Section A: Clarification on effectiveness data

1. In Appendix 1 of the clarification response, data pertaining to PFS by treatment arm (from the PRIMA trial) has been provided. It would be valuable if we could also have data pertaining to EFS in the same format.

Response:

EFS was calculated for the January 2010 clinical data cut-off, and not for the June 2010 snapshot analysis. To clarify, the clinical cut-off date for the latter was January 2010, then there was data cleaning, with the final analysis for PFS rendered in June 2010. The June 2010 PFS analysis was conducted solely for the purposes of this appraisal and the accompanying cost effectiveness model. There was no statistical plan in place to analyse other secondary endpoints therefore we provide below a review of the 2 outcomes based at the 2 different follow-up periods.

Comparison of progression-free survival (PFS) and event-free survival (EFS) (PFS: 14th June 2010 snapshot, EFS: clinical data cut-off 15th January 2010)

Results of the two endpoints, PFS and EFS, were very similar. In total there were 17 events more in EFS compared to PFS (5 events under observation and 12 events under rituximab maintenance). The conclusion based on the log-rank test (<0.0001 for both endpoints), the hazard ratio (stratified HR [redacted] for PFS and [redacted] for EFS, respectively), the dynamic of the Kaplan-Mayer curves and the median to event-time (under observation 1472 days for PFS and 1381 days for EFS, respectively, for neither PFS nor EFS was the median reached under rituximab maintenance) are very similar.

Progression-free survival (PFS)

Patients were assessed for progression-free survival (PFS) from the day of randomization until the first documented day of disease progression or death from any cause, whichever occurred first. Patients who did not experience documented disease progression or death were censored at the last tumour assessment prior to the clinical cut-off date. PFS was compared using a two-sided log-rank test stratified by induction regimen (R-CHOP, R-CVP, R-FCM) and response to induction therapy (CR/CRu, PR).

At the time of the analysis, 221/513 patients in the observation arm and 135/505 patients in the rituximab arm (43.1% vs 26.7%) had experienced a progression event (ie, disease progression or death) since randomization. The vast majority of patients had disease progression as PFS event (218 patients on observation, and 130 patients in the rituximab arm).

Maintenance therapy with rituximab in patients responding to induction therapy reduced the risk of experiencing a progression event by 45% compared with no further treatment (stratified HR [redacted], 95% CI [redacted], p < 0.0001, stratified log-rank test). The Kaplan–Meier estimated median PFS times could not be calculated for rituximab arm as a longer follow-up is required (1472 days in the observation arm). However, the 25th percentile times were calculated as 515 days for patients in the observation arm and 1071 days for patients in the rituximab maintenance arm.

Event-free survival (EFS)

Event-free survival (EFS) was measured from the date of randomization to the date of first documented disease progression (investigator-assessed), relapse, initiation of new anti-lymphoma treatment, or death from any cause, whichever occurred earlier. At the time of the analysis (clinical cut-off January 15, 2010), 373 patients had experienced an EFS event: 44.1% in the observation arm compared with 29.1% in the rituximab arm. The majority of events were disease progression (215 events in the observation arm versus 128 events in the rituximab arm). A total of 22 patients started a new anti-lymphoma treatment prior to documented disease progression (8 patients in the observation arm, and 14 patients in the rituximab arm).

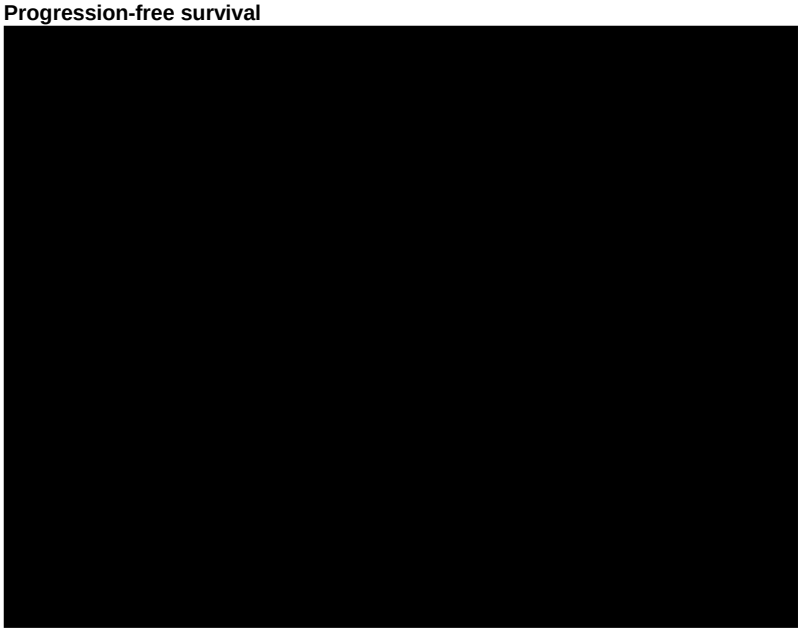
The risk of experiencing an event was reduced by 41% for patients on rituximab as compared to those on observation (stratified [redacted], 95% CI [redacted], p < 0.0001, stratified log-rank test). The median time to event was not reached in the rituximab arm (1381 days in the observation arm). However, there was already a substantial difference at the 25th percentile: 497 days in the observation arm and 1000 days in the rituximab arm.

Table 1: Progression-free survival Vs. event-free survival

	Progression-Free Survival (PFS)		**Event-Free Survival (EFS)**	
	Observation (N=513)	***Rituximab (N=505)***	***Observation (N=513)***	***Rituximab (N=505)***
Composition of time-to-event endpoint[1]				
# of events	221 (100.0%)	135 (100.0%)	226 (100.0%)	147 (100.0%)
Progressive disease	218 (98.6%)	130 (96.3%)	215 (95.1%)	128 (87.1%)
New anti-lymphoma treatment	-	-	8 (3.5%)	14 (9.5%)
Deaths	3 (1.4%)	5 (3.7%)	3 (1.3%)	5 (3.4%)
Time-to-event distribution (days)[2]				
# of events	221 (43.1%)	135 (26.7%)	226 (44.1%)	147 (29.1%)
# of censored	292 (56.9%)	370 (73.3%)	287 (55.9%)	358 (70.9%)
Median [95% CI][3]	1472 [1160, -]	-	1381 [1150, -]	-
25% and 75%-ile[3]	515, -	1071, -	497, -	1000, -
Range[4]	3 to 1577	13 to 1619	1 to 1577	1 to 1619
p-Value (Log-rank test)[5]	<0.0001		<0.0001	
1-year event free rate [95% CI][3]	0.82 [0.79;0.85]	0.89 [0.87;0.92]	0.81 [0.78;0.84]	0.89 [0.86;0.92]
Hazard Ratio [95% CI][6]	[redacted]		[redacted]	
p-Value (Wald's test)	<0.0001		<0.0001	

1. Source : mt_pfscom_l, mt_efscom_l
2. Source : mt_pfssum_l, mt_efssum_l
3. Kaplan-Meier estimate
4. Range including censored observations
5. Log-rank test stratified by induction treatment and derived response to induction (patients without CR, CRu or PR are included in the PR stratum)
6. Hazard ratio stratified by induction treatment and derived response to induction (patients without CR, CRu or PR are included in the PR stratum)

Progression-free survival



Event-free survival

Roche conducted a sensitivity analysis to demonstrate the robustness of the cost effectiveness results and in order to assess the impact of utilising the EFS HR (0.59 according to the January 2010 data cut-off) in the analysis. This was found to have a marginal impact on the cost effectiveness of rituximab in 1st line maintenance. The results of the analysis can be seen in the table below.

Table 2: Cost effectiveness analysis utilising EFS from January 2010 cut-off

	R-maintenance	Observation
Total Cost	£85,574	£66,721
Total QALYs	8.252	7.207
Incremental Cost	£18,853	
Incremental QALYs	1.045	
ICER	£18,033 per QALY	

2. Appendix on the methods used to validate and quality assure the model (missing from submission)

Response:

Please find this as an appendix.

3. Confirmation that there is no AiC/CiC information in the model. If confidential information is included in the model, please highlight which inputs are confidential (and include in confidential checklist which you were sent) and provide a redacted executable version of the model with the CiC information removed (dummy variables can be used to replace CiC information if required to ensure that the model still functions).

Response:

2 versions of the submitted model are being provided:

1. Submitted model with highlighted AIC/CIC information
2. Submitted model with AIC/CIC information removed

Appendix I: Health Economic Model Validation Checklist

1. Internal (technical) validity

Validation Tests - REQUIRED	Done	Comments
Face validity		
Discuss model structure with selected key opinion leaders (KOLs) or an expert panel to validate clinical pathways, input data assumptions, and outcome variables of the model and ensure the plausibility of the model outputs. Use this source also for obtaining best estimates for missing or inconsistent input data	☐ yes ☐ no	
Compare the model structure with the framework of other published models targeting the same indication and treatment (if available)	☐ yes ☐ no	
Debugging		
Recalculation of the main intermediate or final model outcomes (clinical, economic) by means of a hand-held calculator and comparison of results, e.g.		
Number of cases in intervention and control group experiencing key outcome (e.g. progression, death)	☐ yes ☐ no	
Total cost of study drug in intervention group	☐ yes ☐ no	
Total cost of hospitalization in intervention and control group	☐ yes ☐ no	
If societal perspective: total work loss costs in intervention and control group	☐ yes ☐ no	
Other test, specify:	☐ yes ☐ no	
Hypothetical null and extreme value testing, e.g.		
Set mortality rate to 0% → no deaths shall occur	☑ yes ☐ no	Separately set pfsdth_new, pfsdth_com, pfs2dth_new, pfs2dth_com, p2dr, p2do and death rates in 'Mortality Table UK' to 0: → No deaths occur: ✓

Set efficacy rate for study drug to 0% → equal health outcomes as in control group	☑ yes ☐ no	Mortality rates and transition probabilities of both arms set equal KM mode: KM PFS rates of both arms set equal → Health outcomes are equal: ✓ All parametric modes: lambda and gamma values of both arms set equal: → Health outcomes are equal: ✓
Set drug toxicity rate to 0% → no adverse events shall occur	☑ yes ☐ no	Set AE costs to 0: → Total AE costs are 0: ✓
Rise efficacy sequentially from 0% to 100% → with increasing efficacy, the number of events averted shall increase	☐ yes ☑ no	Test cannot be performed with available model settings
Set hospitalization rate to 0% → no inpatient cases shall occur	☐ yes ☑ no	Hospitalizations are not considered in this model
Set medical resource use to 0 →MRU costs shall be zero	☐ yes ☑ no	MRU is not included in this model
Set unit cost for study drug and administration to 0 → total costs of study drug shall be zero	☑ yes ☐ no	Set costs for Rituximab and the corresponding administration costs to 0: → Drug and administration costs are 0: ✓
If societal perspective: set cost per work day lost to 0 → total indirect costs shall be zero	☐ yes ☑ no	Indirect costs not considered in this model
If societal perspective: set average duration of work loss to 0 → total indirect costs shall be zero	☐ yes ☑ no	Indirect costs not considered in this model
Use different discount rates (e.g. 0%, 3%, 7%) For costs → total costs shall decrease with increasing discount rates For health benefits → total number of events shall decrease with increasing discount rates	☑ yes ☐ no	Separately set disc_u and disc_c to different discount rates: → Expected changes in outcomes are produced: ✓
Other test, specify: - Set unit costs for supportive care costs for PFS states and for Progression to 0 → total monthly supportive care costs shall be zero - Set utility values to 0 → utility adjusted health outcomes shall be zero - Set utility values to 1 → utility adjusted health outcomes shall be equal to unadjusted life years	☑ yes ☐ no	→ Corresponding outcomes are 0: ✓ → Corresponding outcomes are 0: ✓ → Corresponding outcomes are equal to life years: ✓
Extensive sensitivity analysis		

Perform sensitivity analysis on all model variables	☐ yes ☐ no	
Replication test		
Re-enter all input values into the original model (by different person) and compare results. In case of different outcomes (deterministic analysis), search for differences in input values between the two input data sets	☐ yes ☐ no	
Validation Tests (cont.) OPTIONAL	**Done**	**Comments**
Debugging: *Double-implementation*		
Re-code Excel model by using different software (e.g. Tree Age). Results should ideally be identical or in a narrow range	☐ yes ☐ no	
Calibration		
Comparison of the model's intermediate and/or final outputs with data from national health statistics or other healthcare databases. Calibration data should come from sources independent of the data used to generate the model input values. Intermediate and/or final model outputs should ideally be identical to or in a narrow range with the calibration data	☐ yes ☐ no	

2. <u>Convergent validity / Corroboration</u>

Convergent validity	**Done**	**Comments**
Compare the outputs of the model with the results of other published peer-reviewed models which are addressing the same or a similar research question and setting (if available)	☐ yes ☐ no	

3. <u>External and predictive validity</u>

<u>Note</u>: By definition, this test is possible only <u>after</u> the full model has been developed and only when such relevant information becomes available in the future

Predictive validity	**Done**	**Comments**
Compare the model's outputs with new published information (e.g. studies, registries) in the modeled disease and treatment area if such data becomes	☐ yes ☐ no	

available. Try to identify the reasons for potential discrepancies in results and revise the model accordingly		
Compare the model's outputs with new information obtained from specifically initiated naturalistic, prospective studies (e.g. disease / product registries) customized to collect additional data matching key outcomes considered in the model. Try to identify the reasons for potential discrepancies in results and revise the model accordingly	☐ yes ☐ no	

Cost-effectiveness Markov Model of Rituximab vs Observation in patients with Non-Hodgkins Lymphoma

Sheet	Range	Work step	Comment
Macros		Checked	No issues
Introduction		Checked spelling and content of text	Typing errors
Model Diagram		Checked diagram and labels	No issues
Model Inputs	All cells	Checked for correctness of spelling and content, formulas and layout	D9, D12: Remove '30 tablets' from label B31, B32: Change labels E45: Cell is marked as input variable but contains a formula G45: Check comment C75: Cell name (s_com) must be assigned to this cell C76: Cell has two names (s_new → correct, s_com → must be assigned to C75)
Administration costs	All cells	Checked for correctness of spelling and content, formulas	C12, D12: Cost value for subsequent administrations is taken for the first attendance during one cycle B14: Label should be 'Cost/administration' B18: Label is for hours of pharmacy time required but variables contain cost values B30-B33: Content does not fit modelled administration schemes
Adverse events	Rows 6-8 + random cells	Checked for correctness of formulas	No issues
AE Cost Data	Rows 3-4 + random cells	Checked	No issues
Results Table	All cells	Checked for correctness of spelling and content, formulas	F14-G21: PFS + progression <> total life years (see errors in 'Simulation' sheet)

Sheet	Range	Work step	Comment
New Therapy	Rows 3-7 + random cells	Checked for correctness of formulas and labels	No issues
Comparator	Rows 3-7 + random cells	Checked for correctness of formulas and labels	No issues
Dose Table	All cells	Checked	No issues
Simulation	Rows 1-9	Checked for correctness of spelling and content, formulas	L9: Time in 2nd line PFS is not incorporated (reference should be (Comparator!E3 + Comparator!I3 + Comparator!R3)/12) O9: Time in 2nd line PFS is not incorporated (reference should be ('New Therapy'!E3 + 'New Therapy'!I3 + 'New Therapy'!R3)/12) BQ6, BR6, BU6: Hardcoded reference in indirect part of formula is wrong
Scatter Plots		Checked for correctness of sources	Net Benefit/QALY plot: Change label (Erl vs Gef) and remove second reference and label (Erl vs Chemo)
CEAC		Checked for correctness of sources	Change label (Erlotinib vs Gefitinib) and remove second reference and label (Erlotinib vs Chemotherapy)
Charts		Checked for correctness of sources	Progression by Treatment Arm: Curve for Rituximab progression is missing (needed formulas in 'New Therapy' column AV are missing)
Distribution Table		Checked for correctness of formulas and sources	J13-J23: Reference to bin number range should start at I13 D66-D76: Reference to bin number range should start at C66 J66-J76: Reference to bin number range should start at I66
Demographic		Checked	No issues
Post-Prog Treatments		Checked	No issues, model algorithms have no link to content
MRU		Empty	
Exponential		No checks performed	
Gamma		No checks performed	
Gompertz		No checks performed	
Log Logistic		No checks performed	
Log Normal		No checks performed	
Weibull		No checks performed	
Transition Probabilities		Checked (most cells are protected)	B6: Check comment
os_EORTC 20891		Checked	No issues
pfs_EORTC 20891		Checked	No issues

Sheet	Range	Work step	Comment
KM OS		Empty	
KM PFS		Checked	No issues
Parametric-Plots		Checked for correctness of sources	No issues
Parametric-KM Plot		Checked for correctness of sources	No issues
KM-Plots		Checked for correctness of sources	No issues
Mortality Table UK		Checked for source of data and correctness of formulas	No issues
References		Empty	