Section A: Clarification on effectiveness data

A1. Priority Question: The patient population in the PRIMA trial (described in Table 15 of the manufacturer's submission) indicates that 118 (10%) patients had Stage I or Stage 2 disease. Patients with NHL at these stages are not usually considered to have advanced disease and are not usually treated with chemotherapy. Please provide clarification of the rationale for patients with Stage I and 2 disease being recruited into the PRIMA trial*.

Response:

Most patients (> 85%) with follicular lymphoma (FL) have widespread disease at diagnosis (Ann Arbor stage III/IV), including involvement of peripheral and central (abdominal and thoracic) lymph nodes and spleen.

In the small proportion of patients with limited stage I–II disease, radiotherapy (involved or extended field, 30–40 Gy) is the preferred treatment option having a curative potential. However, in stage I-II patients with large tumour burden systemic therapy may be applied as indicated for advanced stages (ie with the occurrence of symptoms including B symptoms, haematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression)[i]. Please note, this approach is accepted as standard practice in the UK as confirmed by three independent experts (see below).

Following a scientific advice meeting with the Danish and Dutch Medicines Agencies, it was agreed that the PRIMA trial was acceptable with regards to study design and conduct as a label enabling trial to gain marketing authorisation for MabThera maintenance therapy in previously untreated patients with follicular lymphoma responding to induction therapy. Accordingly, patients were eligible for entry into PRIMA if they had a high tumour burden and required initiation of treatment (Stages I-IV), defined by the presence of at least one of the following (GELF) criteria:

– bulky disease defined as a nodal or extranodal (except spleen) mass > 7 cm in its greater diameter
– B symptoms
– elevated serum lactate dehydrogenase (LDH) or β2-microglobulin
– involvement of at least three nodal sites (each with a diameter greater than 3 cm)
– symptomatic splenic enlargement
– compressive syndrome
– pleural/peritoneal effusion

Almost all patients who entered the maintenance/observation phase (98%) of PRIMA fulfilled one or more of these criteria at study entry. As expected, the great majority of patients (90%) had stage III/IV disease but 10% of patients had stage I (2%) or stage II disease (8%).

Subgroup analyses of efficacy were not performed according to disease stage in the PRIMA study. However, PFS was analyzed in subgroups defined by FLIPI score as

assessed at the start of the induction phase. The FLIPI score is a composite score based on five prognostic factors, one of which is tumour stage (stage I/II = 0 adverse prognostic factors, stage III/IV = 1 adverse prognostic factor). Importantly, all FLIPI subgroups of patients in the PRIMA study, including those with a low FLIPI score (0–1 adverse prognostic factors) benefitted significantly from rituximab maintenance (Figure 9 of our submission; pp 106). This finding strongly suggests that patients with stage I/II disease in the PRIMA study benefitted from maintenance rituximab and that this subgroup of patients should not be excluded from treatment with rituximab maintenance in the future.

For this reason, the proposed licence will support the use of rituximab maintenance in patients with advanced stage (stage III/IV) follicular lymphoma and patients with high tumor burden stage I/II follicular lymphoma, who have responded to first-line therapy.

Opinion from independent UK experts

Dr Christopher McNamara, Consultant haematologist, Royal Free Hospital, London:

"Very few patients with limited stage FL who do not have disease bulk or a mass in a strategic location will require chemotherapy. However, those that do have an accepted indication for treatment if the disease is in discontiguous sites or if the morbidity of radiotherapy is intolerable. The patients that I can think of readily are those that present with a large (>7cm) symptomatic abdominal mass but no nodal disease elsewhere and a clear marrow. This patient has limited stage disease but clearly requires chemotherapy, not radiotherapy."

Dr George Follows, Consultant Haematologist, Addenbrookes Hospital, Cambridge:

"I am confident that our practice in the Anglia cancer network reflects standard practice within the UK.

Standard treatment for most patients with stage I follicular lymphoma is involved field radiotherapy. This applies for both asymptomatic as well as symptomatic patients, although the majority of stage I FL patients are relatively symptom free.

However, many patients with symptomatic stage II disease, have features that make radiotherapy less attractive. These include disease in multiple nodal groups that would necessitate large radiation fields, or disease involving areas that are more likely to associate with radiotherapy side effects, such as mesenteric or oropharygeal disease. Of note, there is always the concern with symptomatic stage II patients, that a proportion have in fact been understaged, for a range of potential reasons. I suspect this concern influences clinicians when they decide between chemotherapy or radiotherapy in these cases.

Although I have not seen the exact breakdown of the 118 patients with stage I/II disease that entered the [PRIMA] trial, I strongly suspect that the majority of these patients would have been stage II, and were therefore treated with R-chemotherapy in line with current standard UK practice."

Dr Andy Haynes, Consultant Haematologist, Nottingham City Hospital:

"In the UK we have always taken:

1. Systemic upset (wt loss > 10% in 6 months and night sweats) due to disease
2. Bone marrow failure
3. Compression syndrome caused by disease - DVT/threatened DVT secondary to bulky iliac or inguinal disease, hydronephrosis secondary to ureteric obstruction by nodal disease, recurrent pleural effusions, ascites from mesenteric/omental disease, extradural cord compression and bowel involvement

as indications to treat. The GELF criteria are slightly more permissive.

In effect localised stage I disease would usually be treated with RT unless bulky or at a difficult site. Stage II disease fulfilling any of the above would usually be treated with RT or systemic chemotherapy as indicated after discussion by an MDT, the usual criteria for chemo would be point 3 above and bulk.

Stage I/II disease would therefore be appropriate for maintenance where a properly constituted MDT considered chemotherapy the appropriate first line therapy. With CT/PET staging some cases would be upstaged anyway from I/II to III/IV."

A2. Priority Question: Section 5.3.1.2.5 (page 67 of manufacturer's submission) is unclear and appears contradictory. Please present this information in a more coherent manner and provide clarification as to:

i) why starting a new anti-lymphocytic treatment was not counted as an event or as a reason for censoring

Response:

Please note, starting a new anti-lymphocytic treatment was not counted as an event for investigator-assessed progression-free survival (PFS) as PFS is defined as the time from the day of randomization to the date of first documented progressive disease or death from any cause, whichever is earlier. As highlighted above, starting a new anti-lymphoma treatment before documented disease progression was also not counted as a reason for censoring in the investigator-assessed PFS analysis.

Starting a new anti-lymphoma treatment was, however, counted as an event in the secondary endpoint, event-free survival (EFS), which was defined as the time from the day of randomization to the date of first documented progressive disease, initiation of any new anti-lymphoma treatment or death from any cause, whichever is earlier. Progression free survival (progression or death) is considered a more objective endpoint whereas starting a new treatment before progression (as included in EFS) is a more subjective event. Nevertheless, the majority of events in the investigator-assessed EFS analysis were disease progression/relapse events ([redacted] events in the observation arm versus [redacted] events in the rituximab arm). A total of only [redacted] patients ([redacted]) started a new anti-lymphoma treatment prior to documented disease progression ([redacted] patients in the observation arm, and [redacted] patients in the rituximab arm) (January 14th 2009 cut-off, pp 124 of submission).

The minimal impact of the small number of patients included in the investigator-assessed PFS analysis who started a new anti-lymphoma treatment before disease progression is reflected in the similar hazard ratios for PFS and EFS (PFS HR = 0.50 [0.39;0.64] p<0.0001; EFS HR = [redacted] [redacted] [redacted]). This is also the case for the updated January 15th 2010 analysis (PFS HR = [redacted] [redacted] [redacted]; EFS HR = [redacted] [redacted] [redacted]).

For the CE analysis of PRIMA PFS all patients starting a new lymphocytic treatment before disease progression were censored at start of new therapy (R=[redacted] and O=[redacted]). This has the effect of reducing the time in PFS more in the R arm as in the observation.

ii) the meaning of 'as images were not collected after the start of a new treatment, patients who started a new anti-lymphoma treatment without IRC-assessed disease progression were censored for the IRC analysis of PFS'

Roche contracted an Independent Review Committee (IRC), BioClinica Inc, to provide an independent assessment of tumour response in the PRIMA trial. This assessment was based on radiographic images with limited clinical information.

In the IRC analysis of PFS, (as per the investigator assessment) initiation of a new anti-lymphoma treatment after randomization to study treatment was not counted as an event nor as a reason for censoring. As specified in the PRIMA protocol, no subsequent CT scans were required following disease progression and patients were followed for survival. In the event of a new subsequent treatment without disease progression, CT scans were also discontinued due the confounding impact of the new treatment. As discussed above, a new anti-lymphoma treatment was started in only [redacted] of patients without documented disease progression. Accordingly, these patients were censored at the time of their last available scan. To be eligible for assessment by the IRC at least one valid paired radiologist/oncologist assessment was required. Consequently, in the absence of an available CT scan the IRC could not assess a response and patients were declared as non-evaluable. Despite this limitation, which was necessitated by the blinded nature of the IRC review, the hazard ratio values were very similar for the investigator and IRC assessed PFS (Inv PFS HR = 0.50 [0.39;0.64] p<0.0001; IRC PFS HR = 0.55 [0.42;0.70] p<0.0001; January 14th 2009 cut-off).

iii) why there appear to be differences in censoring methods between the investigator and IRC assessments

The only difference in censoring methods between the investigator and IRC assessments is described in point ii) above (ie censoring patients for the IRC-analysis of PFS at the time of their last available CT scan).

Please note, in the case of investigator-assessed PFS, although these patients were also censored at the time of their last tumour assessment, this may not necessarily have been a radiological assessment as the investigator may have assessed a response based solely on a physical examination. However, as stated above, despite these limitations the IRC assessed PFS results were very similar to the investigator assessed PFS results. Furthermore, both the investigator-assessed and IRC-assessed PFS benefit were shown to be robust using sensitivity analyses and supportive of each other (section 5.5.2.1.4 of our submission).

A3. Priority Question: In the PRIMA trial, some lymphomas were recorded as having transformed. Please explain i) whether patients whose disease had transformed were followed up and ii) how their data were included in the analysis

In the PRIMA study, a biopsy was obtained at progression, where possible, for central pathological review. Of the 173 patients that progressed on the observation arm 73 patients had samples assessed. From the 91 patients on the rituximab maintenance arm that progressed 41 samples were assessed for transformation.

Please note:

i) There was no difference in the follow up of these patients. Following progression, all patients were followed for their subsequent treatment(s) and survival.

ii) These patients were treated the same as all patients and their progression was counted as an event in the primary analysis. Transformation rate at first progression was a secondary endpoint and is presented in section 5.5.2.2.7 of our submission).

A4. Clinical data used in the economic modelling should be evidenced in the clinical effectiveness section. Therefore, please provide a description of the results for all primary and secondary clinical endpoints from the last data cut-off (June 2010), which is not available in the CSR.

Response:

The operational cut-off for data collection for the updated efficacy and safety analyses was every visit up to and including 15th Jan 2010. Monitoring staff were requested to collect and Source Data Verify every visit that took place up to this date. In turn, Data Management cleaning and Clinical Science review took place on all visits up to this date. Efficacy and safety data from this cut-off date are described in sections 5.5.3 and 5.9.2.13 of our submission respectively and presented in more detail in Table 1 below.

Table 1: Overview of Efficacy Parameters (MITT) 15th Jan 2010 cut-off date

Efficacy Parameter	Observation N = 513	Rituximab N = 505	HR / OR	p-value*
Primary Endpoint: PFS				
Investigator-Assessed PFS				
Median time to event	[redacted] days	[redacted]		
25th percentile	[redacted] days ([redacted] months)	[redacted] days ([redacted] months)	HR = [redacted] [redacted; redacted]	[redacted]
One-year PFS rate [95% CI]	[redacted] [redacted; redacted]	[redacted] [redacted; redacted]		
Secondary Endpoints				
Event-free Survival				
Median time to event	[redacted] days ([redacted] months)	[redacted]		
25th percentile	[redacted] days ([redacted] months)	[redacted] days ([redacted] months)	HR = [redacted] [redacted; redacted]	[redacted]
One-year event-free rate [95%	[redacted] [redacted; redacted]	[redacted] [redacted; redacted]		

CI]				
Overall Survival				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted]	[redacted]	HR = [redacted] [redacted;redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted] [redacted;redacted]	[redacted] [redacted;redacted]		
Time to Next Anti-Lymphoma Treatment				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted] days ([redacted] months)	[redacted] days ([redacted] months)	HR = [redacted] [redacted;redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted] [redacted;redacted]	[redacted] [redacted;redacted]		
Time to Next Chemotherapy Treatment				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted] days ([redacted] months)	[redacted]	HR = [redacted] [redacted;redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted] [redacted;redacted]	[redacted] [redacted;redacted]		
Overall Response Rate at End of Maintenance/Observation				
N excluding patients still ongoing maintenance	[redacted]	[redacted]		
Responders (CR, CRu, PR)	[redacted] ([redacted])	[redacted] ([redacted])	Diff.: [redacted] [redacted;redacted]	[redacted]
Non-responders	[redacted] ([redacted])	[redacted] ([redacted])	OR = [redacted] [redacted;redacted]	
Patients with complete response (CR/CRu)	[redacted] ([redacted])	[redacted] ([redacted])		
partial response (PR)	[redacted] ([redacted])	[redacted] ([redacted])		
stable disease (SD)	[redacted] ([redacted])	[redacted] ([redacted])		
progressive disease (PD)	[redacted] ([redacted])	[redacted] ([redacted])		

Primary endpoint

With a median follow-up of 36 months, [redacted] patients in the rituximab maintenance arm and [redacted] in the observation arm had disease progression, while [redacted] and [redacted] patients, respectively, had died without progression. The 3-year PFS rate was [redacted]% (95% confidence interval [CI] [redacted]) in the rituximab maintenance arm and [redacted]% (95% CI [redacted]) in the observation arm (stratified log-rank, [redacted]) (Figure 1A). The risk of progression was [redacted], with a hazard ratio [HR] of [redacted] (95% CI [redacted]) for the rituximab maintenance arm. Pre-planned analyses of patient subgroups categorized by age, sex, FLIPI score category, induction chemotherapy and response to induction, showed that the effect of rituximab maintenance was [redacted] (Figure 2). In a Cox regression multivariate analysis, PFS was significantly associated with the randomization arm ([redacted]) independently of [redacted], [redacted], [redacted], [redacted] [redacted] and [redacted].

Secondary endpoints

Overall, [redacted] patients in the rituximab maintenance arm and [redacted] patients in the observation arm started a new treatment, consisting of a new chemotherapy regimen in [redacted] and [redacted] patients, respectively. A [redacted] in the risk of starting a new anti-lymphoma treatment (HR=[redacted]; 95% CI [redacted]) (Figure 1B) or starting a new chemotherapy (HR=[redacted]; 95% CI [redacted]) were observed in the rituximab maintenance arm (Figure 1C). With [redacted] deaths observed in the rituximab maintenance arm and [redacted] in the observation arm, there was [redacted] in the risk of death after randomization (HR=[redacted]; 95% CI [redacted]) (Figure 1D).

At the end of the maintenance phase of the study, [redacted] ([redacted]%) patients evaluated in the rituximab maintenance arm were in CR/CRu, compared with [redacted] ([redacted]%) patients evaluated at the same time in the observation arm. More of the patients who were in PR at the time of randomization converted to CR/CRu after [redacted] ([redacted] patients [[redacted]]) compared with the [redacted] ([redacted] patients [[redacted]]), [redacted].

Figure 1: Kaplan–Meier estimates of outcome measures with rituximab maintenance versus observation. (A) Progression-free survival; (B), time to next anti-lymphoma treatment; (C), time to next chemotherapy; and (D) overall survival from randomization.

(A)

[redacted]

(B)

(C)

(D)

Figure 2: Risk of progression with rituximab maintenance versus observation, according to pre-specified subgroups.

FLIPI, follicular lymphoma international prognostic index; R-CHOP , rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; R-FCM, rituximab, fludarabine, cyclophosphamide, and mitoxantrone.

Safety and quality of life

Among the 1,009 patients evaluated for safety, adverse events were reported in [redacted] ([redacted]%) patients in the rituximab maintenance arm and [redacted] ([redacted]%)

patients in the observation arm; severe adverse events were reported in [redacted] ([redacted]) and [redacted] ([redacted]%) patients, respectively. The most common adverse events reported were [redacted] in [redacted] ([redacted]) and [redacted] ([redacted]%) patients, respectively. Grade 3 or 4 adverse events (Table 2) occurred in [redacted] ([redacted]%) patients in the rituximab arm and [redacted] ([redacted]%) patients in the observation arm, while [redacted] and [redacted] events, respectively resulted in treatment discontinuation. Only [redacted] death ([redacted], [redacted]) was reported to be possibly related to treatment toxicity, other causes of deaths before lymphoma recurrence being related to [redacted] ([redacted] cases), [redacted], [redacted], or [redacted] ([redacted]) ([redacted]). [redacted] other patients ([redacted]) [redacted].
At the end of 2 years of rituximab maintenance or observation, median serum levels of immunoglobulin (Ig) isotypes were [redacted] g/L (range [redacted]) and [redacted] g/L ([redacted]), respectively for IgG; [redacted] g/L ([redacted]) and [redacted] g/L ([redacted]), respectively for IgA, and [redacted] g/L ([redacted]) and [redacted] g/L ([redacted]), respectively for IgM (evaluated in [redacted] patients in the experimental arm and [redacted] in the observation arm).

Analysis of quality-of-life scores during observation or maintenance using the FACT-G and EORTC-QLQ-C30 scales [redacted]. The mean adjusted FACT-G total scores were [redacted] (Standard Error [SE] =[redacted]) in the rituximab maintenance arm and [redacted] (SE=[redacted]) in the observation arm (P-value for treatment effect =[redacted]). The EORTC QLQ-C30 global health status mean scores were [redacted] (SE=[redacted]) and [redacted] (SE=[redacted]), respectively (P=[redacted]).

Please note, that an additional exploratory data snap-shot was performed in June 2010 on unlocked data for the purpose of providing the most up-to-date analysis that could be used to inform our economic model. The only outputs available from this snap-shot are PFS and OS (N.B. PFS is the only endpoint extrapolated in our model), as presented in the health economic section of our submission and presented again below (Figures 3 and 4). Given the few additional events included in the June 2010 snapshot relative to the Jan 2010 analysis, the HR for PFS in each case are identical (Table 2).

Figure 3: KM PFS Plots for PRIMA (INV ITT; Snapshot June 14th 2010)

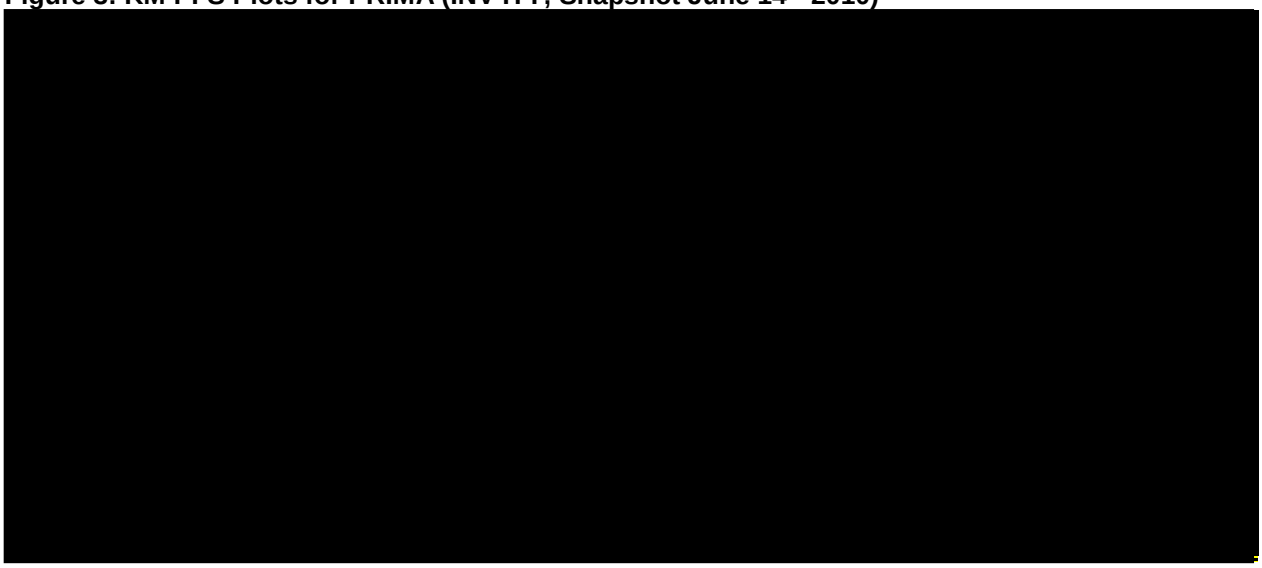


Figure 4: Duration of Overall Survival in First-Line Maintenance with Rituximab (PRIMA INV ITT; Snapshot June 14th 2010)

Table 2: PRIMA study primary endpoint: Progress-free survival (investigator-assessed MITT

PRIMA clinical data cut off date	Observation N = 513 Median PFS	Rituximab N = 505 Median PFS	HR / OR	p-value*
14th January 2009 25 months median – follow-up duration	NE	NE	0.50 [0.39;0.64]	p <0.0001
15th January 2010 36 months median – follow-up duration	[redacted]	[redacted]	[redacted]	[redacted]
Snapshot 14th June 2010* 38 months median – follow-up duration	[redacted]	[redacted]	[redacted]	[redacted]

HR: hazard ratio; OR: odds ratio; NE: not estimable.

*p-values and hazard ratios were calculated using the stratified log-rank test and stratified Cox regression for time-to-event endpoints, respectively. Stratification factors were induction treatment received and response to induction treatment. p-values for response rate were calculated using the χ^2 test, and odds ratios w ere calculated by using logistic regression (response rate analyses were unadjusted).

A5. With reference to Section 5.4.2, please provide a complete quality assessment for the PRIMA study. It is noted that the table on page 349 of the manufacturer's submission has not been completed.

Response:

Apologies, this table was accidently omitted from the final submission. Please find below.

Trial no. MO18264 (PRIMA)		
Study question	How is the question addressed in the study?	Grade (yes/no/not

		clear/N/A)
Was randomisation carried out appropriately?	Centralised, stratified block randomisation procedure	Yes
Was the concealment of treatment allocation adequate?	Randomization of eligible patients was performed centrally by fax from the GELA randomization center (GELARC) at Hôpital Saint Louis–Centre Hayem. The random allocation sequence was generated by an SAS programmer according to the specifications of a biostatistician. The SAS database that was imported in the GELARC randomization tool was not readable. Thus, neither the physicians nor the randomization assistants had access to the random allocation sequence, which was kept by the biostatistics department	Yes.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The treatment groups were well balanced with respect to follicular lymphoma international prognostic index (FLIPI) scores (see section 5.3.4, Table 14)	Yes

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	PRIMA was an open-label study, therefore, it is likely that the aforementioned parties were aware of treatment allocation. However, the assessment of follicular lymphoma post-treatment is very objective and it is therefore unlikely that this will have biased results. In addition, an IRC comprising three hemato-oncologists and seven radiologists (including two adjudicators) assessed all patients randomized in the maintenance/observation phase in a blinded manner for response and progression based on computed tomography (CT) scans and reports of pertinent clinical findings (including physical examination and laboratory results) according to the IRC Charter.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	263 patients (26%) discontinued during the maintenance/observation phase (Table 10). More patients in the observation arm than in the rituximab arm withdrew from the study (162 patients vs 101 patients; 32% vs 20%). See section 5.3.1.2.18 for details.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All pre-defined primary and secondary outcomes have been reported.	No

(i) Did the analysis include an intention-to-treat analysis? (ii) If so, was this appropriate and were appropriate methods used to account for missing data?	As detailed in section 5.3.1.2.16. Efficacy and economic analyses are subsequently presented for the intention-to-treat population. This was an appropriate approach in order to preserve the randomisation scheme and avoid selection bias. A sensitivity analysis of investigator-assessed PFS was performed to account for missing data.	(i) Yes (ii) Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Section B: Clarification on cost-effectiveness data

B1. Priority Question: In the economic model, neither age nor response status following induction therapy have been considered as determining factors in treatment efficacy. Please provide Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the most recent follow-up PRIMA trial data for progression-free survival (PFS) and consider the following:

- ***I. PFS by treatment arm (maintenance rituximab, and 'watch and wait')***
- ***II. PFS by 3 patient populations defined by age and by treatment arm (i.e. 3 x 2 Kaplan-Meier analyses) as follows:***
  - ***first tertile (33% youngest patients)***
  - ***second tertile (33% mid-age patients)***
  - ***third tertile (33% oldest patients)***
- ***III. PFS by 3 patient populations defined by induction response and by treatment arm (i.e. 3 x 2 Kaplan-Meier analyses) as follows:***
  - ***complete responders***
  - ***partial responders***
  - ***unconfirmed complete responders***

In each case please provide a Product-Limit Survival table (e.g. using SAS LIFETEST procedure - see example below) showing for each event time:

- ***time of event from baseline (days)***
- ***product-limit estimate of survival proportion***
- ***standard error of survival proportion***
- ***number of patients failed***
- ***number of patients remaining at risk***

In addition for each table please provide the estimated mean survival time from the relevant baseline (i.e. randomization or disease progression) up to the time of last recorded event, together with the standard error of the mean estimate.

Example of output (SAS) required from analyses

The LIFETEST Procedure

Product-Limit Survival Estimates						
SURVIVAL		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58

Product-Limit Survival Estimates						
SURVIVAL		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
8.000		**.**	**.**	**.**	**5**	**57**
8.000		**.**	**.**	**.**	**6**	**56**
8.000		**0.8871**	**0.1129**	**0.0402**	**7**	**55**
10.000		**0.8710**	**0.1290**	**0.0426**	**8**	**54**
SKIP…		**0.8548**	**0.1452**	**0.0447**	**9**	**53**
389.000		**0.1010**	**0.8990**	**0.0417**	**52**	**5**
411.000		**0.0808**	**0.9192**	**0.0379**	**53**	**4**
467.000		**0.0606**	**0.9394**	**0.0334**	**54**	**3**
587.000		**0.0404**	**0.9596**	**0.0277**	**55**	**2**
991.000		**0.0202**	**0.9798**	**0.0199**	**56**	**1**
999.000		**0**	**1.0000**	**0**	**57**	**0**

Response:

I. PFS by treatment arm (maintenance rituximab, and 'watch and wait')

The requested tabulation of the data has been provided in Appendix I for rituximab maintenance and 'watch and wait' from the PRIMA trial (June snapshot).

II. PFS by 3 patient populations defined by age and by treatment arm (i.e. 3 x 2 Kaplan-Meier analyses) as follows:

- first tertile (33% youngest patients)

- second tertile (33% mid-age patients)

- third tertile (33% oldest patients)

Roche provided in the original submission an analysis of the treatment effect by 2 age groups; <60 years and >=60 years. This analysis was predefined in the study protocol and patients were stratified by this patient baseline characteristic. The forest plot illustrating the hazard ratios for PFS with 95% confidence intervals (observation vs rituximab) for pre-specified patient subgroups are shown in figure 9 of the submission.

Roche is unclear to what purpose the ERG would request this bespoke age category evidence, given the pre-specified age related data already provided within the submission.

However Roche has provided an analysis that demonstrates that, irrespective of age a consistent treatment effect is observed in which patients treated with rituximab maintenance experience at least a 30% reduction in the risk of progression. It is important to note here that the analyses are based on a non-randomised limited number of events, patient numbers and any variations may be confounded by other explanatory variables. The odds ratios by age can be seen in the figure below. The table below summarises the event counts and censoring for the 2 arms for each of the 3 age sub-groups requested.

Table 3: PRIMA PFS events (maintenance) by treatment and the age tertiles (Jun 2010 snapshot)

Age range	**Observation arm (n=513)**		**Rituximab arm (n= 505)**	
	Event	*Censored*	*Event*	*Censored*
23-43 years	44	46	16	57
44-64 years	132	167	85	224
65-85 years	47	77	36	87

Further details on the number of events per sub-group can be found in appendix 2.

III. PFS by 3 patient populations defined by induction response and by treatment arm (i.e. 3 x 2 Kaplan-Meier analyses) as follows:

- ***complete responders***
- ***partial responders***
- ***unconfirmed complete responders***

The table showing odds ratios and figure below showing the event rates for the sub-group of patients by induction response category demonstrate that the treatment effect is maintained in the 3 patient populations.

[redacted]

Table 4: PRIMA PFS events (maintenance) by treatment and response to induction (Jun 2010 snapshot)

Induction to response	**Observation arm (n=513)**		**Rituximab arm (n= 505)**	
	Event	*Censored*	*Event*	*Censored*
CR	76	119	46	159
uCR	75	90	50	105
PR	72	80	39	100

Further details can be found in appendix 3.

B2. Priority Question: Rituximab doses are administered based on body surface area (BSA) which is different for women and men. The costs in the manufacturer's submission appear to have not taken these gender differences into account. Please provide BSA summary data (mean, standard deviation and number of patients) for men and women separately for the following five age-related subgroups based on age at randomisation (i.e. 2 x 5 subgroups):

- ***i) patients aged under 47 years***
- ***ii) patients aged 47-52 years***
- ***iii) patients aged 53-58 years***
- ***iv) patients aged 59-65 years***
- ***iv) patients aged 66+ years***

Response:

The data requested can found in the table below.

Table 5: Summary statistics for BSA by treatment, gender and age group

TRTC	Sex	AGRP	Obs	Mean	Std Dev	Median	Minimum	Maximum
OBSERVATION	FEMALE	< 47	47	1.69	0.16	1.68	1.37	2.3
		47 - 52	39	1.78	0.2	1.75	1.51	2.32
		53 - 58	50	1.69	0.17	1.7	1.22	2.11
		59 - 65	64	1.72	0.17	1.73	1.33	2.18
		65 +	50	1.63	0.13	1.63	1.27	1.91
	MALE	< 47	75	1.97	0.18	1.96	1.55	2.44
		47 - 52	36	1.99	0.15	1.99	1.64	2.28
		53 - 58	48	1.96	0.18	1.96	1.65	2.45
		59 - 65	47	1.96	0.16	1.96	1.59	2.3
		65 +	57	1.88	0.17	1.9	1.44	2.2
RITUXIMAB	FEMALE	< 47	46	1.77	0.19	1.72	1.45	2.31
		47 - 52	27	1.73	0.14	1.75	1.51	2.12
		53 - 58	38	1.7	0.17	1.68	1.43	2.18
		59 - 65	64	1.76	0.17	1.74	1.46	2.21
		65 +	60	1.67	0.18	1.68	1.28	2.1
	MALE	< 47	61	1.98	0.18	1.98	1.68	2.67
		47 - 52	31	1.99	0.18	1.97	1.67	2.49
		53 - 58	65	1.94	0.17	1.96	1.38	2.28
		59 - 65	63	1.96	0.18	1.94	1.58	2.47
		65 +	50	1.88	0.16	1.85	1.47	2.27

Additionally we provide the patient height and weight by gender in the table below.

Table 6: Summary statistics for height and weight by gender

Sex	N	Label	Mean	Std Dev
FEMALE	485	Height in cm	161.44	6.75
		Weight in kg	67.83	14.39
MALE	533	Height in cm	175.01	7.3
		Weight in kg	79.68	13.34

B3. In Section 6.3.6 some variables used in the economic model are listed in table 98. Please indicate if any other variables are missing from this list (including deterministic variables) and provide their values (and appropriate estimates of uncertainty), range (distribution) and source.

Response:

A full list of variables can be found in appendix 4.

B4. Section 6.4.11 states that patient experience is described in section 6.4.1. This section however does not provide information for each health state. Please provide more information on the impact of NHL on a patient's quality of life for each health state included in the economic model.

Response:

The course of progressive follicular lymphoma is typified by sequential remissions and relapses, disease dissemination, and eventual resistance to current treatment approaches. There is a paucity of relevant literature and research on the quality of life of patients with follicular lymphoma over the course of their disease and impact of different states such progression free (PF) and progressive disease (PD) following first line and subsequent lines of treatment.

Progression free survival (PF1) – It has been assumed that HRQoL remains constant in this state of disease. According to Pettengell and colleagues, newly diagnosed patients either undergoing watch and wait or active treatment had highest mean scores on patient related outcomes (FACT-LYM) score. The authors hypothesised this is because these patient have yet to experience relapse following successful treatment. It is therefore logical to assume that these patients who are progress free following first successful treatment will have higher utility values compared to those who have experience relapse.

Progression free survival (PF2) – It has been assumed that HRQoL remains constant in this state of disease however utility values will be lower than those in PF1. Pettengell and colleagues reported that it seems likely that each time a patients relapses they are likely to experience a worse HRQoL. Issues such as uncertainty (especially in relation to relapse), perceived lack of control, feelings of dependency, anxiety and depression are also important in a recurrent cancer such as follicular lymphoma.

Progressive disease (PD) – It has been assumed that HRQoL remains constant in this state of disease however due to lack of response to the treatment or worsening disease, these patients have the lower utility values compared to those in if progression free states.

B5. In Section 6.5.1 (page 280 of manufacturer's submission), year 1-2 costs in table 104 have been correctly calculated over 24 months but the caption states this is calculated over a 12 month period ("year 1-2 (12 months))". Please confirm the time period for these calculations.

Response:

The parentheses in this table should indeed read "(24 months)".

B6. In Section 6.7.3, Markov traces for the intervention and comparator arms in tables 115 and 116 appear identical. Please confirm whether this information is correct.

Response:

This was a typographical error. Table 115 of the submission is correct. Table 116 is incorrect the correct version of this table can in appendix 5.

B7. The values for mean life years appear to not be discounted in table 117 (i.e. they are the same as the undiscounted values in table 111). Please confirm the correct values for these tables and also confirm that the values in tables 112 – 119 are also correct.

Response:

This is a typographical error. Values in table 111 are discounted. The correct version of tables 112-119 are given in appendix 5.

B8. In table 123, the mean life years (comparator arm) is 4.579 whereas in table 118, this figure is listed as 4.597. Please confirm the correct value.

Response:

The correct value for the life years gained in table 118 for the comparator arm is 4.597 as per table 118

B9. Please provide sensitivity analyses that will examine how sensitive the ICERs are to alternative assumptions on subsequent lines of treatments.

Response:

There are 4 variables that determine the efficacy of subsequent treatments in 2nd line. These are defined by

1. the probability of progressing from PF2 to PD when patients receive R-chemo-R in 2nd line (prr)
2. the probability of progressing from PF2 to PD when patients receive chemotherapy (induction) followed by observation in 2nd line (poo)
3. the probability of dying in PD when patients had received R-chemo-R in 2nd line (p2dr)
4. the probability of dying in PD when patients had received chemotherapy (induction) followed by observation in 2nd line (p2do)

A range for these variables was obtained by running PSA for 500 iterations and determining the confidence intervals for each variable.

Table 7: Variables determining subsequent treatment efficacy and confidence intervals (monthly probabilities)

Variables	prr	poo	p2dr	p2do
Confidence intervals	(0.016, 0.023)	(0.047, 0.064)	(0.020, 0.025)	(0.044, 0.056)

The ranges defined by the confidence intervals in the table above were tested in a one way sensitivity analysis.

The resulting ICERs can be found in the table below.

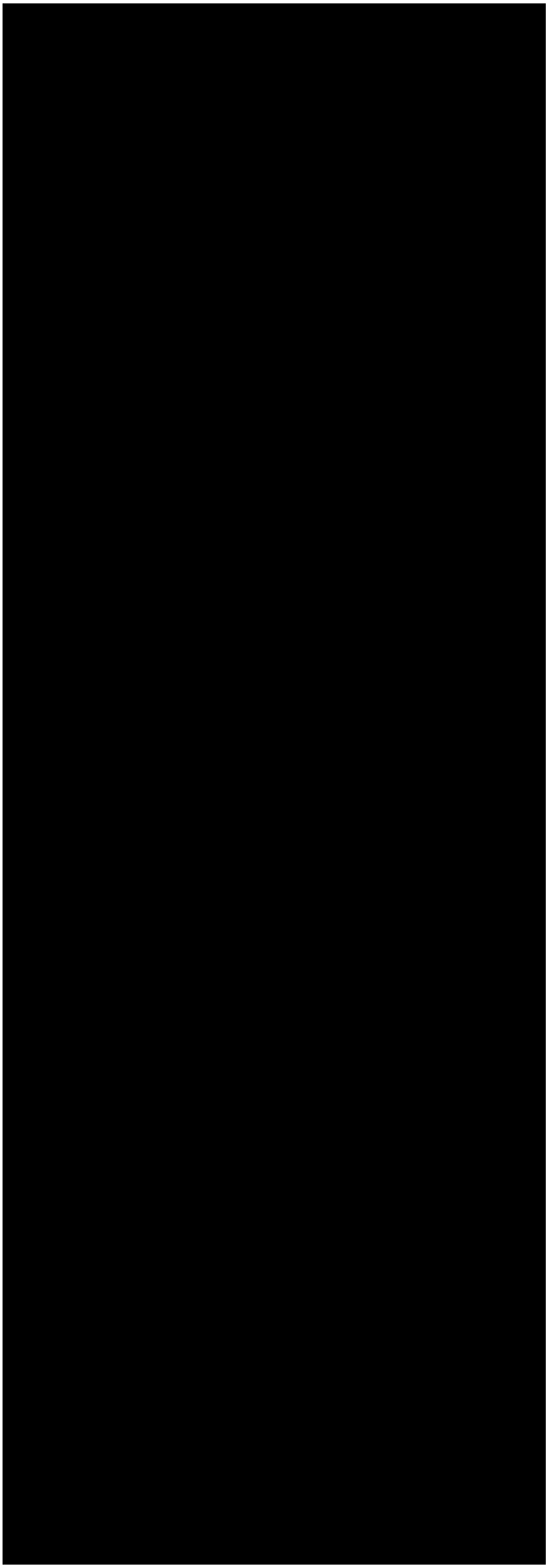
	prr	poo	p2dr	p2do
Base-case probability	0.01954	0.05510	0.02219	0.04996

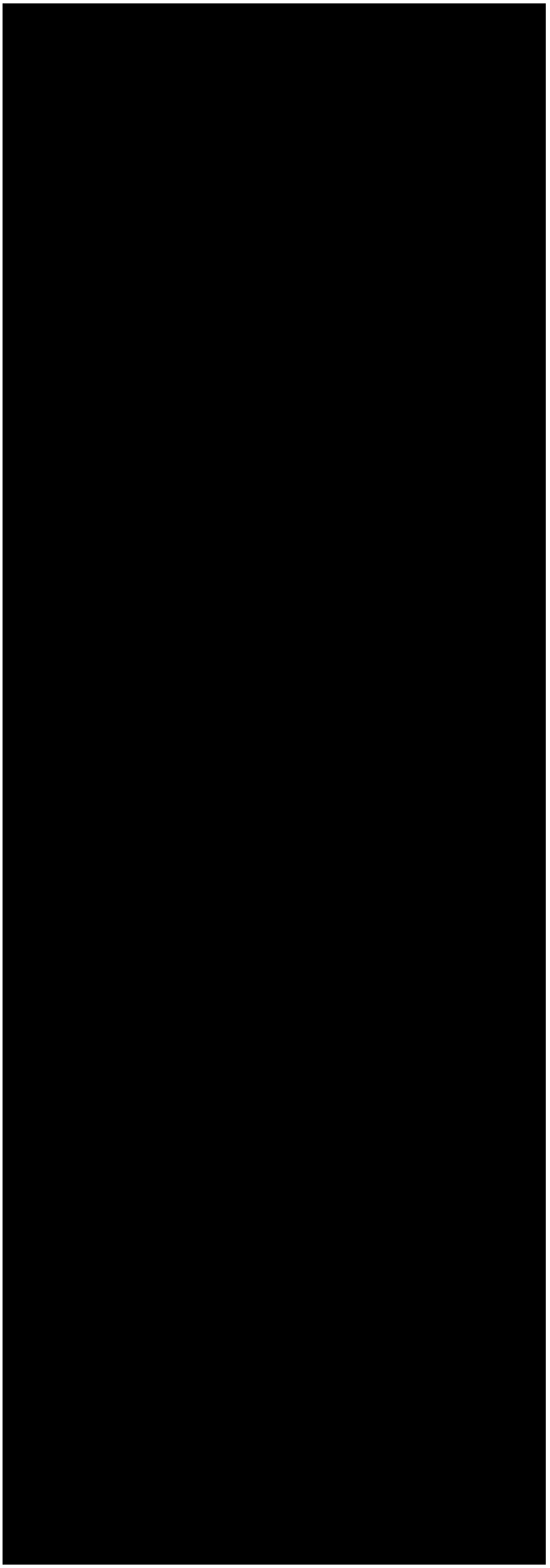
assumption				
ICER (£ per QALY)	**15,978**			
Upper limit probability assumption	0.023	0.064	0.025	0.056
ICER (£ per QALY)	**15,932**	**15,862**	**15,951**	**15943**
lower limit probability assumption	0.016	0.047	0.020	0.044
ICER (£ per QALY)	**16,048**	**16,120**	**16,005**	**16,020**

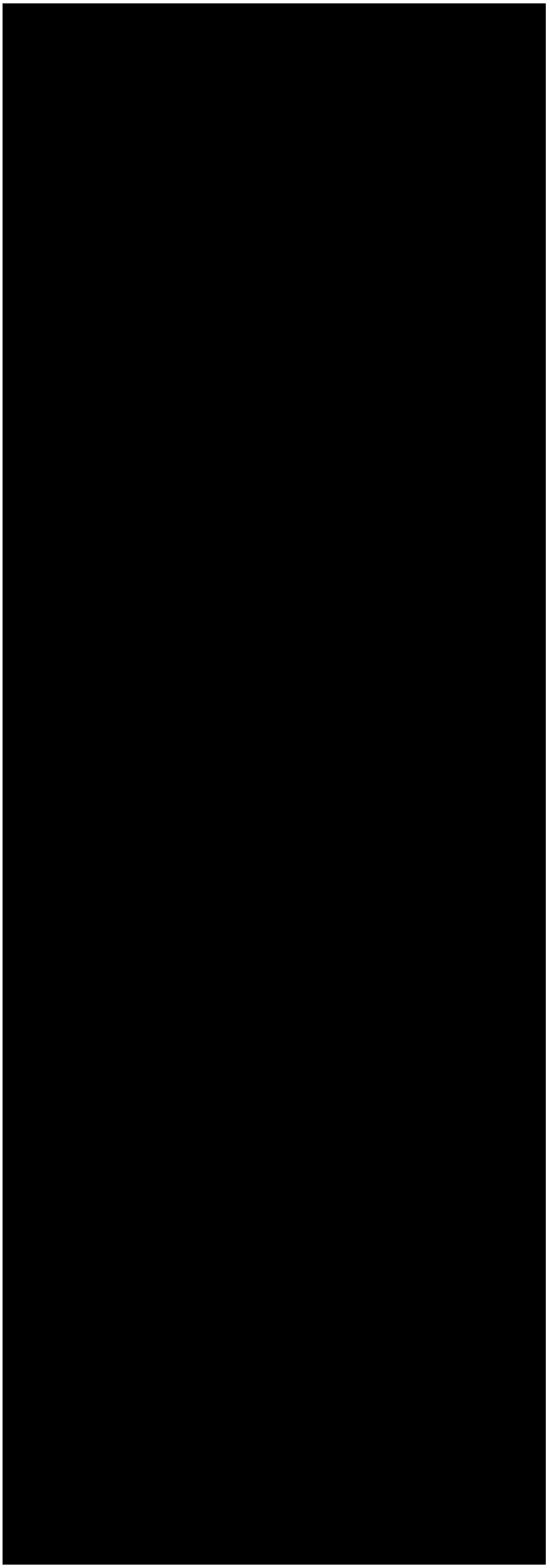
The analysis above demonstrates that the model is not sensitive to the assumptions relating to efficacy of subsequent treatments in the treatment algorithm. This is mainly because the same efficacy assumptions have been applied in the 2 arms of the model (intervention or comparator).

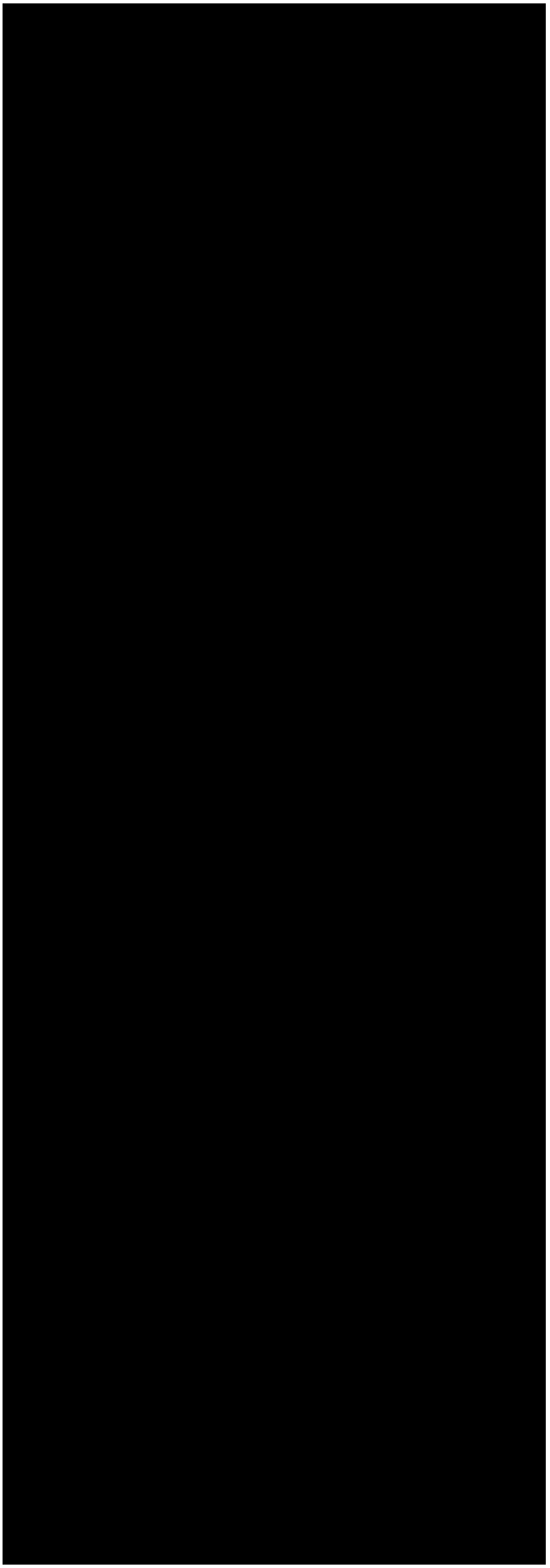
Appendix 1:

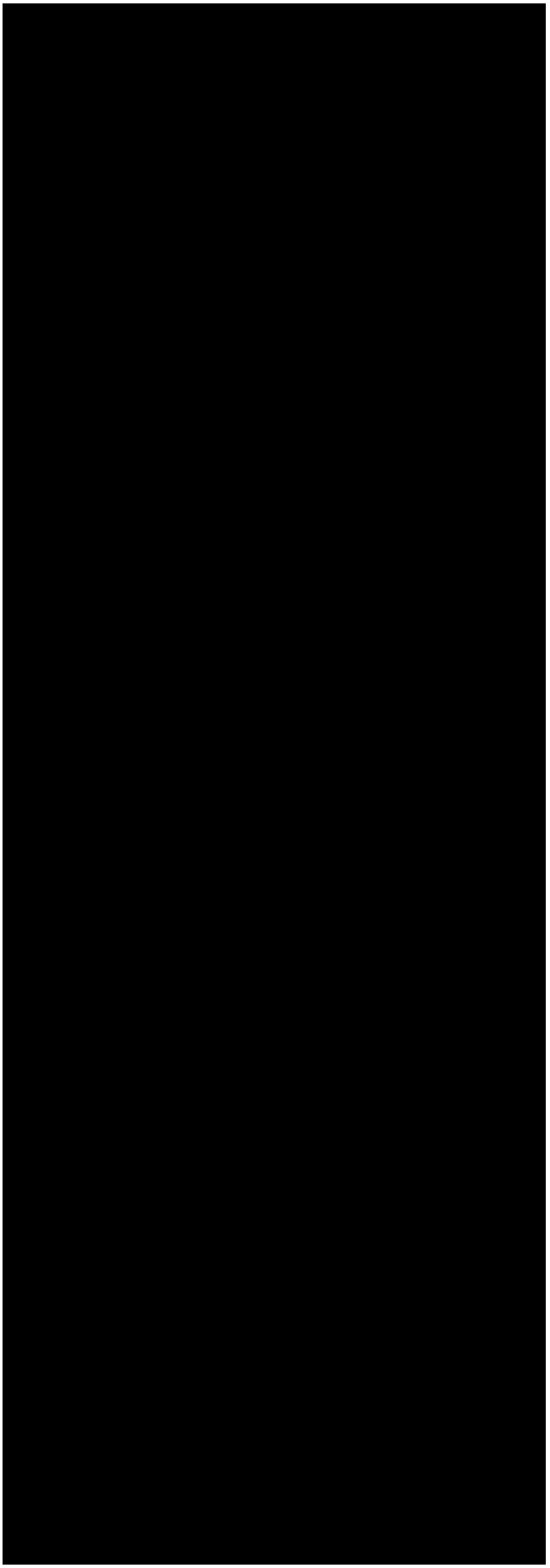
[redacted]

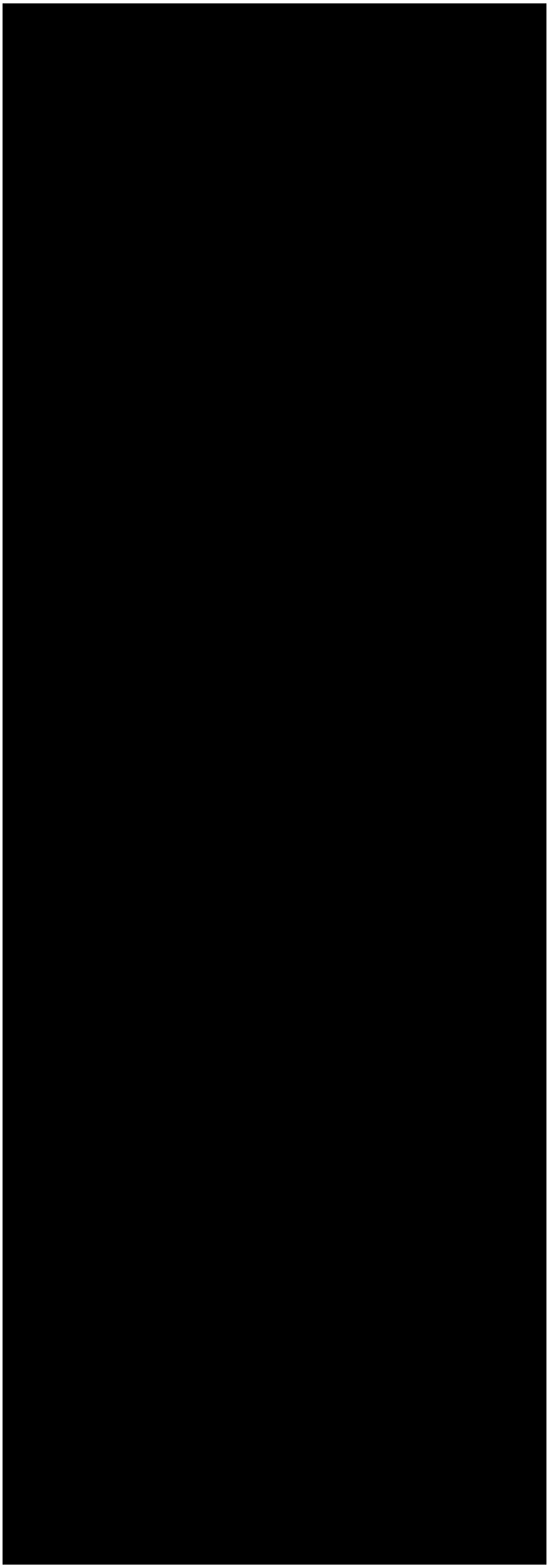












NOTE: The marked survival times are censored observations.

Summary Statistics for Time Variable PFSTIME

Quartile Estimates

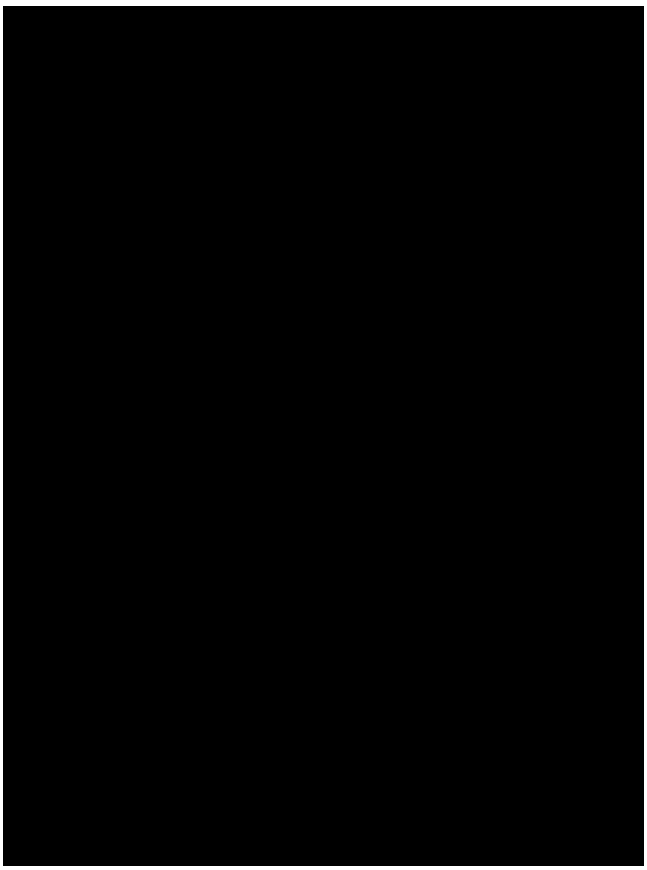
Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75			
50	48.3614	42.0862	
25	16.9199	14.3901	21.3881

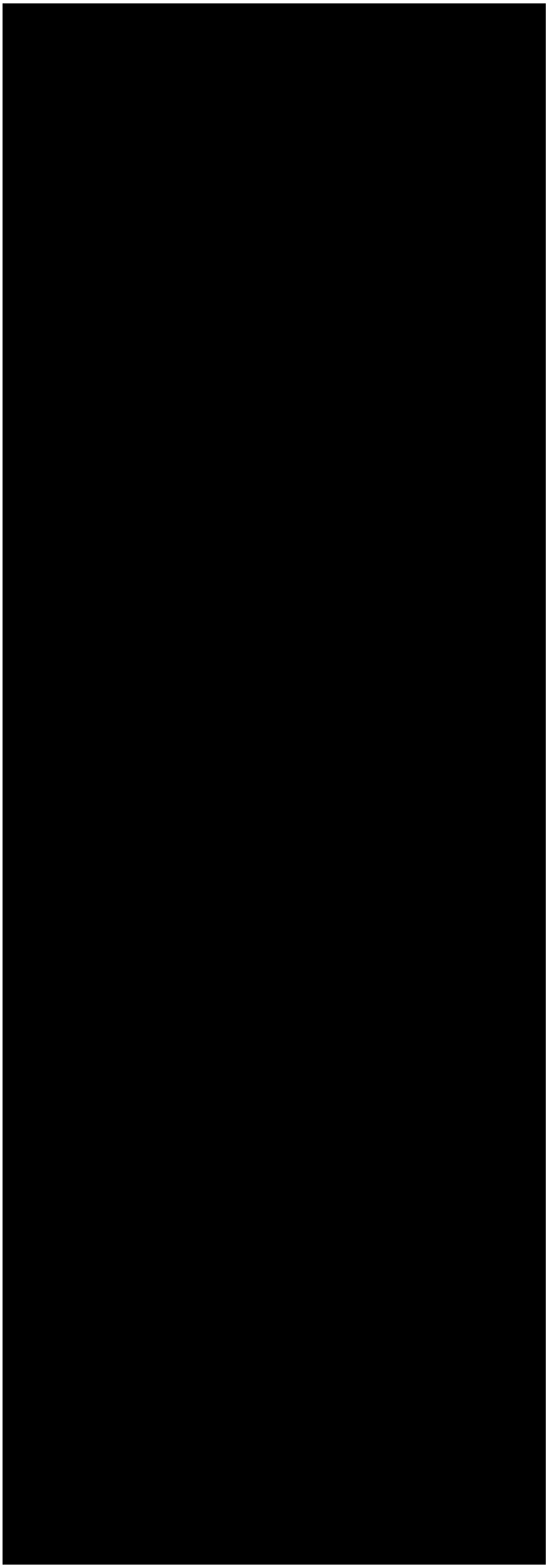
Mean	Standard Error
34.1111	0.7655

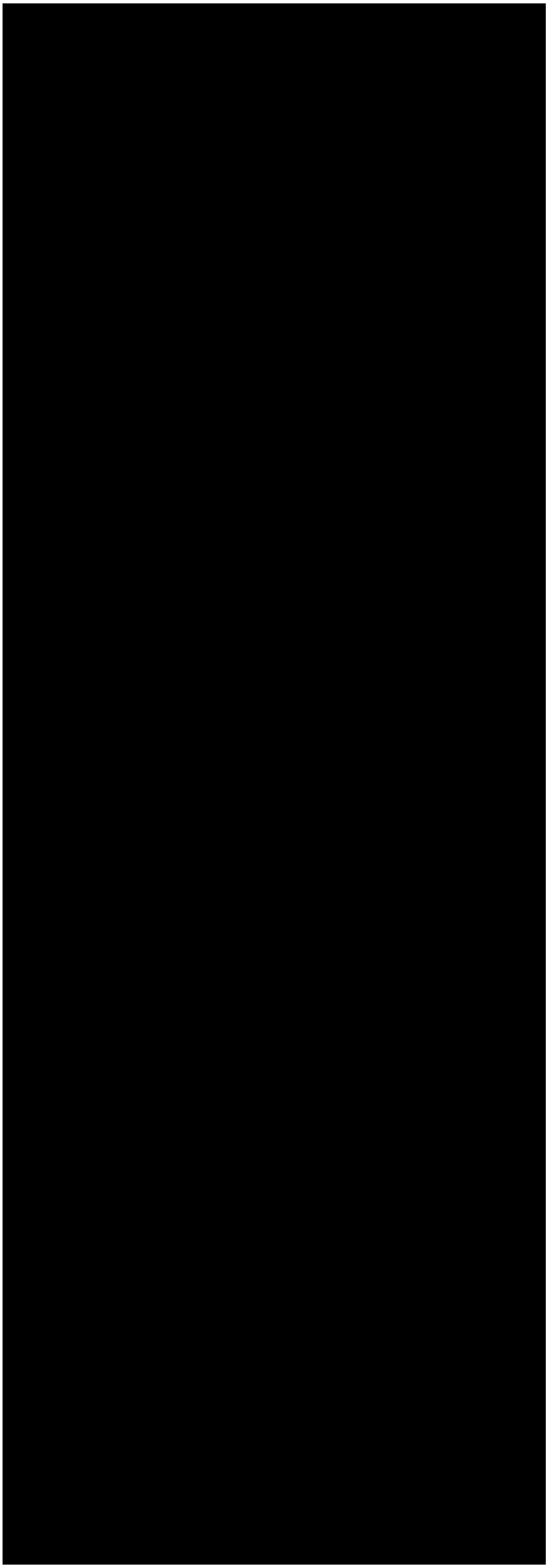
The LIFETEST Procedure

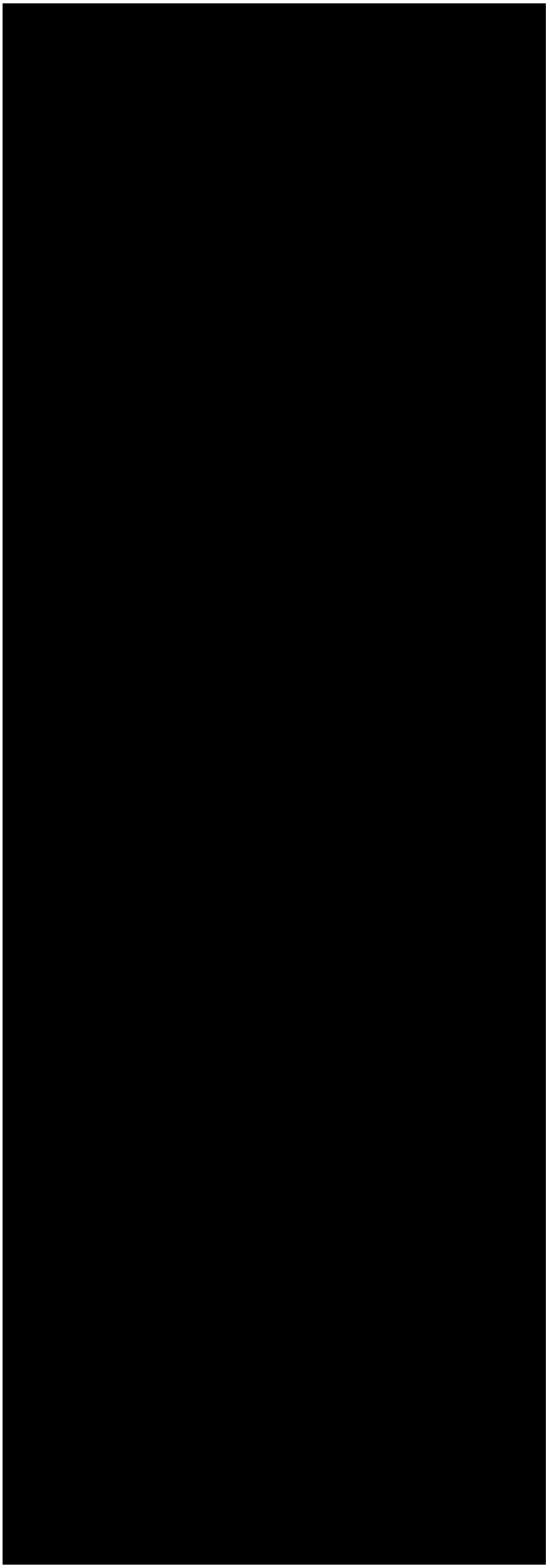
Stratum 2: TRTC = **RITUXIMAB**

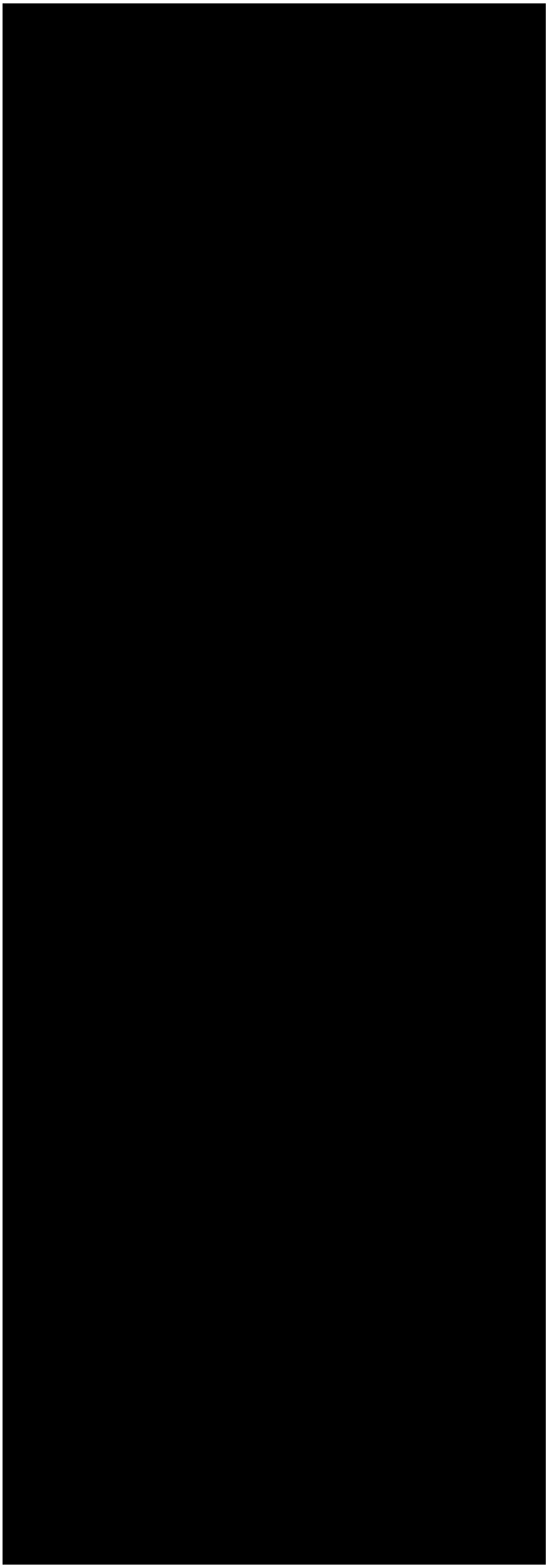
Product-Limit Survival Estimates

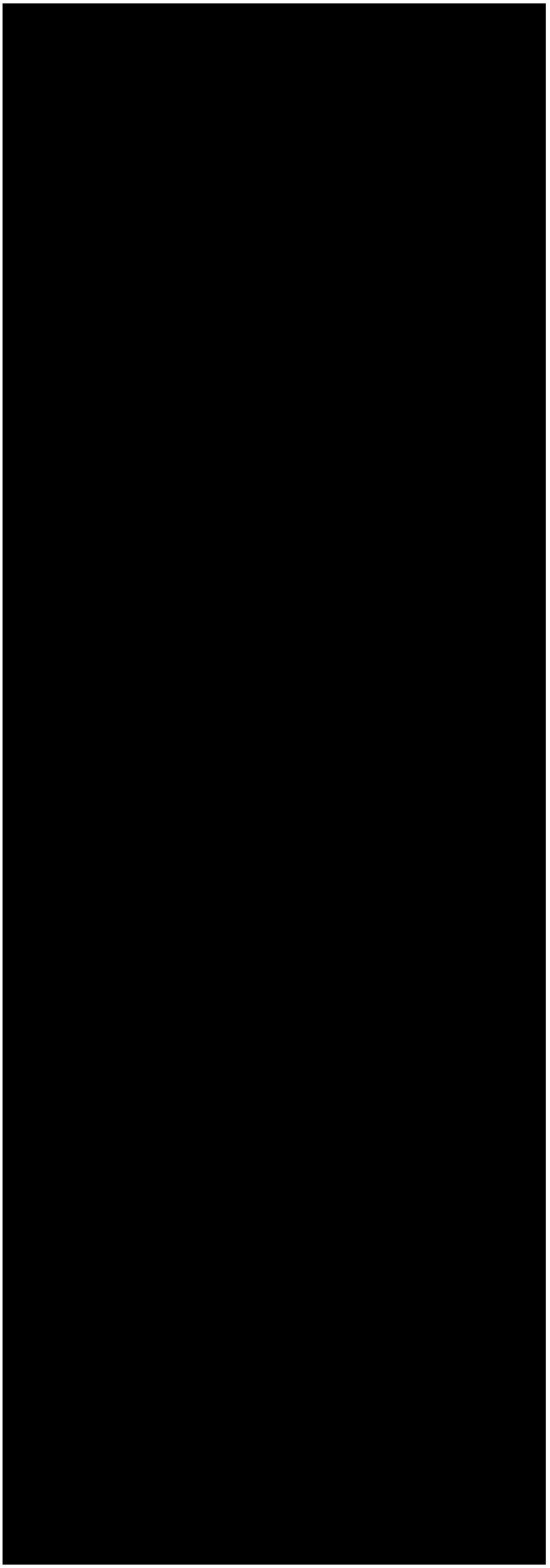


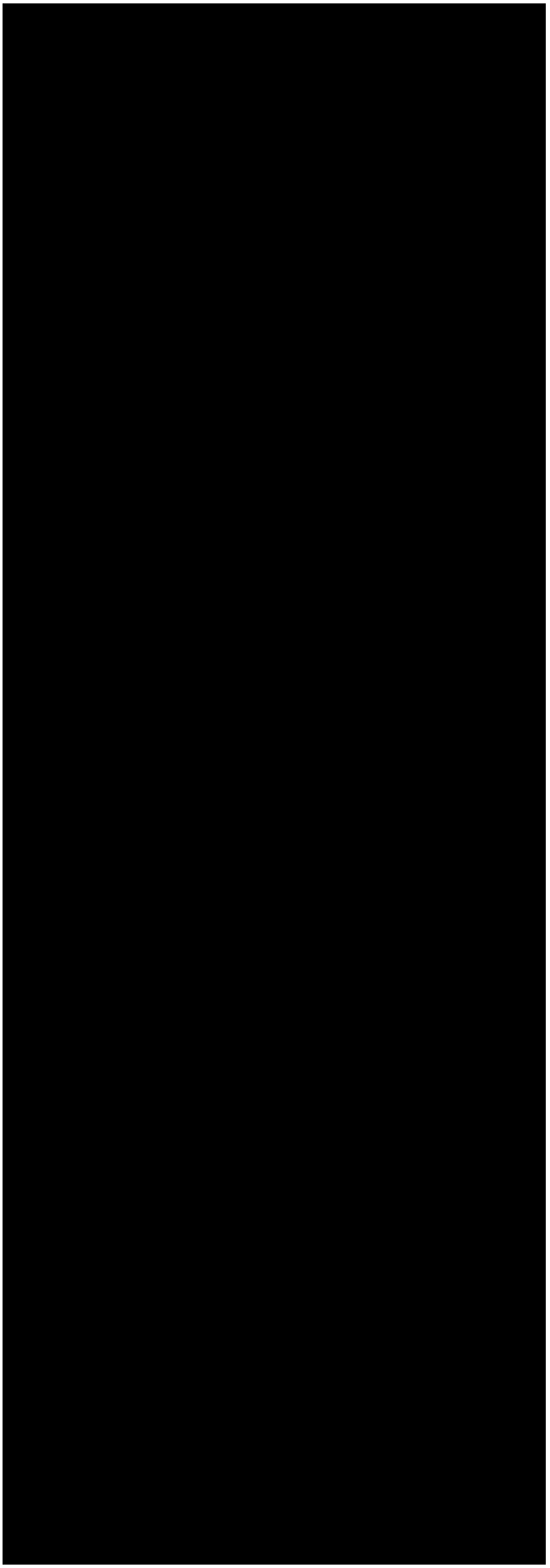












The LIFETEST Procedure

Summary Statistics for Time Variable PFSTIME

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75			
50			
25	36.7639	31.2772	40.9692

Mean	Standard Error
38.8844	0.6443

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

Summary of the Number of Censored and Uncensored Values

Stratum	TRTC	Total	Failed	Censored	Percent Censored
1	OBSERVATION	513	223	290	56.53
2	RITUXIMAB	505	137	368	72.87
Total		1018	360	658	64.64

Appendix 2:
PFS Status: Disposition of Patients (Maintenance) by Treatment and Age Group

MabThera Study MO18264(PRIMA) in NHL

The FREQ Procedure

TRTC	PFSCEN	AGEGRP	Frequency	Percent	Cumulative Frequency	Cumulative Percent
OBSERVATION	Censored	23 - 43	46	4.52	46	4.52
OBSERVATION	Censored	44 - 64	167	16.40	213	20.92
OBSERVATION	Censored	65 - 85	77	7.56	290	28.49
OBSERVATION	Event	23 - 43	44	4.32	334	32.81
OBSERVATION	Event	44 - 64	132	12.97	466	45.78
OBSERVATION	Event	65 - 85	47	4.62	513	50.39
RITUXIMAB	Censored	23 - 43	57	5.60	570	55.99
RITUXIMAB	Censored	44 - 64	224	22.00	794	78.00
RITUXIMAB	Censored	65 - 85	87	8.55	881	86.54
RITUXIMAB	Event	23 - 43	16	1.57	897	88.11
RITUXIMAB	Event	44 - 64	85	8.35	982	96.46
RITUXIMAB	Event	65 - 85	36	3.54	1018	100.00

Appendix 3:
PFS Status: Disposition of Patients (Maintenance) by Treatment and Induction Response

MabThera Study MO18264(PRIMA) in NHL

The FREQ Procedure

TRTC	A_IRSP	PFSCEN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
OBSERVATION	COMPLETE RESPONSE	Censored	119	11.77	119	11.77
OBSERVATION	COMPLETE RESPONSE	Event	76	7.52	195	19.29
OBSERVATION	PARTIAL RESPONSE	Censored	80	7.91	275	27.20
OBSERVATION	PARTIAL RESPONSE	Event	72	7.12	347	34.32
OBSERVATION	UNCONFIRMED COMPLETE RESPONSE	Censored	90	8.90	437	43.22
OBSERVATION	UNCONFIRMED COMPLETE RESPONSE	Event	75	7.42	512	50.64
RITUXIMAB	COMPLETE RESPONSE	Censored	159	15.73	671	66.37
RITUXIMAB	COMPLETE RESPONSE	Event	46	4.55	717	70.92
RITUXIMAB	PARTIAL RESPONSE	Censored	100	9.89	817	80.81
RITUXIMAB	PARTIAL RESPONSE	Event	39	3.86	856	84.67
RITUXIMAB	UNCONFIRMED COMPLETE RESPONSE	Censored	105	10.39	961	95.05
RITUXIMAB	UNCONFIRMED COMPLETE RESPONSE	Event	50	4.95	1011	100.00

Appendix 4:

Variable Name	Location in Excel Sheet	Description
c_ae_new	='Adverse events'!$AC$6	Cost of AE's in New Therapy arm
c_ae_com	='Adverse events'!$P$6	Cost of AE's in Comparator arm
ompest_e	=Exponential!$B$11:$C$13	parameter of exponential functions (see Exponential sheet)
Ofpest_e	=Exponential!$B$5:$C$7	parameter of exponential functions (see Exponential sheet)
olce	=Exponential!$C$30	parameter of exponential functions (see Exponential sheet)
ogce	=Exponential!$C$31	parameter of exponential functions (see Exponential sheet)
omcmat_e	=Exponential!$D$11:$F$13	parameter of exponential functions (see Exponential sheet)
Ofcmat_e	=Exponential!$D$5:$F$7	parameter of exponential functions (see Exponential sheet)
olne	=Exponential!$G$30	parameter of exponential functions (see Exponential sheet)
ogne	=Exponential!$G$31	parameter of exponential functions (see Exponential sheet)
Mpest_e	=Exponential!$J$11:$K$13	Parameter estimates: exponential (MFU data) - not used in model
fpest_e	=Exponential!$J$5:$K$7	Parameter estimates: exponential (full data)
plce	=Exponential!$K$30	parameter of exponential functions (see Exponential sheet)
pgce	=Exponential!$K$31	parameter of exponential functions (see Exponential sheet)
Mcmat_e	=Exponential!$L$11:$N$13	Covariance matrix: exponential (median follow up data (MFU) data) - not used in model
fcmat_e	=Exponential!$L$5:$N$7	Covariance matrix: exponential (full data)
plne	=Exponential!$O$30	parameter of exponential functions (see Exponential sheet)
pgne	=Exponential!$O$31	parameter of exponential functions (see Exponential sheet)
ompest_ga	=Gamma!$B$11:$C$14	parameter of gamma functions (see Gamma sheet)
Ofpest_ga	=Gamma!$B$5:$C$8	parameter of gamma functions (see Gamma sheet)
olcga	=Gamma!$C$38	parameter of gamma functions (see Gamma sheet)
ogcga	=Gamma!$C$39	parameter of gamma functions (see Gamma sheet)
odcga	=Gamma!$C$40	parameter of gamma functions (see Gamma sheet)
omcmat_ga	=Gamma!$D$11:$G$14	parameter of gamma functions (see Gamma sheet)
Ofcmat_ga	=Gamma!$D$5:$G$8	parameter of gamma functions (see Gamma sheet)
od	=Gamma!$E$23	parameter of gamma functions (see Gamma sheet)
og	=Gamma!$E$24	parameter of gamma functions (see Gamma sheet)
ok	=Gamma!$E$25	parameter of gamma functions (see Gamma sheet)
ogd	=Gamma!$E$26	parameter of gamma functions (see Gamma sheet)
obc	=Gamma!$E$27	parameter of gamma functions (see Gamma sheet)
obn	=Gamma!$E$28	parameter of gamma functions (see Gamma sheet)
opd	=Gamma!$E$30	parameter of gamma functions (see Gamma sheet)
opg	=Gamma!$E$31	parameter of gamma functions (see Gamma sheet)
opk	=Gamma!$E$32	parameter of gamma functions (see Gamma sheet)

opgd	=Gamma!$E$33	parameter of gamma functions (see Gamma sheet)
opbc	=Gamma!$E$34	parameter of gamma functions (see Gamma sheet)
opbn	=Gamma!$E$35	parameter of gamma functions (see Gamma sheet)
olnga	=Gamma!$G$38	parameter of gamma functions (see Gamma sheet)
ognga	=Gamma!$G$39	parameter of gamma functions (see Gamma sheet)
odnga	=Gamma!$G$40	parameter of gamma functions (see Gamma sheet)
Mpest_ga	=Gamma!$I$11:$J$14	Parameter estimates: gamma (MFU data) - not used in model
fpest_ga	=Gamma!$I$5:$J$8	Parameter estimates: gamma (full data)
plcga	=Gamma!$J$38	parameter of gamma functions (see Gamma sheet)
pgcga	=Gamma!$J$39	parameter of gamma functions (see Gamma sheet)
pdcga	=Gamma!$J$40	parameter of gamma functions (see Gamma sheet)
Mcmat_ga	=Gamma!$K$11:$N$14	Covariance matrix: gamma (MFU data) - not used in model
fcmat_ga	=Gamma!$K$5:$N$8	Covariance matrix: gamma (full data)
d	=Gamma!$L$23	d- parameter of gamma functions (see Gamma sheet)
g	=Gamma!$L$24	parameter of gamma functions (see Gamma sheet)
k	=Gamma!$L$25	parameter of gamma functions (see Gamma sheet)
gd	=Gamma!$L$26	parameter of gamma functions (see Gamma sheet)
bc	=Gamma!$L$27	parameter of gamma functions (see Gamma sheet)
bn	=Gamma!$L$28	parameter of gamma functions (see Gamma sheet)
pd	=Gamma!$L$30	parameter of gamma functions (see Gamma sheet)
pg	=Gamma!$L$31	parameter of gamma functions (see Gamma sheet)
pk	=Gamma!$L$32	parameter of gamma functions (see Gamma sheet)
pgd	=Gamma!$L$33	parameter of gamma functions (see Gamma sheet)
pbc	=Gamma!$L$34	parameter of gamma functions (see Gamma sheet)
pbn	=Gamma!$L$35	parameter of gamma functions (see Gamma sheet)
plnga	=Gamma!$N$38	parameter of gamma functions (see Gamma sheet)
pgnga	=Gamma!$N$39	parameter of gamma functions (see Gamma sheet)
pdnga	=Gamma!$N$40	parameter of gamma functions (see Gamma sheet)
ompes_go	=Gompertz!$B$11:$C$13	parameter of gompertz functions (see Gompertz sheet)
Ofpest_go	=Gompertz!$B$5:$C$7	parameter of gompertz functions (see Gompertz sheet)
omcmat_go	=Gompertz!$D$11:$F$13	parameter of gompertz functions (see Gompertz sheet)
Ofcmat_go	=Gompertz!$D$5:$F$7	parameter of gompertz functions (see Gompertz sheet)
Mpest_go	=Gompertz!$I$11:$J$13	Parameter estimates: gompertz (MFU data) - not used in model
fpest_go	=Gompertz!$I$5:$J$7	Parameter estimates: gompertz (full data)
plcgo	=Gompertz!$J$30	parameter of gompertz functions (see Gompertz sheet)
pgcgo	=Gompertz!$J$31	parameter of gompertz functions (see Gompertz sheet)
Mcmat_go	=Gompertz!$K$11:$M$13	Covariance matrix: gompertz (MFU data) - not used in model
fcmat_go	=Gompertz!$K$5:$M$7	Covariance matrix: gompertz (full data)
plngo	=Gompertz!$N$30	parameter of gompertz functions (see Gompertz sheet)
pgngo	=Gompertz!$N$31	parameter of gompertz functions (see Gompertz sheet)
Pfsdth_new	='KM PFS'!$M$11	New Therapy arm: monthly probability of death while in PFS (1L)
pfs2dth_new	='KM PFS'!$M$48	New Therapy arm: monthly probability of death while in PFS (2L)

Pfsdth_com	='KM PFS'!$P$11	Comparator arm: monthly probability of death while in PFS (1L)
pfs2dth_com	='KM PFS'!$P$48	Comparator arm: monthly probability of death while in PFS (2L)
ompest_ll	='Log Logistic'!$B$11:$C$13	parameter of log logistic functions (see log logistic sheet)
Ofpest_ll	='Log Logistic'!$B$5:$C$7	parameter of log logistic functions (see log logistic sheet)
olcl	='Log Logistic'!$C$30	parameter of log logistic functions (see log logistic sheet)
ogcl	='Log Logistic'!$C$31	parameter of log logistic functions (see log logistic sheet)
omcmat_ll	='Log Logistic'!$D$11:$F$13	parameter of log logistic functions (see log logistic sheet)
Ofcmat_ll	='Log Logistic'!$D$5:$F$7	parameter of log logistic functions (see log logistic sheet)
olnl	='Log Logistic'!$G$30	parameter of log logistic functions (see log logistic sheet)
ognl	='Log Logistic'!$G$31	parameter of log logistic functions (see log logistic sheet)
Mpest_ll	='Log Logistic'!$J$11:$K$13	Parameter estimates: log logistic (MFU data) - not used in model
fpest_ll	='Log Logistic'!$J$5:$K$7	Parameter estimates: log logistic (full data)
plcl	='Log Logistic'!$K$30	parameter of log logistic functions (see log logistic sheet)
pgcl	='Log Logistic'!$K$31	parameter of log logistic functions (see log logistic sheet)
Mcmat_ll	='Log Logistic'!$L$11:$N$13	Covariance matrix: log logistic (MFU data) - not used in model
fcmat_ll	='Log Logistic'!$L$5:$N$7	Covariance matrix: log logistic (full data)
plnl	='Log Logistic'!$O$30	parameter of log logistic functions (see log logistic sheet)
pgnl	='Log Logistic'!$O$31	parameter of log logistic functions (see log logistic sheet)
ompest_ln	='Log Normal'!$B$11:$C$13	parameter of log normal functions (see log normal sheet)
Ofpest_ln	='Log Normal'!$B$5:$C$7	parameter of log normal functions (see log normal sheet)
olcn	='Log Normal'!$C$30	parameter of log normal functions (see log normal sheet)
ogcn	='Log Normal'!$C$31	parameter of log normal functions (see log normal sheet)
omcmat_ln	='Log Normal'!$D$11:$F$13	parameter of log normal functions (see log normal sheet)
Ofcmat_ln	='Log Normal'!$D$5:$F$7	parameter of log normal functions (see log normal sheet)

olnn	='Log Normal'!$G$30	parameter of log normal functions (see log normal sheet)
ognn	='Log Normal'!$G$31	parameter of log normal functions (see log normal sheet)
mpest_ln	='Log Normal'!$J$11:$K$13	Parameter estimates: log normal (MFU data) - not used in model
fpest_ln	='Log Normal'!$J$5:$K$7	Parameter estimates: log normal (full data)
plcn	='Log Normal'!$K$30	parameter of log normal functions (see log normal sheet)
pgcn	='Log Normal'!$K$31	parameter of log normal functions (see log normal sheet)
mcmat_ln	='Log Normal'!$L$11:$N$13	Covariance matrix: log normal (MFU data) - not used in model
fcmat_ln	='Log Normal'!$L$5:$N$7	Covariance matrix: log normal (full data)
plnn	='Log Normal'!$O$30	parameter of log normal functions (see log normal sheet)
pgnn	='Log Normal'!$O$31	parameter of log normal functions (see log normal sheet)
psa_sw	='Model Inputs'!$AB$4	Probabilistic senstivity analysis switch (true or false)
psa	='Model Inputs'!$AB$5	Probabilistic senstivity analysis switch (1 or 0)
study	='Model Inputs'!$B$75	name of study (header on all sheets)
newname	='Model Inputs'!$B$76	name of New Therapy
comname	='Model Inputs'!$B$77	name of comparator
compare	='Model Inputs'!$C$79	Not used in model
dose	='Model Inputs'!$C$80	dose variable 1 = Planned Include wastage, 2 = Planned Exclude wastage, 3 = Actual Include wastage, 4 = Actual Exclude wastage
t_horizon	='Model Inputs'!$C$82	model time horizon (see Model Menu dropdown)
nr_simulate	='Model Inputs'!$C$83	Number of simulations
s_com	='Model Inputs'!$C$84	sample size Comparator arm
s_new	='Model Inputs'!$C$85	sample size New therapy arm
distn	='Model Inputs'!$C$86	distribution variable (1 = Weibull, 2 = exponential, 3 = log logistic, 4 = log normal, 5 = gompertz, 6 = gamma, 7 = KM)
cyclen	='Model Inputs'!$C$87	Cycle length (1st line)
cyclen2	='Model Inputs'!$C$88	Cycle length (2nd line)
day2mon	='Model Inputs'!$C$89	Conversion day to month (30.4375 days = 1 month)
cyc2mon	='Model Inputs'!$C$90	Cycle to month value in 1st line maintenance
cyc2mon2	='Model Inputs'!$C$91	Cycle to month value in 2nd line maintenance
ful_mf	='Model	Switch parameter: Use Full or truncated data (not used in

u	Inputs'!$C$92 ='Model	model; only full data is used due to degree of censoring)
age	Inputs'!$E$19 ='Model	age of patient
bsa_new	Inputs'!$E$22 ='Model	Average Body Surface area (all patients)
c_drug_new	Inputs'!$E$27 ='Model	Cost of Rituximab
c_adm_1	Inputs'!$E$32 ='Model	Cycle 1 cost of adminstering Rituximab
c_adm_2	Inputs'!$E$33 ='Model	Subsequent costs of administering Ritixuimab (cycle 2 - 12)
c_rchop	Inputs'!$E$36 ='Model	Cost of R-CHOP induction
c_rcvp	Inputs'!$E$37 ='Model	Cost of R-CVP induction
c_rfcm	Inputs'!$E$38 ='Model	Cost of R-FCM induction
c_chop	Inputs'!$E$39 ='Model	Cost of CHOP induction
c_cvp	Inputs'!$E$40 ='Model	cost of CVP Induction
c_fcm	Inputs'!$E$41 ='Model	Cost of FCM induction
c_pfs	Inputs'!$E$45 ='Model	Monthly Supportive care cost in PFS (1L) : Rituximab arm
c_pfso	Inputs'!$E$47 ='Model	Montly Supportive care cost in PFS (1L): Observation arm
c_pfs2	Inputs'!$E$49 ='Model	Monthly Supportive care cost in PFS (2L) - both arms
cProg	Inputs'!$E$51 ='Model	Monthly Support care cost in Progression
ocPro	Inputs'!$E$53 ='Model	Progression supportive care costs
u_PFS	Inputs'!$E$56 ='Model	Utility value: Progression Free (1st line)
pu_pfs	Inputs'!$E$57 ='Model	PFS (1L) utility: probabilistic value
u_pfs2	Inputs'!$E$58 ='Model	Utility value: Progression Free (2nd line)
pu_pfs2	Inputs'!$E$59 ='Model	PFS (2L) utility: probabilistic value
u_prog	Inputs'!$E$60 ='Model	Utility value: Progressive state
pu_prog	Inputs'!$E$61 ='Model	Progression utility: probabilistic value
disc_c	Inputs'!$E$63 ='Model	Discount rate: Costs
disc_u	Inputs'!$E$64 ='Model	Discount rate: Efficacy
wtp	Inputs'!$E$66 ='Model	Willingness to pay value
pc_pfs	Inputs'!$E$69 ='Model	New therapy PFS (1L) costs: probabilistic value
currency	Inputs'!$E$7 ='Model	Currency symbol
pc_pfso	Inputs'!$E$70 ='Model	Comparator PFS (1L) supportive care costs: probabilistic value
pc_pfs2	Inputs'!$E$71 ='Model	PFS (2L) supportive care costs: probabilistic value
pc_prog		Progression supportive costs New therapy arm: probabilistic

g	Inputs'!$E$72	value
opc_pr	='Model	Progression supportive costs Comparator arm: probabilistic
og	Inputs'!$E$73	value
t_mort	='Mortality Table UK'!$B$6:$C$106	age vector (column B) of the Mortality table sheet
pptx	='Post-Prog Treatments'!$H$2	Cost of post progression therapies (see post progression treatments sheet)
psa1_sw	='Results Table'!$Z$5	Probabilistic senstivity analysis switch (true or false)
psa1	='Results Table'!$Z$6	Probabilistic senstivity analysis switch (1 or 0)
r_2_r	='Transition Probabilities'!$D$10	proportion of patients that will transition from rituximab (1L) to Rituximab (2L)
o_2_r	='Transition Probabilities'!$D$11	proportion of patients that will transition from observation (1L) to Rituximab (2L)
r_2_o	='Transition Probabilities'!$E$10	proportion of patients that will transition from rituximab (1L) to observation (2L)
o_2_o	='Transition Probabilities'!$E$11	proportion of patients that will transition from observation (1L) to observation (2L)
prr	='Transition Probabilities'!$F$56	Monthly transition probability: Transitioning from Rit (2L) to Progression given Rit (1L)
por	='Transition Probabilities'!$F$58	Monthly transition probability: Transitioning from Rit (2L) to Progression given Obs (1L)
p2dr	='Transition Probabilities'!$F$63	Monthly transition probability: Transitioning from Progression to death given Rit (2L)
pro	='Transition Probabilities'!$G$56	Monthly transition probability: Transitioning from Obs (2L) to Progression given Rit (1L)
poo	='Transition Probabilities'!$G$58	Monthly transition probability: Transitioning from Obs (2L) to Progression given Obs (1L)
p2do	='Transition Probabilities'!$G$63	Monthly transition probability: Transitioning from Progression to death given Obs (2L)
ompes t_w	=Weibull!$B$11:$C$13	parameter of weibull function (see weibull sheet)
ofpest_w	=Weibull!$B$5:$C$7	parameter of weibull function (see weibull sheet)
olcw	=Weibull!$C$30	parameter of weibull function (see weibull sheet)
ogcw	=Weibull!$C$31	parameter of weibull function (see weibull sheet)
omcmat_w	=Weibull!$D$11:$F$13	parameter of weibull function (see weibull sheet)
ofcmat_w	=Weibull!$D$5:$F$7	parameter of weibull function (see weibull sheet)
olnw	=Weibull!$G$30	parameter of weibull function (see weibull sheet)
ognw	=Weibull!$G$31	parameter of weibull function (see weibull sheet)
mpest_w	=Weibull!$I$11:$J$13	Parameter estimates: weibull (MFU data) - not used in model
fpest_w	=Weibull!$I$5:$J$7	Parameter estimates: weibull (full data)
plcw	=Weibull!$J$30	parameter of weibull function (see weibull sheet)

pgcw	=Weibull!$J$31	parameter of weibull function (see weibull sheet)
mcmat_w	=Weibull!$K$11:$M$13	Covariance matrix: weibull (MFU data) - not used in model
fcmat_w	=Weibull!$K$5:$M$7	Covariance matrix: weibull (full data)
plnw	=Weibull!$N$30	parameter of weibull function (see weibull sheet)
pgnw	=Weibull!$N$31	parameter of weibull function (see weibull sheet)

Appendix 5:
Correct version of tables 112-119

Table 1128: Summary of model results compared with clinical data (comparator – observation)

Outcome	Clinical trial result	Model result (mean years)
Progression-free survival PF1	42.09 months median PFS	**4.597**
Progression-free survival PF2 with R-chemo-R	N/A	**2.257**
Progression-free survival PF2 with chemo-obs	N/A	**0.219**
Progressed survival PD with R-chemo-R in 2L	N/A	**1.717**
Progressed survival PD with R-chemo-obs in 2L	N/A	**0.228**
Overall survival	NA	**9.017**

(Half-cycle corrected results, **discounted**)

Table 113: Markov trace of survival for the intervention arm (R-maintenance)

year	PF1	PF2 – (R-chemo-R)	PD - (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)	Death
0	0.996	0.004	0.000	0.000	0.000	0.996
1	0.871	0.070	0.008	0.008	0.002	0.871
2	0.762	0.112	0.025	0.010	0.006	0.762
5	0.510	0.149	0.075	0.009	0.010	0.510
10	0.184	0.148	0.114	0.007	0.009	0.184
15	0.062	0.074	0.087	0.002	0.004	0.062
20	0.020	0.029	0.045	0.001	0.001	0.020
25	0.007	0.009	0.019	0.000	0.000	0.007

**Half-cycle corrected and discounted values*

Table 114: Markov trace of survival for the comparator arm (observation)

year	PF1	PF2 – (R-chemo-R)	PD – (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)	Death
0	0.992	0.006	0.000	0.001	0.000	0.000
1	0.799	0.116	0.013	0.023	0.007	0.042
2	0.643	0.177	0.040	0.029	0.017	0.094
5	0.000	0.206	0.112	0.021	0.025	0.636
10	0.112	0.117	0.118	0.008	0.012	0.634
15	0.038	0.050	0.070	0.002	0.004	0.837
20	0.012	0.018	0.032	0.001	0.001	0.935
25	0.004	0.005	0.013	0.000	0.000	0.977

**Half-cycle corrected and discounted values*

Table 115: Markov trace of accrued utility for the intervention arm (R-maintenance)

year	PF1	PF2 – (R-chemo-R)	PD – (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)

0	0.876	0.003	0.000	0.000	0.000
1	0.767	0.056	0.005	0.006	0.001
2	0.671	0.088	0.015	0.008	0.004
5	0.449	0.118	0.047	0.007	0.006
10	0.162	0.117	0.070	0.006	0.006
15	0.054	0.059	0.054	0.002	0.002
20	0.018	0.023	0.028	0.001	0.001
25	0.006	0.007	0.012	0.000	0.000

**Half-cycle corrected and discounted values*

Table 116: Markov trace of accrued utility for the comparator arm (observation)

year	PF1	PF2 – (R-chemo-R)	PD – (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)
0	0.873	0.005	0.000	0.001	0.000
1	0.703	0.092	0.008	0.018	0.004
2	0.566	0.140	0.025	0.023	0.011
5	0.000	0.163	0.069	0.017	0.015
10	0.099	0.092	0.073	0.006	0.007
15	0.033	0.039	0.043	0.002	0.002
20	0.011	0.014	0.020	0.001	0.001
25	0.004	0.004	0.008	0.000	0.000

**Half-cycle corrected and discounted values*

Tables 117, 118 and 119 are correct.

[i] Dreyling M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow up. Annals of Oncology 2010; 21 (supp 5): v181-v183