19	5.33	£34,924	1.76	3.04	

Source: Table 61 in the CS.[1]
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

Comparison C

In Comparison C, real-world TTP data from the UK and Ireland CUP for idelalisib and for previous line therapy (as a proxy for chemotherapy) were used in the model. These data were extracted from Eyre et al. 2017.[35] Details of Comparison C were already discussed in the Section 5.2.6 of the CS.[1] Results from Comparison C are presented in Table 5.16. The costs pertaining to idelalisib and chemotherapy arms seem to be similar to the base-case. However, Comparison C resulted in a lower total QALYs for idelalisib and greater total QALYs for chemotherapy, when compared to the base-case (Comparison A). Therefore, this scenario resulted in an ICER significantly higher than in the base-case.

Table 5.16: Comparison C: Analysis including UK&I CUP data results, including idelalisib CCD

	Costs	QALYs	Life Years	Incremental			ICER
				Costs	QALYs	Life Years	
Chemotherapy Regimens	[redacted]	2.92	5.18	-	-	-	£47,011
Idelalisib	[redacted]	3.41	5.88	£22,712	0.48	0.70	

Source: Table 62 in the CS.[1]
CCD = confidential commercial discount; CUP = compassionate use programme; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.
*Note that the "Life years" results provided in the table are undiscounted

Comparison D

In Comparison D, it is assumed that patients in the comparator arm were ineligible for chemotherapy and they were assumed that they received palliative care. In the comparator arm it is assumed that patients progress immediately. Further details of this comparison were already discussed in Section 5.2.6. Results from Comparison D are presented in Table 5.17. The results for idelalisib arm in Comparison D were unchanged from the base-case, however, the life years, costs and QALYs associated with the BSC have decreased substantially since the patients were assumed to progress immediately. Based on Comparison D, idelalisib provided additional 1.21 QALYs at an additional cost of £30,473 when compared to best supportive care for patients who are ineligible for chemotherapy. The estimated incremental cost effectiveness ratio for idelalisib was thus £25,272 per QALY gained, which can be considered in the ballpark of the base-case ICER.

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: The cost effectiveness analyses were correctly performed and well-presented in general. 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 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 D: Study 101-09 vs. Study 101-09 (BSC) results, including idelalisib CCD

	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]

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Explanation of the ERG adjustments

After all the considerations discussed in Section 5.2, the ERG decided to change the company base-case. Some of the programming of these changes were already provided by the company in the model submitted together with its response to the clarification letter.

As discussed in Section 5.2, the ERG considers that the decision should be based on the cost effectiveness estimates considering all comparisons, hence the cost effectiveness threshold should be satisfied in all comparisons. Therefore, these changes will be incorporated to all comparisons. The adjustments made by the ERG were subdivided into the following three categories (according to Kaltenthaler et al.)[78]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

After these changes are implemented additional scenario analyses were performed in order to explore the impact of alternative assumptions on the cost effectiveness analyses results for each comparison.

Fixing errors

1. Fixing errors consisted of:
    a. Correcting the transition probabilities from pre-progression state, by incorporating the conditional probability of surviving from the previous cycle correctly. This correction has an impact on Comparisons A, C and D.
    b. Implementing the post-progression survival extrapolation to the model correctly. This involved adding tunnel states to the model to trace the time spent in the progression state. Also, a logical constraint was added that the post-progression mortality rate in a cycle would be always higher than the pre-progression mortality rate. This correction did not change the company base-case as exponential distribution (with memoryless property) was used in the PPS extrapolation. When other distributions are chosen, this correction will impact Comparisons A, C and D.
    c. Applying the HR=0.75 to the ToT extrapolation used in Comparison B, from the prior line therapy from Study 101-09.

Fixing violations

2. Incorporating half cycle correction.
3. Using the mean ToT estimate from the most recent data cut-off date while calculating AE cycle probabilities.

Matter of judgement

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]

Additional scenarios

The ERG conducted several additional scenario analyses where the structural uncertainties were explored after the above preferred changes had been implemented. The additional scenario analyses conducted by the ERG are listed below.

Scenario 1: Assuming price reduction for rituximab due to biosimilar availability

In this scenario, it will be assumed that the biosimilar uptake will be 100% and the biosimilar price is 50% of the original rituximab price.

Scenario 2: Assuming HR=1 for correcting time to event extrapolations from prior line therapy

In this scenario, instead of the HR=0.75 value used in the base case, HR=1 will be used to adjust for the relevant time-to-event extrapolations from prior line therapy

Scenario 3: Using different utility inputs from TA472

In this scenario, instead of using Wild et al, utility data from GADOLIN trial (3a) and from Bec et al. 2014[55] (3b) will be used.

Scenario 4: Using different CMV monitoring frequencies

In this scenario, the ERG inflates the CMV monitoring frequency estimates provided by the clinical expert by 100%

Scenario 5: Assuming different chemotherapy costs for the comparator arm

In this scenario, the ERG assumes that the cycle drug costs for the chemotherapy arm are based on the CHOP regimen (one of the least expensive chemotherapy options), and equal to £16.54 per cycle. The effectiveness is assumed to remain the same.

Scenario 6: Using minimum function instead of maximum, while calculating patient disposition

In this scenario analysis, minimum function is applied to the original time-to-event curves for logical constraints (for instance OS should be always larger than PFS, hence the number of progression free patients in a cohort would be the multiplication of cohort size with the minimum of PFS and OS at a given cycle). In the base-case, maximum function was used.

Scenario 7: Using different time to event extrapolation scenarios

Instead of the base-case extrapolation curves, the ERG will assume other plausible distributions in the extrapolations for the relevant time-to-event endpoints in each comparison. It should be noted that some of these choices were made to demonstrate the sensitivity of the cost-effectiveness estimates.

For TTP, exponential distribution is chosen as it was the second best fitted distribution in terms of BIC for both idelalisib and prior line treatment TTP.

For ToT, lognormal distribution is chosen as it was the second best fitted distribution in terms of both AIC and BIC for idelalisib.

For PPS, lognormal distribution is chosen as it was the best fitted distribution in terms of both AIC and BIC.

For OS, lognormal provided the best fit for idelalisib OS in terms of AIC and for PFS, log-logistic distribution provided the second-best fit for idelalisib PFS in terms of both AIC and BIC.

5.3.2 Results from the ERG preferred analyses

Due to the inherent uncertainty in each comparison, the ERG will provide the results for all four comparisons (A, B, C and D) and considers that the cost effectiveness from all four comparisons should be considered.

Therefore, the ERG preferred analysis and scenario analysis results will be presented for each of the four comparisons. Since the correct implementation of the PPS required the inclusion of an extensive number of tunnel states, the speed of the electronic model slowed down substantially, and therefore the ERG could not conduct the PSA for these comparisons within the time frame of the appraisal.

Comparison A

The results of Comparison A, after the ERG implemented its changes are given in Table 5.19 below

Table 5.19: (Comparison A) cost effectiveness results, after the ERG changes, including idelalisib CCD

Technologies	Total costs	Total LYs*	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Chemotherapy Regimens	[redacted]	4.99	2.71	-	-	-	-
Idelalisib	[redacted]	6.03	3.43	£23,599	1.04	0.72	£32,882

CCD = confidential commercial discount; ICER = incremental cost effectiveness ratio; Lys = life years; QALYs = quality-adjusted life years.
*Note that all the LYs results provided are undiscounted

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.

Comparison B

The results of Comparison B, after the ERG implemented its changes are given in Table 5.20 below

Table 5.20: (Comparison B) cost effectiveness results, after the ERG changes, including idelalisib CCD

Technologies	Total costs	Total LYs*	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Chemotherapy Regimens	[redacted]	2.28	1.38	-	-	-	-
Idelalisib	[redacted]	5.32	3.10	£37,164	3.04	1.72	£21,559

CCD = confidential commercial discount; ICER = incremental cost effectiveness ratio; Lys = life years; QALYs = quality-adjusted life years. *Note that all the LYs results provided are undiscounted

After the ERG changes were implemented, in Comparison B, 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.

Comparison C

The results of Comparison C, after the ERG implemented its changes are given in Table 5.21 below

Table 5.21: (Comparison C) cost effectiveness results, after the ERG changes, including idelalisib CCD

Technologies	Total costs	Total LYs*	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Chemotherapy Regimens	[redacted]	5.14	2.82	-	-	-	-
Idelalisib	[redacted]	5.70	3.21	£22,712	0.56	0.39	£58,754

CCD = confidential commercial discount; ICER = incremental cost effectiveness ratio; Lys = life years; QALYs = quality-adjusted life years.
*Note that all the LYs results provided are undiscounted

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.

Comparison D

The results of Comparison D, after the ERG implemented its changes are given in Table 5.22 below

Table 5.22: (Comparison D, for chemotherapy ineligible) cost effectiveness results, after the ERG changes, including idelalisib CCD

Technologies	Total costs	Total LYs*	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
BSC	[redacted]	4.62	2.43	-	-	-	-
Idelalisib	[redacted]	6.03	3.43	£29,426	1.41	0.99	£29,639

BSC = best supportive care; CCD = confidential commercial discount; ICER = incremental cost effectiveness ratio; Lys = life years; QALYs = quality-adjusted life years.
*Note that all the LYs results provided are undiscounted

After the ERG changes were 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.

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). Hence the ERG suggests that the results of Comparison B should be interpreted with caution.

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.

Table 5.23: Results from the additional scenario analyses conducted by the ERG after its changes to Comparison A

Scenarios	Idelalisib		chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
CS base-case	[redacted]	3.71	[redacted]	2.8	£23,762	0.91	£26,076
After the ERG preferred changes	[redacted]	3.43	[redacted]	2.71	£23,599	0.72	£32,882
Scenario 1 – Price reduction rituximab (due to biosimilar)	[redacted]	3.43	[redacted]	2.71	£25,264	0.72	£35,202
Scenario 2 – HR=1 for adjusting prior line treatment outcomes	[redacted]	3.43	[redacted]	2.80	£22,454	0.62	£35,980
Scenario 3a –Utility inputs from Bec et al. 2014	[redacted]	2.89	[redacted]	2.24	£23,599	0.65	£36,526
Scenario 3b –Utility inputs from GADOLIN trial	[redacted]	3.93	[redacted]	3.27	£23,599	0.66	£35,893
Scenario 4 – Increased CMV monitoring frequency	[redacted]	3.43	[redacted]	2.71	£23,983	0.72	£33,416
Scenario 5 – Cheaper chemotherapy costs	[redacted]	3.43	[redacted]	2.71	£27,239	0.72	£37,953
Scenario 6 – Applying minimum function instead of maximum to operationalise logical constraints on time to event extrapolation curves	[redacted]	3.43	[redacted]	2.71	£23,599	0.72	£32,882
Scenario 7a – Using different TTP extrapolation (exponential)	[redacted]	3.30	[redacted]	2.71	£23,329	0.59	£39,542
Scenario 7b – Using different ToT extrapolation (lognormal)	[redacted]	3.43	[redacted]	2.71	£24,785	0.72	£34,542
Scenario 7c – Using different PPS extrapolation (lognormal)	[redacted]	4.76	[redacted]	3.91	£24,843	0.84	£29,455

AE = adverse event; CHOP = Cyclophosphamide, doxorubicin, vincristine and prednisone; CMV= cytomegalovirus; CS = company submission; CVP = Cyclophosphamide, vincristine, and prednisone; ERG = evidence review group; ICER = incremental cost effectiveness ratio; INV = local investigator; PD = progressed disease; PS = post progression survival; QALYs = quality adjusted life years; ToT= time on treatment; TTP = time to progression.

Table 5.24: Results from the additional scenario analyses conducted by the ERG after its changes to Comparison B

Scenarios	idelalisib		chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
CS Comparison B	[redacted]	3.19	[redacted]	1.44	£34,924	1.76	£19,872
After the ERG preferred changes	[redacted]	3.10	[redacted]	1.38	£37,164	1.72	£21,559
Scenario 1 – Price reduction rituximab (due to biosimilar)	[redacted]	3.10	[redacted]	1.38	£38,082	1.72	£22,091
Scenario 2 – HR=1 for adjusting prior line treatment outcomes	[redacted]	3.10	[redacted]	1.38	£36,155	1.72	£21,004
Scenario 3a –Utility inputs from Bec et al. 2014	[redacted]	2.63	[redacted]	1.20	£37,164	1.42	£26,081
Scenario 3b –Utility inputs from GADOLIN trial	[redacted]	3.52	[redacted]	1.43	£37,164	2.09	£17,766
Scenario 4 – Increased CMV monitoring frequency	[redacted]	3.10	[redacted]	1.38	£37,558	1.72	£21,787
Scenario 5 – Cheaper chemotherapy costs	[redacted]	3.10	[redacted]	1.38	£39,201	1.72	£22,740
Scenario 6 – Applying minimum function instead of maximum to operationalise logical constraints on time to event extrapolation curves	[redacted]	3.10	[redacted]	1.38	£37,155	1.72	£21,579
Scenario 7a – Using different PFS extrapolation – (loglogistic)	[redacted]	3.13	[redacted]	1.45	£36,725	1.69	£21,791
Scenario 7b – Using different ToT extrapolation – (lognormal)	[redacted]	3.10	[redacted]	1.38	£38,851	1.72	£22,560
Scenario 7c – Using different OS extrapolation (lognormal)	[redacted]	4.20	[redacted]	1.47	£46,066	2.73	£16,855

AE = adverse event; CHOP = Cyclophosphamide, doxorubicin, vincristine and prednisone; CMV= cytomegalovirus; CS = company submission; CVP = Cyclophosphamide, vincristine, and prednisone; ERG = evidence review group; ICER = incremental cost effectiveness ratio; INV = local investigator; PD = progressed disease; PS = post progression survival; QALYs = quality adjusted life years; ToT= time on treatment; TTP = time to progression.

Table 5.25: Results from the additional scenario analyses conducted by the ERG after its changes to Comparison C

Scenarios	idelalisib		chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
CS Comparison C	[redacted]	3.41	[redacted]	2.92	£22,712	0.48	£47,011
After the ERG preferred changes	[redacted]	3.21	[redacted]	2.82	£22,712	0.39	£58,754
Scenario 1 – Price reduction rituximab (due to biosimilar)	[redacted]	3.21	[redacted]	2.82	£24,323	0.39	£62,922
Scenario 2 – HR=1 for adjusting prior line treatment outcomes	[redacted]	3.21	[redacted]	2.97	£21,408	0.23	£92,801
Scenario 3a –Utility inputs from Bec et al. 2014	[redacted]	2.69	[redacted]	2.34	£22,712	0.35	£65,305
Scenario 3b –Utility inputs from GADOLIN trial	[redacted]	3.72	[redacted]	3.37	£22,712	0.35	£64,103
Scenario 4 – Increased CMV monitoring frequency	[redacted]	3.21	[redacted]	2.82	£23,095	0.39	£59,746
Scenario 5 – Cheaper chemotherapy costs	[redacted]	3.21	[redacted]	2.82	£26,236	0.39	£67,870
Scenario 6 – Applying minimum function instead of maximum to operationalise logical constraints on time to event extrapolation curves	[redacted]	3.21	[redacted]	2.82	£22,712	0.39	£58,754
Scenario 7a – Using different TTP extrapolation (exponential)	[redacted]	3.06	[redacted]	2.82	£22,332	0.23	£95,120
Scenario 7b – Using different ToT extrapolation (lognormal)	[redacted]	3.21	[redacted]	2.82	£23,900	0.39	£61,772
Scenario 7c – Using different PPS extrapolation (lognormal)	[redacted]	4.60	[redacted]	4.00	£24,710	0.60	£41,131

AE = adverse event; CHOP = Cyclophosphamide, doxorubicin, vincristine and prednisone; CMV= cytomegalovirus; CS = company submission; CVP = Cyclophosphamide, vincristine, and prednisone; ERG = evidence review group; ICER = incremental cost effectiveness ratio; INV = local investigator; PD = progressed disease; PS = post progression survival; QALYs = quality adjusted life years; ToT= time on treatment; TTP = time to progression.

Table 5.26: Results from the additional scenario analyses conducted by the ERG after its changes to Comparison D

Scenarios	idelalisib		BSC		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
CS Comparison D	[redacted]	3.71	[redacted]	2.5	£30,473	1.21	£25,272
After the ERG preferred changes	[redacted]	3.43	[redacted]	2.43	£29,426	0.99	£29,639
Scenario 1 – Price reduction rituximab (due to biosimilar)	[redacted]	3.43	[redacted]	2.43	£29,575	0.99	£29,789
Scenario 2 – HR=1 for adjusting prior line treatment outcomes	[redacted]	3.43	[redacted]	2.43	£29,426	0.99	£29,639
Scenario 3a –Utility inputs from Bec et al. 2014	[redacted]	2.89	[redacted]	2.00	£29,426	0.89	£32,979
Scenario 3b –Utility inputs from GADOLIN trial	[redacted]	3.93	[redacted]	3.01	£29,426	0.92	£32,081
Scenario 4 – Increased CMV monitoring frequency	[redacted]	3.43	[redacted]	2.43	£29,809	0.99	£30,025
Scenario 5 – Cheaper chemotherapy costs	[redacted]	3.43	[redacted]	2.43	£29,746	0.99	£29,961
Scenario 6 – Applying minimum function instead of maximum to operationalise logical constraints on time to event extrapolation curves	[redacted]	3.43	[redacted]	2.43	£29,426	0.99	£29,639
Scenario 7a – Using different TTP extrapolation (exponential)	[redacted]	3.30	[redacted]	2.43	£29,145	0.86	£33,771
Scenario 7b – Using different ToT extrapolation (lognormal)	[redacted]	3.43	[redacted]	2.43	£30,371	0.99	£30,596
Scenario 7c – Using different PPS extrapolation (lognormal)	[redacted]	4.76	[redacted]	3.69	£29,914	1.07	£27,990

AE = adverse event; CHOP = Cyclophosphamide, doxorubicin, vincristine and prednisone; CMV= cytomegalovirus; CS = company submission; CVP = Cyclophosphamide, vincristine, and prednisone; ERG = evidence review group; ICER = incremental cost effectiveness ratio; INV = local investigator; PD = progressed disease; PS = post progression survival; QALYs = quality adjusted life years; ToT= time on treatment; TTP = time to progression.

5.4 Conclusions of the cost effectiveness section

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal. The Embase/Medline update searches referenced recognised study design filters to identify relevant information regarding costs, resource use and HRQL. The ERG was concerned that the inclusion of a facet for disease stage in the strategies may have been overly restrictive, however the broad range of searches and additional reference checking may have mitigated against some loss of recall.

The company developed a cohort-level state transition decision analytical model to assess the cost effectiveness of idelalisib for double-refractory FL, compared to the standard of care. The standard of care is chemotherapy regimens for chemotherapy eligible patients and best supportive care for patients who are not eligible for chemotherapy.

The model used a cycle length of one week and the horizon of the analysis could be considered as life-time. It consisted of five health states: pre-progression on treatment, pre-progression off treatment, post-progression, palliative care, and death. The simulation cohort enters the model in the 'pre-progression on treatment' state. In this state patients can either stop treatment (transition to the pre-progression without treatment state), experience disease progression (transition to post-progression state) or enter end-of-life palliative phase before death. In the pre-progression off treatment state, patients can experience disease progression or enter the before-death palliative phase. In progressed disease, patients can only stay in the progressed disease state or go to pre-death palliative care state. Patients remain in the palliative care state for eight cycles/weeks.

In the CS, four different comparisons were defined: A) idelalisib vs. chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09, B) idelalisib from Study 101-09 vs. chemotherapy regimens as observed in the HMRN database, C) idelalisib vs. chemotherapy regimens as used in the previous line of treatment as observed in the UK & Ireland compassionate use programme, and D) idelalisib from Study 101-09 vs. best supportive care.

Each comparison has a unique structure and different underlying set of modelling/input assumptions. Earlier versions of the same model were used in submissions to the SMC, NCPE and AWMSG for idelalisib in the same patient population.

Transition between model states under idelalisib treatment is based predominantly on Study 101-09.

Only in Comparison C (idelalisib compared to chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme) time to progression under idelalisib is based on data from the UK and Ireland compassionate use programme.

Different sources of data (prior line therapy from Study 101-09 for Comparison A, MAIC adjusted the Haematological Malignancy Research Network dataset for Comparison B, and prior line therapy from the UK & Ireland compassionate use programme) are used to describe the transition of the cohort through the model under standard of care, depending on the comparison.

Parametric extrapolations were used for all transitions in the economic model. No evidence on post treatment survival for patients on standard of care was available for Comparisons A, C and D. Therefore, in these comparisons, no difference in post progression survival between treatment alternatives was assumed. Differences in survival between treatment alternatives in those comparisons are driven by differences in progression free survival.

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. This was omitted based on the opinion of one clinical expert, and this might be subject to substantial uncertainty.

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 analyses conducted to derive these comparative effectiveness inputs were not fully in line with the recommendations outlined in NICE DSU TSD 17, which could lead to bias. The ERG considered that a covariate adjusted survival analysis might have provided a less biased 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.

The ERG identified some programming errors in Comparison A, B and C. In Comparison D, it was assumed that the patients who are receiving palliative care progresses immediately, the ERG considers that this assumption was too strong. In the literature it was suggested that some patients may respond well to the palliative care, and thus these patients receiving palliative care do not necessarily progress immediately.

The ERG concluded that the evidence and assumptions underlying each of the four different comparisons has its own limitations and shortcomings. Therefore, the decision should be based on the cost effectiveness estimates considering all comparisons.

Regarding the survival modelling done on data from Study 101-09, the ERG noted that the parametric distributions do not appear to have been chosen systematically. Additionally, the ERG thought that different distribution possibilities (joint modelling or separate modelling with the flexibility of choosing different type of distributions per arm) could have been explored by the company. The "sample inflation" method applied in the survival analysis of the MAIC data and its implications could not be verified, since the necessary details were not provided to the ERG. The ERG also has some concerns regarding the underestimation of parametric uncertainty of the survival regression coefficient estimates, due to the use of a sample inflation approach leading to artificially reduced variance. For the Erye et al. data, it was unclear to the ERG how the analyst classified the idelalisib progression and death events from the OS and PFS idelalisib KM curves.

The adverse event profile for idelalisib and chemotherapy were assumed to be the same in the CS, due to lack of data. The company argued that this is conservative for idelalisib. The ERG considers that this statement is speculative as it was not grounded on any evidence.

The utility inputs used in the model were based on a conference proceeding from 2004, and the actual values were not reported on the abstract. The ERG was wondering why the company did not use some of the mapping algorithms published in the literature. When asked in the clarification letter, the company reiterated their position, justifying by not using mapping algorithms with the typical limitations. However, the ERG thought that the estimates derived from this exercise would be still useful, considering that the utility estimate in the base-case is from a non-verifiable study dating back to 2004.The ERG identified some additional utility sources from a previous appraisal in the refractory FL. Also, the ERG considered that age-based utility decline should be implemented, since assuming the same utility for a patient who stays in the same health state for consecutive years would overestimate the actual utility that patient experiences.

In terms of resource use, the ERG identified that wastage costs for idelalisib and mean dose intensity for chemotherapy were not included in the economic model. Furthermore, the rituximab prices were not reflecting the biosimilar rituximab availability in the market. The ERG deemed that the choice of inputs for the resource use estimates from the literature and expert meetings were rather arbitrarily.

The ERG has serious concerns on the lack of the reporting of the model validation efforts. The company declined to provide these, even tit 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 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). Hence the ERG suggests that the results of Comparison B should be interpreted with caution.

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.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG preferred changes to the company base-case were presented in Section 5.3.

These changes are applied to each comparison. In Table 6.1, it can be seen how each individual change affects the ICER for Comparison A (company's base-case); and the last row shows the combined effect of all changes simultaneously.

Table 6.1: Revised Comparison A, incorporating corrections and amendments identified by the ERG

Scenarios	idelalisib		chemotherapy		Inc Costs (£)	Inc QALYs	ICER (£)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
0. CS base-case	[redacted]	3.71	[redacted]	2.8	£23,762	0.91	£26,076
1. Fixing errors	[redacted]	3.53	[redacted]	2.79	£22,803	0.75	£30,449
(1+2a). Fixing errors and half cycle correction	[redacted]	3.53	[redacted]	2.79	£22,471	0.74	£30,315
(1+2b). Fixing errors and applying the most recent ToT for the adverse event probability calculation	[redacted]	3.54	[redacted]	2.79	£22,378	0.75	£29,834
(1+3). Fixing errors and wastage costs	[redacted]	3.53	[redacted]	2.79	£24,118	0.75	£32,205
(1+4). Fixing errors and applying mean dose intensity to chemotherapy arm	[redacted]	3.53	[redacted]	2.79	£23,036	0.75	£30,760
(1+5). Fixing errors and applying age based utility decline	[redacted]	3.43	[redacted]	2.71	£22,803	0.72	£31,488
(1 to 5 all) Comparison A after the ERG preferred changes	[redacted]	3.43	[redacted]	2.71	£23,599	0.72	£32,882

AE = adverse event; CHOP = Cyclophosphamide, doxorubicin, vincristine and prednisone; CMV= cytomegalovirus; CS = company submission; CVP = Cyclophosphamide, vincristine, and prednisone; ERG = evidence review group; ICER = incremental cost effectiveness ratio; INV = local investigator; PD = progressed disease; PS = post progression survival; QALYs = quality adjusted life years; ToT= time on treatment; TTP = time to progression.

7. END OF LIFE

In the 2016 addendum to NICE methods guide, the end of life criteria are described as follows[79]:

In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

The company describes the end of life considerations in section B.2.13 (page 77-78) of the CS. According to the company, FL patients with double-refractory disease have a life expectancy that typically falls below 24 months with current treatment options. In addition, the estimated life years gained with idelalisib range from 0.70 to 3.04 years in economic modelling. Therefore, the company concludes that idelalisib for the treatment of double-refractory FL is thought to meet NICE end of life criteria.

ERG comment: Based on UK HMRN data the two-year OS rate in FL patients with disease refractory to rituximab and an alkylating agent and treated with chemotherapy at third-line was [redacted]; and the median OS in FL patients with disease refractory to rituximab and an alkylating agent and treated with chemotherapy at third-line was [redacted] months. The company then present the same data for a population with characteristics matched to the study 101-09 population. It is unclear why this done as the UK HMRN population is a better reflection of the population in the NICE scope than the Study 101-09 population (See section 3.1 of this report). The ERG concludes that based on UK HMRN data, the life expectancy of FL patients with double-refractory disease is very close to 24 months. In addition, in the economic model, the number of life years gained for standard of care was never below two years in all comparisons.

The second criterion is based on a matched adjusted indirect comparison; therefore, the results are very uncertain and are certainly not robust.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The company presented evidence from four idelalisib studies. The main trial is Study 101-09, this is a multi-centre, single arm study investigating the efficacy and safety of idelalisib in patients with iNHL refractory to rituximab and an alkylating agent. Study 101-09 enrolled patients with different types of iNHL, but the FL population was the largest population (72 of 125). Data collected via the disease registry for the HMRN ([redacted]) was included to provide evidence for the comparator: chemotherapy regimens currently used to treat double-refractory FL in UK practice.

Results from Study 101-09 based on the June 2014 database lock were used in the HMRN matching-adjusted indirect comparison and in the economic analyses. Results based on the June 2015 database lock were presented in the main submission. Where possible we have presented both data sets. Median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks. Median PFS was 11.0 months in the FL population for both data-sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 data-set, this was not reported for the June 2014 data-set.

In the FL population, the overall response rate (ORR, 95% CI) was 55.6% (43.4, 67.3) as assessed by the independent review committee (IRC), comprising 10 complete responses (CRs, 13.9%) and 30 partial responses (PRs, 41.7%) in the June 2015 data-cut. Response data from June 2014 are similar using IRC assessment, but were not reported for investigator assessment.

Health-related quality of life (HRQL) was assessed with the Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) scale. Median best change from baseline in FACT-Lym total score was 7.5 (95% CI: -39.0 to 47.0). The confidence interval was quite wide and the median did not exceed the minimally important difference threshold of 10-11.

The company performed a matching-adjusted indirect comparison (MAIC), comparing idelalisib with alternative chemotherapy, using data from the 101-09 study for idelalisib and HMRN data for the comparator. The MAIC included 72 patients with FL from study 101-09 and [redacted] Variables for matching included in the MAIC were [redacted] The respective two-year OS rate of FL patients treated with idelalisib in study 101-09 was 69.8% and the one-year PFS rate was 43.0%, in the data-cut used for MAIC (11 June 2014 DBL).

The majority of patients enrolled in Study 101-09 experienced at least one AE, many of which were deemed to be treatment-related; 25% of FL patients discontinued treatment due to an AE. In both the total population and the FL population, the most common Grade ≥3 AE was neutropenia, occurring in 27 (21.6%) and 16 (22.2%) patients, respectively. Other common Grade ≥3 AEs included diarrhoea and pneumonia, both reported by more than 10% of patients.

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). Hence the ERG suggests that the results of Comparison B should be interpreted with caution.

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 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.

8.2 Strengths and limitations of the assessment

The ERG had several problems with the way the company performed the MAIC. First of all, it seems counter-intuitive to try to match the HMRN data to the baseline characteristics of Study 101-09 patients. The HMRN population includes all relevant patients who have been prescribed idelalisib in a real-world UK setting; as such the HMRN population seems more representative of the population defined in the NICE scope than the 101-09 study population. Study 101-09 had specific inclusion criteria, such as, 'Karnofsky performance score of 60 or higher (on a scale of 0=death and 100=complete absence of symptoms)' and 'radiographically measurable disease (defined as ≥1 lymph node with perpendicular dimensions measuring ≥2.0 x ≥1.0cm)', that may have influenced patient characteristics. Therefore, the ERG would have preferred to match the 101-09 study population to the characteristics of the HMRN population. That way, the resulting adjusted population might have been larger than the resulting adjusted HMRN sample size of [redacted] Secondly, the ERG did not agree with the exclusion of variables from the MAIC. [redacted] However, given the small sample sizes, not taking characteristics from one or a few patients into account in the analyses may similarly give too much weight to the characteristics of the remaining patients. [redacted] However, even though variables

may be correlated, these variables might still be important for matching the populations in the MAIC. Therefore, we asked the company to repeat the MAIC by using the Study 101-09 data as the source of IPD and matching it to summary HMRN data, using the most recent data for Study 101-09; and to provide MAIC results including all variables (see Clarification letter questions A19b and A23). However, the company declined to repeat the MAIC by using the Study 101-09 data as the source of IPD and matching it to summary HMRN data. The analysis including all variables in the MAIC model [redacted]. These differences illustrate the concerns about the reliability of the MAIC analyses.

Overall, there is uncertainty associated with these analyses, primarily stemming from the small sample of FL patients with disease refractory to rituximab and an alkylating agent identified in the HMRN cohort and because some variables were excluded from the MAIC, such that potentially meaningful differences in treatment history could not be adjusted for.

The main strength of the cost effectiveness submission is the searches conducted. The majority of the cost effectiveness searches in the CS were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. The Embase/Medline update searches referenced recognised study design filters to identify relevant information regarding costs, resource use and HRQL. The ERG was concerned that the inclusion of a facet for disease stage in the strategies may have been overly restrictive, however the broad range of searches and additional reference checking may have mitigated against some loss of recall.

Also, the structure of the model developed by the company is in line with other, commonly used models used in oncology. The model includes relevant adverse events, utilities and costs. The cost calculations were quite detailed. Sensitivity analyses were performed on the model parameters.

The main weakness of the cost effectiveness section of the company submission is the non-systematic way of synthesising different pieces of clinical evidence, stemming from different studies, without proper statistical adjusting as outlined in analysis guidelines (e.g. NICE TSD 17). As the company provided multiple comparisons, some comparing the same comparators, but they are differed not only in terms of clinical inputs used but also in terms of underlying modelling assumptions/structure, sometimes it is impossible to pinpoint the actual reason of a discrepancy between the outcomes of the comparisons.

The health-related quality of life section of the company submission is also lacking transparency. The main utility source, Wild et al, is just a conference proceeding, dates back to 2004, and the utility values were unverifiable (by the ERG). The choice of different utility inputs seems also have a significant impact on the cost effectiveness results.

According to the ERG, additional scenarios could have been conducted, given the inherent structural uncertainties in the comparisons provided in the CS. Furthermore, the ERG considers that the reporting of the validation efforts for the CS was clearly inadequate, together with the errors identified in the model and the gap between the model and trial outcomes, have decreased the level of confidence to the economic analysis.

8.3 Suggested research priorities

A randomised controlled trial in patients with double-refractory FL in order to determine the comparative efficacy of idelalisib in relation to available treatment options or best supportive care (BSC) is warranted.

Given the lack of randomised evidence, the comparative effectiveness estimates should be obtained from non-randomised evidence using well-established, recommended techniques (covariate adjusted regression analysis) as outlined in NICE TSD 17.

As the utility estimates are from a non-transparent source, dating back to 2004 any utility elicitation study, including mapping algorithms from FACT-Lym using FACT-G scores, despite their limitations, would be useful.

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Appendix 1: Additional limitations of the CS search strategies

Additional limitations of the CS searches not covered in the main body of the report:

Clinical effectiveness:

- Missing trade name zydelig for idelalisib in all searches. However, any loss of recall would have been mitigated by use of Emtree in the Embase search and is unlikely to have greatly affected the recall of results.
- Limited use of synonyms and CAS registry numbers for Rituximab i.e. blitzima or ctp10 or idec 102 or rg105 or ritemvia or or rixathon or riximyo or ro 452294 or ro452294 or truxima or tuxella or 174722-31-7. However, any loss of recall would have been mitigated by use of Emtree in the Embase search and is unlikely to have greatly affected the recall of results.
- Redundant terms in the interventions facet, however this would not have impacted on the overall recall of results.
- The ERG queried the final results line of the Embase search (Table 1, Appendix D). Line #129 (all facets + RCT filter/English only /1990-2014) reported retrieving 2775 records and line #131 (all facets + Observational studies filters/English only /1990-2014) retrieved 3387. However, the final line which combined both sets of results only reported retrieving 368. In their response to clarification the company confirmed that this was due to a typographical error and confirmed that the final total should have read 3,688 and provided a full corrected strategy.

Cost effectiveness

- The ERG queried an inconsistency in the line number for Tables 25 and 26, appendix G where the line numbers appeared incorrect (i.e. did not start at #1 which did not match combinations within the lines). However, this appeared to be a reporting error and did not affect line combinations within the strategy. The company provided revised strategies in their response to clarification.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **15 August 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Misleading ERG criticisms of model validity

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
There are several instances where the validity of the cost-effectiveness model is unfairly criticised and where the queried validity of the model is conflated with other criticisms including falsely described *"programming errors*" (Issue 2): Page 15: "*The ERG has serious concerns regarding the lack of the reporting of the model validation efforts. The company declined to provide these, when this was requested in the clarification letter. This, in combination with the programming errors in the model and the gap between trial outcomes and the model outcomes decreased our level of confidence in the validity of the economic model*" Page 16, repeated verbatim on Page 122: "*Furthermore, the ERG considers that the reporting of the validation efforts for the CS was clearly inadequate, and that together with the errors identified in the model and the gap between*	Please remove all unjustified and misleading criticisms of model validity and any conflation of invalid criticisms for the company's cost-effectiveness analysis.	In response to ERG Clarification Question B22, requesting "all the details of the validation exercise mentioned in the CS" and querying whether our validation exercise aligned with the ERG-identified *AdvisHE* tool, we replied as follows: "*We developed our submission in accordance with the NICE Single technology appraisal user guide for company evidence submission template (nice.org.uk/process/pmg24) and guide to the methods of technology appraisal (nice.org.uk/process/pmg9). The exact details of the model quality control process are the confidential commercial property of the company who built the economic model and cannot be shared, but we can confirm that the aspects of validation outlined in the AdvisHE publication the ERG refers to were considered as standard. We encourage the ERG to provide independent and fair comment on the validity of our approach to cost-effectiveness analysis as part of their function in this appraisal process, to help the committee to reach a fair and*	Describing the company's validation efforts as lacking is justified as is presented in Section 5.2.12 of the ERG report. Despite including the internal quality-control checklist from the company who built the model in the proforma response, this does not seem to be filled in. How the model passed (or did not) the tests in the checklist are not discussed either. Thus, the ERG has no reason at this time to change the last sentence of the first paragraph in Section 5.2.12: "The details and results of the technical validation of the economic model were not reported". The gap between trial outcomes and model outcomes are discussed for example in the text accompanying Table 5.18 in the ERG report. This table

the model and trial outcomes, these factors have decreased the level of confidence in the economic analysis." Page 101: "*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*." Page 102: "*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*		*important decision*." We stand by this reply and are disappointed that the ERG have let down the stakeholders of this appraisal in their failure to provide independent, informed and fair critique of the validity of our approach to cost-effectiveness analysis. In the interest of transparency and the hope that the fairest possible and evidence-based decision can be made by the committee, the company who built the economic model have assented to share the internal quality-control checklist used as commercial-in-confidence material, alongside this proforma response. In summary and conclusion sections of their report, the ERG cite "*programming errors*" and "*the gap between trial outcomes and the model outcomes*" as additional reasons to mistrust our economic analysis. As described in Issue 2, these "programming errors" comprise: (i) one oversight that affected Comparison B scenario analysis only and (ii) two approaches to modelling that are as intended and as described in the CS and cannot be described as errors. As the ERG have therefore identified no errors in the economic base case, it is misrepresentative in the extreme for the	shows a difference in modelled median OS and observed median OS of 20 months. This is not even discussed in the CS, despite this gap indicating a clear issue with the internal validity of the model. Regarding the errors identified (and corrected) by the ERG we refer to the response to issue 2. Overall, the ERG considers that while the company is free to disagree, the criticisms of model validity are properly justified in the ERG report. The company points out that on Page 101 of the ERG report in Section 5.2.11, the ERG state "*The cost effectiveness analyses were correctly performed and well-presented in general*". We see how this might be misleading in the context of our critique on the validity of the model. Thus, we have now changed the sentence into "Even though the results were presented in an appropriate way, the ERG

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." Page 115: "*The ERG has serious concerns on the lack of the reporting of the model validation efforts. The company declined to provide these, even tit* [sic] *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*."		ERG to refer to "*programming errors*" in key summary sections of their report in a way that is guaranteed to lessen an independent reader's confidence in the company's economic analysis. On Page 101 of the ERG report in Section 5.2.11, the ERG state "*The cost effectiveness analyses were correctly performed and well-presented in general*". This ERG statement reflects the absence of errors in the company base case and the clarity and transparency of implementation of a flexible decision model, but does not reflect the summary or conclusion sections of the ERG report. The "gap" between trial outcomes and model outcomes is a transparent and noted feature of the base case analytical approach. It is not explained by the ERG why they feel that this is a reason for mistrust, and certainly should not be conflated with other dubious issues to falsely critique the validity of the economic model. Overall, we hope and trust that the justification for our proposed amendment is clear, as this is an important issue with a potential to misinform committee members.	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". Finally, the company has indicated a typo on page 115 of the ERG report. This has been amended.

Issue 2 False and poorly explained account of "errors" and ERG corrections and implementation of ERG changes to the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In the *Explanation of the ERG adjustments* on Page 103 of the ERG report, "*Fixing errors*" is defined explicitly as "*correcting the model where the company's electronic model was unequivocally wrong*", and go on to state the following: "*Fixing errors consisted of:* *a. Correcting the transition probabilities from pre-progression state, by incorporating the conditional probability of surviving from the previous cycle correctly. This correction has an impact on Comparisons A, C and D.* *b. Implementing the post-progression survival extrapolation to the model correctly. This involved adding tunnel states to the model to trace the time spent in the progression state. Also, a logical constraint was added that the post-progression mortality rate in a cycle would be always higher than the pre-progression mortality rate. This*	We request removal of all false descriptions of ERG adjustments "a." and "b." as "fixing errors". We also request addition to the ERG report of careful and accurate description and justification of the ERG adjustments made to the company approach to health state transitions in the cost-effectiveness model. We note that it is good and usual practice for the ERG to clearly report model code changes in an appendix to the ERG report. Kleijnen Systematic Reviews ERG took this good and usual approach in NICE TA 494, and it is not clear why a lower-quality approach has been taken by the same ERG in this appraisal. We also note that it is good, transparent and usual practice for the ERG to programme their changes to the CS model as reversible switches to allow the user to understand easily the implications of each change, and to report the iterative effect of ERG changes to the model, from CS base case to ERG-preferred base case. This allows the committee to understand the importance of the different ERG amendments for results, to allow that information to inform their preferred base case. In this case, the ERG hard-coded changes they defined as "fixing errors" in the model,	The application of transition probabilities from the pre-progression state in the company model is logical and consistent with the description of the model in Section B.3.2 of the CS and should not be described as erroneous. The ERG's imposed changes to this logic cannot be described as "corrections" without explanation, including the changes to assumptions that the ERG's amendment creates. We encourage the ERG's analyst(s) to think carefully about what they are imposing and explain their rationale. Given the contents of the ERG Clarification Questions and the apparent misunderstanding of the limitations of the prior line effectiveness data in the CS shown at that stage, we ask that the ERG takes time to objectively reconsider their preferred approach here. The company's implementation of the post-progression health state is consistent with the model	This is not a factual error. Regarding the remark from the company that 'it is good, transparent and usual practice for the ERG to programme their changes to the CS model as reversible switches', this is something that can only be done if time allows. In other situations, the ERG may have multiple versions of the model in order to assess step by step the impact of changes. However, in case of clear errors in programming, the ERG will always correct these together, as it is unlikely that the committee will want to decide which programming-errors to accept and which not. The errors identified by the ERG are summarised in the beginning of Section 5.3.1 of the ERG report. Errors regarding transition probabilities are discussed in Section 5.2.6. The solution proposed by the ERG was mentioned in sections 5.2.6 and 5.3.1 of the ERG report.

correction did not change the company base-case as exponential distribution (with memoryless property) was used in the PPS extrapolation. When other distributions are chosen, this correction will impact Comparisons A, C and D. *c. Applying the HR=0.75 to the ToT extrapolation used in Comparison B, from the prior line therapy from Study 101-09*."	overriding the CS approach. This lacks transparency and is not amenable to the provision of useful iterative results for decision makers, moving from the CS testing different ERG preferences. With recognition that ERG adjustments for a. and b. cannot be defined as "fixing errors", we request that the ERG reimplement these changes with the functionality to reverse back to CS assumptions, and amend ERG report Table 6.1 to show the committee and other stakeholders the impact of a. and b. upon the CS base case, corrected for c.	description in Section B.3.2 of the CS and should not be described as an error. For the ERG to provide a definition of an error and then illustrate poor understanding of their definition of an error on the same page of the ERG report is extremely concerning. The ERG's reprogramming of the "post-progression survival" health state into over 2000 tunnel states is a modelling choice. If the ERG prefer this approach, they should both recognise this as a choice and reflect on its negative consequences. The addition of tunnel states means an extra 2,000 columns containing over 4,000,000 calculation-containing cells in each patient flow worksheet in the ERG-amended model versus the CS model. As well as the quality control implications of such substantial expansion of model logic, the model execution time is noticeably affected. A 4,000-iteration probabilistic sensitivity analysis can be executed in <15 minutes with the CS model versus >5 hours with the ERG-amended model, on the same machine.	However, the ERG acknowledges that this might require a more detailed explanation. Therefore, further details are given below: The *first error* relates to the probability to go from pre-progression to post-progression, column AA on the sheets "PF_Idela" and "PF_CurrCare". At some time point, these probabilities become *negative*, which obviously indicates an error in the formula. The company claims that the model works as intended, but the ERG cannot imagine that the model was intended to have negative (and thus invalid) probabilities included in the calculations. The formula looks as follows ((1-AB16)*K15-K16)/K15. This can be simplified to (1-AB16) – (K16/K15) or in words to 1- death – prob(preprog to preprog). Based on the fact that the formula did not use this simplified form but a more complex one, we assumed that what was intended was (1-death)*(1-prob(preprog to preprog)) or in excel form (1-AB16)*(K15-K16)/K15. After the correction in this column, it is clear that now the previous column (Z) also needs to be corrected, as the 3 probabilities

			from pre-progression no longer add up to 1. The most obvious way to correct this is to make the unconditional probability to stay in pre-progression conditional on being alive, i.e. by multiplying the unconditional probability by (1-death), just as for column AA. Therefore, the error in the formula is unequivocal, but it is possible that our way of correcting this is not in line with the intentions the programmers had before making the error. Regarding the *second error*, the problem lies in the fact that patients transitioning from pre-progression to post-progression do so at various points in time. Once that happens, according to the model structure, patients are supposed to follow the PPS curve. In the Excel model, patients that enter into the post-progression state at time t are assigned the probability of PPS at time t. However, these patients should start the curve at t=0, as all newly progressed patients are not the same as patients who progressed for example 20 cycles earlier. In the base case, where PPS is

			estimated by an exponential distribution this ‘error’ does not cause an effect to the ICER, since an exponential distribution leads to the same transition probability for each cycle. So this makes the claim of the company in this proforma that this feature of the model is as intended seem reasonable. However, in the CS it is not discussed that this was the reason to select the exponential distribution. Other reasons unrelated to this issue are presented in the CS (see e.g. pp. 94-96). Furthermore, as shown in Table 60 of the CS, a scenario was implemented using a lognormal distribution instead of the exponential, without highlighting the problems of assuming a non-exponential distribution. Hence, without any statement in the CS that for PPS only the exponential distribution can be used as the current functionality of the model (no tunnel states) does not allow for different distributions, the ERG cannot treat this feature ‘as intended’, which makes it an error. Finally, in column CCC of the ‘ERG model’, a minor change was made to correct for potential negative

			costs based on a relapse event. Finally, the company remarks on the significantly increased computational time when running a PSA with the model that includes the tunnel states. Whilst this is unfortunate, obviously a correct model is to be preferred over a quick model.

Issue 3 Misleading and unbalanced critique of key cost-effectiveness scenarios (Comparisons B, C and D)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The CS provided a balanced account of three different data-driven approaches to estimate the expected cost-effectiveness of idelalisib for chemotherapy-suitable patients; Comparisons A (base case comparison to Study 101-09 prior therapy), B (scenario comparison to MAIC-adjusted HMRN data) and C (incorporation of Eyre et al reported Compassionate Use Programme (CUP) idelalisib and prior therapy data to Comparison A where possible); yet the ERG seem to have critiqued Comparison B to a far greater extent than Comparison C. In doing so, the ERG may have lost sight of the	Please provide balanced critique of the absolute and relative limitations of Comparisons B, C and D, in summary and conclusion sections in particular.	The ERG report's unbalanced representation of the absolute and relative limitations of key cost-effectiveness scenarios generally, and Comparisons B and C in particular, are potentially misleading to the committee. The limitations of Comparison C were documented alongside limitations of other comparisons in the CS, and in the ERG report's critique of indirect comparisons as part of the Clinical Effectiveness critique (Page 55), the ERG state the following: "*The ERG requested details of the statistical analysis methods used for the indirect comparisons between idelalisib and prior therapy but they were not provided by the company (clarification response A24). Full details of the data collection methods*	The ERG considers that the critique of Comparisons B, C and D is balanced. If Comparison B is critiqued in a greater extent, this is simply because it involves a more complicated methodology (MAIC). Comparisons C and D are in that sense (methodologically) rather simple. In any case, limitations of all four comparisons are discussed in the ERG comments, for example after Section 5.2.6. In particular, as mentioned on page 72, "Comparison C is identical to Comparison A, except for the source of the TTP data for idelalisib and chemotherapy". Therefore, it is obvious that "all the issues related to Comparison A are

relative limitations of the different Comparisons, and this carries a risk of misleading the committee and other stakeholders who look to the ERG report as an evidence summary. The ERG report urges the reader to interpret Comparison B with caution in key summary and conclusion sections but does not use the same language for other Comparisons. This seems to be driven at least partly by the fact that idelalisib is estimated to be more cost-effective in this comparison versus others. As an illustrative example, on Page 120, in their *Statement of principle findings*, the ERG state the following: "*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). Hence the ERG suggests that the results of Comparison B should be interpreted with caution*." While chemotherapy-eligible patients who receive chemotherapy may be expected to have better survival prospects than chemotherapy-ineligible patients who receive BSC, the		*were also not available and for Study 101-09, the company states in their response to clarification letter (question A.24) that these data were "primarily based on clinician recall (presumably supported with data collected in routine clinical practice)". This suggests that these data were retrospectively collected and may have been subject to selection bias and error. As the data were retrospective and from the same study the estimates for idelalisib and chemotherapy were based on the same patients but different time periods for the two treatments. This means that survival cannot be accurately measured and should not be statistically compared between the two groups. Without knowing whether the analysis was a simple statistical test between the groups or a more complex survival model adjusting for other factors, or how censoring was performed, it is not possible to judge whether this analysis was reliable.* *"As the company themselves highlight in their response to clarification letter (Question B.9b), the inability to differentiate the effect of idelalisib versus chemotherapy upon patient outcomes from the effect of an additional line of therapy on patient outcomes using study 101-09 data [highlights] the difficulty of answering the decision problem generally. The ERG considers that comparisons between idelalisib and last prior therapy using the same patient population from the same*	relevant for Comparison C". Comparison D is also similar to Comparison A (idelalisib arm is the same) except for the comparator arm. Therefore, the ERG felt that a more detailed discussion of Comparisons C and D was not needed. The ERG agrees with the second issue raised by the company here. The reason why results from Comparison B should be interpreted with caution is not that it leads to a lower ICER but because of the methodological limitations discussed throughout the ERG report. The sentence "*Hence the ERG suggests that the results of Comparison B should be interpreted with caution*" mentioned by the company (page 120) may suggest otherwise. Therefore, this has been removed from the ERG report.

difference between Comparison B and D outcomes is surely more likely to be explained by the transparent limitation of Comparison D than by reasons to interpret Comparison B with caution.		*study is highly unreliable and should be interpreted with extreme caution*." The only ERG comment on any of these issues in relation to cost-effectiveness Comparison C appears on Page 83 of the ERG report: "*It was unclear to the ERG how the analyst classified the idelalisib progression and death events from the OS and PFS idelalisib KM curves from Eyre et al. 2017. The details of this classification process were not provided despite the ERG's request*." The ERG's reporting of non-provision of information is in itself misleading, but the important point here is that there is no further mention of the limitations of Comparison C or how CUP data limitations affect cost-effectiveness results based on CUP evidence anywhere else in the ERG report, let alone in the summary and conclusion sections where the ERG-perceived limitations of Comparison B and the underpinning MAIC analysis of HRMN data are clearly set out. The imbalance in the ERG's approach carries a real risk of misleading the reader and ultimately, could mislead decision-makers.	

Issue 4 Provision of evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
There are several instances where it is noted that no evidence was provided: Page 10 - “No evidence was provided for best supportive care in people for whom chemotherapy is unsuitable.” Page 11 - “No adverse events were reported for comparators. Therefore, it is not possible to say anything about the relative safety profile in comparison to chemotherapy or best supportive care.” Page 22 (Table 3.1) - “No clinical effectiveness evidence is presented for BSC as a comparator.” Page 25 - “No clinical effectiveness evidence was provided for best supportive care in people for whom chemotherapy is unsuitable.” Page 50 - “No adverse events were reported for comparators. Therefore, it is not possible to say anything about the relative safety profile in comparison to chemotherapy or best supportive care.” Page 56 - “No evidence was	In all instances, please revise wording to represent the paucity of evidence available and make it clear that no evidence for best supportive care (in people for whom chemotherapy is unsuitable) or adverse event data for either comparator (chemotherapy or best supportive care) was identified through systematic review. For example: “No evidence was identified for best supportive care in people for whom chemotherapy is unsuitable” “No adverse event data were identified for comparators in the target population” “No clinical effectiveness evidence was identified for BSC as a comparator”	It is important for the NICE committee and other relevant decision makers (including patients) to understand the limitations of the evidence base available to help address the decision problem, and to recognise that all relevant evidence identified has been provided in the CS.	Not a factual error.

provided for best supportive care in people for whom chemotherapy is unsuitable." Page 57 - "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." Page 120 - "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."			
On page 19 the ERG note: "However, it would be more relevant for the CS to present up-to-date survival rates (in the rituximab era) instead of pre-rituximab era rates."	Please revise wording to recognise that up-to-date survival rates are provided for the target population being considered as part of clinical effectiveness data presentation and end-of-life considerations. For example: "Although it would be more relevant for the CS to present up-to-date survival rates (in the rituximab era) instead of pre-rituximab era rates; these data are presented for the target population in subsequent sections."	The current summary misrepresents the data that have been presented within the CS.	Not a factual error.
When discussing comparators in Section 3.3 (page 25), it is noted that data for chemotherapy was collected via the HMRN but additional sources of chemotherapy evidence are not acknowledged.	Please fully outline the comparator evidence provided. For example, add the following: "Additional data for the main comparator (chemotherapy regimens) are also provided from prior line therapy analysis in study 101-09 and the UK and Ireland CUP."	The current summary is missing detail on all comparator evidence provided.	Not a factual error. This is clearly reported in the remainder of the ERG report.

Issue 5 Misrepresentative critique of company approach alignment with NICE Technical Support Document 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG makes and repeats several factually misrepresentative criticisms of the company approach with reference to NICE Technical Support Document 17. Unless amended appropriately or removed, these may mislead the Committee: Page 16, repeated Page 122: "*The main weakness of the cost effectiveness section of the company submission is the non-systematic way of synthesising different pieces of clinical evidence, stemming from different studies, without proper statistical adjusting as outlined in analysis guidelines (e.g. NICE TSD 17).*" Page 70*: "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. Firstly, the method selection algorithm sketched in Figures 2 and 3 in TSD 17 was not used."* Page 113: "*The company generated comparative clinical effectiveness inputs for the*	Please amend or remove these statements, to reflect the care and justification provided in the CS and reiterated and further explained in response to ERG Clarification Question B8.	The ERG's critique of the company's alignment with NICE Technical Support Document 17 directly discredits the robustness of the economic evidence presented by the company, and so it is important that such critique is specific, justified and accurate. We find the ERG's factually misrepresentative criticisms of the company approach with reference to NICE TSD 17 surprising and disappointing given our care to spell out our approach with respect to TSD 17 recommendations in our response to ERG Clarification Question B8.	This is not a factual error. We refer to the text below on Page 71 of the ERG report: "The ERG disagrees with the company on the last two points. Firstly, the suspected correlation between the "number of prior line therapies" and "the treatment received after the last progression" is not a reason to dismiss covariate adjustment analysis, but on the contrary, it suggests that "the number of prior line therapies" is either a confounding or an intermediate factor, and therefore the analysis should be adjusted for, together with other possibly confounding/intermediate factors. Secondly, the PFS, OS, PPS and PrePS data associated with the previous line treatment in Study 101-09 should be available to the company. Basically, the PFS of the previous line treatment is the same as the TTP of the previous line treatment, since there is no pre-progression

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 analyses conducted to derive these comparative effectiveness inputs were not fully in line with the recommendations outlined in NICE DSU TSD 17, which could lead to bias." Page 123: "*Given the lack of randomised evidence, the comparative effectiveness estimates should be obtained from non-randomised evidence using well-established, recommended techniques (covariate adjusted regression analysis) as outlined in NICE TSD 17*."			death. Therefore, PrePS would be equal to 1. If idelalisib was initiated immediately after the previous line treatment progression, the PPS associated with the previous line treatment would be the OS after idelalisib initiation, and finally the OS related with previous line treatment would be the sum of the TTP (of previous line) and the OS after idelalisib initiation. This would lead to a situation that OS of the prior line therapy is always higher than the OS of idelalisib, and this might be attributable to the study design, and the fact that no deaths occurred during prior line therapy. However, given the uncertainties of the clinical effectiveness, the ERG would have liked to see an area under the curve approach based analysis, using the PFS and OS from idelalisib and prior line therapy as discussed above."

Issue 6 Applicability of study 101-09 data to UK patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
There are several instances where it is noted that the study	Aligning to the ERG comment on Page 14 that "It was not obvious to the ERG to what extent	This would better reflect the evidence and full consideration	Not a factual error.

101-09 population may not be representative of UK patients: Page 10 - “The population of double-refractory FL patients in this study may not be representative of UK patients in the typical clinical setting (see section 3.1).” Page 24 - “The population of double-refractory FL patients in this study may not be representative of UK patients in the typical clinical setting .” Page 56 - “The population of double-refractory FL patients in this study may not be representative of UK patients in the typical clinical setting (see section 3.1).” Page 118 - “It is unclear why this done as the UK HMRN population is a better reflection of the population in the NICE scope than the Study 101-09 population (See section 3.1 of this report).”	the population from Study 101-09 was reflective of the double refractory FL population in the UK.” please consider revising wording of other mentions of applicability to clearly acknowledge that there is no clear conclusion on how representative the 101-09 patients are of UK patients in the typical clinical setting. For example: “It is not obvious how the population of double-refractory FL patients in study 101-09 reflect UK patients in the typical clinical setting”	given to this point, covering both supporting and questioning factors summarised below. <u>Supporting factors</u> As patients in the UK are typically treated with R-chemo at first- and second-line, the double-refractory nature of disease associated with study 101-09 patients aligns to this practice. Clinical expert opinion is that baseline patient characteristics and treatment history of the study 101-09 population is generally reflective of NHSE FL patients who would benefit from idelalisib.(1) <u>Questioning factors</u> There were no UK sites involved in the study and therefore no UK patients enrolled. The CADTH previously noted that patients were asymptomatic and somewhat younger than patients in the typical clinical setting. This is a common limitation of clinical trial evidence versus real-world evidence. Differences are observed across the HMRN double-refractory FL and study 101-09 datasets, but it is acknowledged in the CS that these datasets are investigating different	

		populations, and differences can be associated to these rather than a question of applicability per se. For example, HMRN data were cut to look at patients receiving third-line chemotherapy whereas study 101-09 offered a new treatment to patients who had exhausted current options. In the UK setting, there are likely patients representing both datasets that could be considered for idelalisib treatment. Of note, differences across HMRN and study 101-09 do not all align to a more favourable prognosis for the study population: more patients in study 101-09 had bulky disease, a longer duration of disease and a more extensive treatment history. The previous CADTH comment that the patient population studied in the trial might be "more favourable than in the typical clinical setting" does not therefore necessarily hold for the UK setting.	

Issue 7 Quality assessment of included studies from clinical SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
When commenting on the quality assessment for the clinical SLR, there is a misrepresentation of the approach taken where the ERG	Please remove this comment.	The description of tools used to assess studies identified in the economic SLR have been incorrectly applied to the clinical	Not a factual error.

comment that: Page 30 - “No formal, validated quality assessment or risk of bias tools were used to assess the quality of included studies. Instead, a custom tool was presented, which comprised nine questions that were informed by two documents: Drummond and Jefferson and the NICE methodology checklist. However, both of these documents are designed to assess studies that report economic data; therefore, this tool is not appropriate to assess the quality of studies reporting clinical effectiveness and the conclusions regarding study quality must therefore be interpreted with caution.”		SLR. The CS does not describe the basis of the quality assessment tool applied to the clinical SLR. Given there is no single validated quality assessment or risk of bias tool for non-RCT data, questions were posed to query potential causes of bias and generally align to recommended appraisal checklists for clinical trials (RCT and quantitative intervention studies) as per NICE guidelines.(2)	
When reviewing the CS assessment of quality the ERG note: Page 30 - “Further, it is unclear what threshold is being used to inform the final grade (Yes, No, Not Clear, N/A) associated with each question. Some studies are designated to only partially address a particular question but are still awarded a ‘yes’ grade to denote high quality in the assessment domain. This appears profoundly	Please consider the strength of this comment, particularly the conclusion which seems unfairly harsh when considered in the full context (see Justification for amendment). For example: “It isn’t entirely clear what threshold is being used to inform the final grade (Yes, No, Not Clear, N/A) associated with each question but the overall conclusions appear appropriate when considered in full context.”	There are only two examples of studies noted to partially address a particular question: both relate to internal validity of RWE study analyses and include a qualitative explanation as to how bias was still minimised and measures were appropriate for the study type, hence why the risk of bias relating to the question in hand remains low.	Not a factual error.

inappropriate.”			
The ERG also note that: Page 30 - “Finally, no information was provided on the number of reviewers involved in the quality assessment, meaning error and bias may be present.”	Please remove this comment.	The two-reviewer process described for study selection and data extraction applied to all stages of the review.	Not a factual error. This was not clear from the CS.

Issue 8 Clinical SLR eligibility criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
When commenting on the eligibility criteria for the clinical SLR, there is a misrepresentation of the approach taken where the ERG comment that: Page 30 - “The exclusion of abstract-only records published prior to 2012 was questionable, particularly given that the four articles that were finally included in the original systematic review were all abstracts. This means that relevant studies may have been missed.”	Please remove this comment or revise wording to accurately reflect the approach taken. Abstract-only records published prior to 2012 were not routinely excluded. As described in the CS (Appendix D.1), studies dated before 2012 for which only an abstract was available were excluded. While the four articles included in the original systematic review were abstracts of study 101-09 and study 101-02/99, full manuscript publications of both studies were released within one year of conference presentation and thus were never at risk of exclusion based on abstract-only data presentation.	The current comment highlights a misunderstanding of the approach taken, and warrants revised consideration based on the clarification provided here.	Not a factual error.

Issue 9 Factually incorrect reporting of company actions and statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: "*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. This was omitted based on the opinion of one clinical expert, and this might be subject to substantial uncertainty*."	Please amend to "*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. Evidence for obinutuzumab with bendamustine in patients refractory to two prior lines of therapy is lacking and one clinical expert advised that obinutuzumab with bendamustine would be used before idelalisib monotherapy in the treatment pathway.*"	It is important for the NICE committee and other relevant decision makers (including patients) to understand the limitations of the evidence base available to help address the decision problem, and to recognise that all relevant evidence identified has been provided in the CS.	The sentence on Pages 14 and 113 have been changed to: "*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.*"
Page 84: "*In Study 101-09, HRQL in the target population was measured using the FACT-Lym instrument. The company stated that there was no mapping algorithm for this instrument to EQ-5D utilities available, and therefore this source of evidence on HRQL could not be used in the cost effectiveness analysis*." Page 85:	Please remove the false ERG statements that the company stated "*that there was no mapping algorithm for this instrument to EQ-5D utilities available*" and "*that mapping from Study 101-09 data to UK EQ-5D utility values was not possible*".	The ERG's statements are plainly false. The CS text relating to mapping comprised the following: "*The search for published HRQL evidence identified no studies mapping FACT-Lym patient data to EQ-5D values, and scant published evidence in general, in the specific FL population relevant to this appraisal. There are no mapping algorithms or publicly available and suitable data Gilead are aware of that would allow mapping from*	This is not a factual error. If mapping was not possible, then the results of the mapping exercise are not available. We think both statements come down to the same thing.

"*…the company stated that mapping from Study 101-09 data to UK EQ-5D utility values was not possible*."		*Study 101-09 data to UK EQ-5D utility values*." The difference in meaning between this and what the ERG state the company stated is hopefully clear.	

Issue 10 False reporting and description of Comparison D outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 5.18 of the ERG report is erroneous in the following ways: • The table mislabels 'BSC' as 'Chemotherapy' • The table falsely reports Median PFS from Comparison D for 'BSC' (mislabelled as 'Chemotherapy') from the model, but the CS Model does not report median PFS for Comparison D since it is assumed in the model that patients on BSC progress immediately	Please relabel the table correctly and check for other instances of mislabelling of Comparison D comparator outcomes as "chemotherapy" outcomes elsewhere in the ERG report. Please amend the table contents to report the intended information.	Correction for ERG reporting error.	The caption of Table 5.18 is incorrect. This table is based on Appendix J Table 35. Therefore, it refers to Comparison A. It has been replaced by Table 5.18: Comparison A mean PFS and OS model predictions vs. observed data

Issue 11 Tabulation errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Baseline characteristics of CUP	Please correct the table in line with the problems	The current presentation of data	This has been amended.

and HMRN patients are not represented correctly in Table 4.4 of Page 40: 1. HMRN Disease Stage data are presented in the Performance Status field rather than the Disease Stage III or IV field 2. CUP and HMRN FL subtype data are noted as “NR” but all patients in these datasets had FL 3. HMRN Prior therapy data are noted as “NR” but all patients had received prior rituximab and prior alkylating agent 4. HMRN Prior therapy to which disease was refractory data are noted as “NR” but all patients were refractory to rituximab and an alkylating agent	described.	does not accurately reflect the known baseline characteristics of patients across datasets.	
Baseline characteristics of HMRN adjusted population are not represented correctly in Table 4.11 of Page 52: 1. The proportion of patients ≥62 years are reported as median age	Please remove the adjusted HMRN column from this table, and complement with a table showing the pre- and post-adjustment characteristics based on variables adjusted for (as per Table 17 of the CS) rather than combining these data.	The current presentation of data for the adjusted HMRN population is incorrect for several fields.	This has been amended.

2. The proportion of patients ≥4.7 years are reported as median time since diagnosis 3. The 2-year OS rate is reported as median lines of prior therapy 4. The 1-year PFS rate is reported as prior ASCT Please also highlight differences between measurements across trials.	Please add footnotes to the following characteristics: 1. Bulky disease definition which should be (one or more nodes with at least one dimension of 5cm or more) for study 101-02/99 2. Baseline thrombocytopenia which is reported as 'any grade' for study 101-02/99 and Please rename HIGH FLIPI risk score at baseline as FLIPI risk score at baseline and note that study 101-09 data are patients with FLIPI risk score 3-5 OR add the definition of HIGH FLIPI risk score into the field title (3-5) and remove presentation of data for patients with FLIPI risk score 0-2 in the CUP cohort.	Clarification (some misreporting carried over from the CS)	

Issue 12 Text corrections / clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Where presenting data in text, please clarify the population for which data are presented. Specifically, please refer to the FL population for which OS data are presented in text on: Page 10 - “Median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks.” Page 56 - “Median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks.” Page 119 - “Median OS had not been reached at the time of the	Please add a note to the population for which data are presented. For example: “For the FL population, median OS had not been reached at the time of the June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks.”	The current presentation of data could be applied to the total population in error.	Not a factual error. This is clear from the report.

June 2014 database lock and was 38.1 months at the time of the June 2015 database lock. Based on Kaplan–Meier (KM) estimates, the estimated probability of survival at two years was 69.8% at the time of the June 2014 database lock; while in June 2015, 88.4% of patients were still alive at 48 weeks ."			
Where presenting data in text, please clarify the analyses for which data are presented. Specifically, please refer to the IRC assessment method for PFS data presented in text on: Page 10 - "Median PFS was 11.0 months in the FL population for both data sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 dataset, this was not reported for the June 2014 dataset." Page 56 - "Median PFS was 11.0 months in the FL population for both data-sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 data-set, this was not reported for the June 2014 data-set." Page 119 - "Median PFS was 11.0 months in the FL population for	Please add a note to the analyses for which data are presented. For example: "Median PFS (IRC assessed) was 11.0 months in the FL population for both data sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 dataset, this was not reported for the June 2014 dataset."	The current presentation of data could be considered investigator-assessed PFS in error.	

both data-sets and approximately half of all patients were progression-free at 48 weeks in the June 2015 data-set, this was not reported for the June 2014 data-set.”			
For the MAIC, post-matching, the median OS decreased to [redacted] months, not [redacted] months as reported in text on: Page 11 - [redacted] Page 57 - [redacted] Page 119 - [redacted]	Please correct all presentations of median OS data for the adjusted HMRN population. For example: [redacted]	The current transcription of data is incorrect.	Not a factual error. This was taken from page 61 of the CS.

[redacted]			
On page 21, the ERG comment that: "The company provided an adapted pathway which appears to be sensible. However, based on recent data from the M7-FLIPI study,22 and considering that each patient is highly heterogenous in the presentation of their disease, a personalised therapeutic approach based on the genomic and clinical features of a patient's individual disease may represent the preferred approach. Consequently, idelalisib may not be considered the optimal fit for all double-refractory FL patients."	Please consider the removal of the however conjunction as follows: "The company provided an adapted pathway which appears to be sensible. Based on recent data from the M7-FLIPI study,22 and considering that each patient is highly heterogenous in the presentation of their disease, a personalised therapeutic approach based on the genomic and clinical features of a patient's individual disease may represent the preferred approach. Consequently, idelalisib may not be considered the optimal fit for all double-refractory FL patients."	The current sentence structure suggests the M7-FLIPI study in some way contradicts the treatment approach described in the CS, but the personalised therapeutic approach discussed is in line with the CS description of treatment decisions being made at an individual clinician (and patient) level.	Not a factual error.
In Table 3.1 (Page 22) the ERG state that: "For the comparator, only overall survival and progression free survival were reported." Page 25 (outcomes) - "These were all assessed in Study 101-09 for idelalisib. However, for the comparator only overall survival and progression-free survival were	Please correct these statements to reflect the fact that response data were also provided for chemotherapy with regard to previous line of treatment data from study 101-09 (see Page 54 of the CS), and acknowledge that all data available were presented (associated with Issue 4). For example: "For the comparator, data were reported for response, overall survival and progression free survival; data were not available for adverse effects of treatment or health-related quality of	The current statement does not accurately reflect the data reported in the CS, or make it clear enough that data not reported were not available.	Not a factual error.

reported."	life."		
In Table 4.2 (Page 34), data are presented under the header: "Compassionate use programme: UK"	Please retitle these data to confirm that the CUP was conducted across the UK and Ireland as follows: "Compassionate use programme: UK & Ireland"	Clarification	Not a factual error.
In Table 4.3 (Page 37), eligibility criteria for patients in study 101-02/99 are reported to include: "World Health Organization performance status ≥2" This is what was reported in the CS	Apologies for our initial error, please correct this criteria as follows: "World Health Organization performance status ≤2"	Factual inaccuracy (carried over from the CS)	This has been amended.

References

1. Gilead Sciences Ltd. Consultant Haematologist cost-effectiveness analysis validation meeting report. 2018.
2. National Institute for Health and Care Excellence (NICE). Process and methods guides, Devloping NICE guidelines: the manual appendix H 2015 [Available from: https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-appendix-h-pdf-2549711485.

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 ≤ 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]