[redacted]

Friday 26th October 2007

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BY E-MAIL

Dear Chris,

SINGLE TECHNOLOGY APPRAISAL –
Rituximab for the treatment of relapsed or refractory follicular lymphoma

Thank you very much for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal.

Roche welcomes this opportunity to be able to provide further analysis and clarification to demonstrate the clinical and cost effectiveness of rituximab since we do not presently agree with the current conclusions of the Appraisal Committee as regards rituximab not being cost effective for use as both an induction and maintenance treatment for relapsed follicular lymphoma (FL).

It appears that the current ICER of £43,000 for this "dual therapy" strategy (as referred to within the ACD) is primarily driven by the exclusion of any extrapolation of the Kaplan Meier survival data of the EORTC study when estimating the ICER. Considering that the NICE reference case clearly stipulates that costs and benefits must be estimated over a lifetime time horizon, Roche believes that the ERG estimated ICER of £43,000 is presently not a fair or reliable estimate upon which to base final guidance.

Our feedback below explains our position in more detail and provides robust evidence to suggest why rituximab dual therapy should be recommended by the Appraisal Committee for the treatment of relapsed FL patients.

Section One: Further clarification requested by the Appraisal Committee

Introduction

Following Roche's review of the ACD and the ERG Report it is clear that the increases in the Roche estimated ICER of rituximab reported within the ACD and the subsequent uncertainty is largely driven by three modifications to the Roche economic model made by the Liverpool ERG and summarised in Table 1 below.

Table 1: Impact of ERG modifications to Roche estimated ICER of rituximab dual therapy

ERG modification	Change in ICER	ICER
Increase in assumed cost of drug administration	+£1,500	£18,204
Refinement of assumed progressive disease health treatment costs	+£6,000	£22,688
Application of Kaplan Meier survival data with a 4 year time horizon and not an extrapolated survival curve with a lifetime time horizon	+£20,000	£36,718
Cumulative Impact	+£26,000	£43,000

As illustrated in table 1, the use of Kaplan Meier survival data alone by the ERG and the exclusion of any parametric survival analysis is the largest driver which raises the final ICER for rituximab dual therapy to over £40,000.

Roche acknowledges that any extrapolation of survival data is subject to uncertainty and this is inherent in any long-term disease modelling exercise. However such uncertainty is of course usually managed in other appraisals through evaluating alternative extrapolation methods, varying the assumed duration of treatment benefit of the new intervention and providing probabilistic sensitivity analysis.

As requested within the ACD, Roche has therefore provided further analysis for managing the uncertainty around curve extrapolation that will illustrate to the Appraisal Committee that the original extrapolation methodology selected by Roche is both fit for purpose and, arguably, conservative when estimating the incremental lifetime clinical benefits of rituximab dual therapy in relapsed FL.

Background to Further Analysis

Both the ERG and the Appraisal Committee have raised a series of issues relating to the assumptions around parametric survival analysis. These include the following choices of assumptions:

- Use of truncated or un-truncated Kaplan Meier data
- Inclusion or exclusion of "event-free" period of EORTC Kaplan Meier data
- Use of independent or same shaped (proportional hazard) curves
- Selection of parametric curve (Weibull, log logistic, Gompertz, exponential or log normal)

However, when considering these choices are applicable to both the overall and progression free survival curves and for up to 6 population groups within the EORTC study, to fully evaluate all scenarios would require an estimated 320 separate curve estimations.

Consequently, considering the time constraint for providing our response and the ability to effectively evaluate/present such a volume of evidence, our further analysis attempts to comprehensively address all questions within the ACD, whilst also excluding those scenarios that would add very little to the overall assessment of uncertainty.

As requested in section 4.14 of the ACD, all results subsequently reported include the cost refinements made by the ERG to the Roche economic model, except for the terminal care cost assumption. This was excluded due to our inability to reliably replicate this assumption; however including this assumption actually lowers the ICER for rituximab by approximately £200. However as outlined in our response to the ACD in section two, Roche believes the ERG progressive disease cost methods would represent a step down in the hierarchy of available evidence adopted by the Appraisal Committee. When incorporating the ERG cost assumptions, the original ICER for dual therapy rituximab rises to £24,161 and forms the base case for the following additional analysis requested in section 4.14 of the ACD provided below.

As the current "minded not to recommend" guidance relates to the decision problem of using dual therapy rituximab compared to single use maintenance, the reported ICERs throughout the further analysis relates to this scenario only.

1. The effect on cost effectiveness estimates of assuming an event-free period during induction therapy in the four-arm model

The original Roche analysis fitted a parametric survival curve to the observed Kaplan Meier data reported in the EORTC study. The purpose of this extrapolation was to estimate clinical outcomes beyond the follow-up period of the trial. As reported in the original Roche submission, the economic model utilises the observed Kaplan Meier data for the first 2 years, with the Weibull extrapolation only being applied beyond this time-point.

Consequently this "event fee period" is already included in the Roche estimates of the ICER.

Within the EORTC study, all patients who received maintenance therapy (regardless of induction therapy) experienced no events (death or progression) in the first 126 days of the trial. Consequently and as expected, there is a horizontal line for the first 126 days of the Kaplan Meier curves for these patients. The Weibull curve fitted to the KM data by Roche included this horizontal / event free period as it was considered representative of the actual clinical outcomes for this specific patient group. For those patients who did progress or die within the first 126 days and were not re-randomised, their outcomes are captured in a separate Kaplan Meier curve (see Roche submission figure 18, page 121), which is also extrapolated and incorporated within the Roche economic model.

After further clarification with the NICE technical team (teleconference, Wednesday 24th October), it was confirmed to us that the Appraisal Committee had requested that the impact of *excluding* this event free period when performing the extrapolation of the KM data should be evaluated; along with its subsequent impact upon the ICER. Details of the

extrapolation results excluding the event-free period, along with goodness of fit measures and graphical illustrations are outlined as requested in question 2 below.

The impact on the ICER of either including or excluding the event-free period when estimating the extrapolated curves is illustrated in the table below. As there appears to have been confusion over whether the original model included or excluded an event-free period, both scenarios are included below to provide further clarity.

Table 2: Impact upon Dual Therapy ICER of including or excluding event free period when performing curve extrapolation

Kaplan Meier Data	Parametric Function*	ICER; Rituximab Dual Therapy**
Event Free Included	Weibull	£24,161
Event Free Excluded	Exponential	£16,183
Event Free Excluded	Weibull	£21,379

**assuming proportional hazard*
***including ERG cost refinements*

The exclusion of an event-free period from the extrapolation projections reduces the ICER to £21,379 when using the original Weibull curve. However, once the event-free period is excluded, as illustrated in the response to question 2 below, the best fitting curve is now the exponential, which when applied to the economic model generates an ICER of £16,183.

In conclusion, if the event-free period of the original Kaplan Meier is excluded from the survival analysis, the Dual Therapy ICER reduces to £16,183 when the subsequent best fit curve is applied.

2. The effect on Cost Effectiveness of alternative survival models should be assessed, justifying the choice of distribution with "goodness of fit" statistics and graphical representations of models to RCT data.

Within both the original Roche submission and our subsequent response to the ERG clarification letter, Roche presented evidence and a rationale for its selection of curve extrapolation. Goodness of fit statistics were supplied, along with predicted incremental clinical benefit in Table 22 of our original Roche submission and replicated again below in Appendix 1. Therefore, this further analysis of goodness of fit relates to curve fitting where the event-free period is excluded. This analysis therefore provides more detail on the selection of the exponential curve described in our response to question 1 above. Please note the Kaplan Meier curves for non-responders to RCHOP or CHOP are not subject to an event-free period and therefore are excluded from this particular sensitivity analysis.

Selection of optimal survival model – Including event free period

(see Appendix 1)

Selection of optimal survival model – Excluding event free period

Several alternative parametric functions were evaluated to assess the optimal goodness of fit for each model when the event-free period was excluded. The measure of goodness of fit for each curve is presented below.

Table 3: Goodness of Fit Statistics (event-free period excluded)

		BIC		AIC	
Treatment	**Distribution**	**OS**	**PFS**	**OS**	**PFS**
CHOP + (MabThera or Observation)	Exponential	-91.24	-180.59	-90.75	-180.10
	Log Logistic	-91.56	-182.26	-90.58	-181.29
	Log Normal	-92.04	-183.16	-91.06	-182.18
	Weibull	-91.63	-182.82	-90.65	-181.84
	Gompertz	NC	NC	NC	NC
R-CHOP + (MabThera or Observation)	Exponential	-87.87	-212.89	-87.25	-212.27
	Log Logistic	-88.23	-214.07	-86.99	-212.83
	Log Normal	-88.98	-213.69	-87.74	-212.45
	Weibull	-87.99	-215.46	-86.74	-214.22
	Gompertz	NC	NC	NC	NC

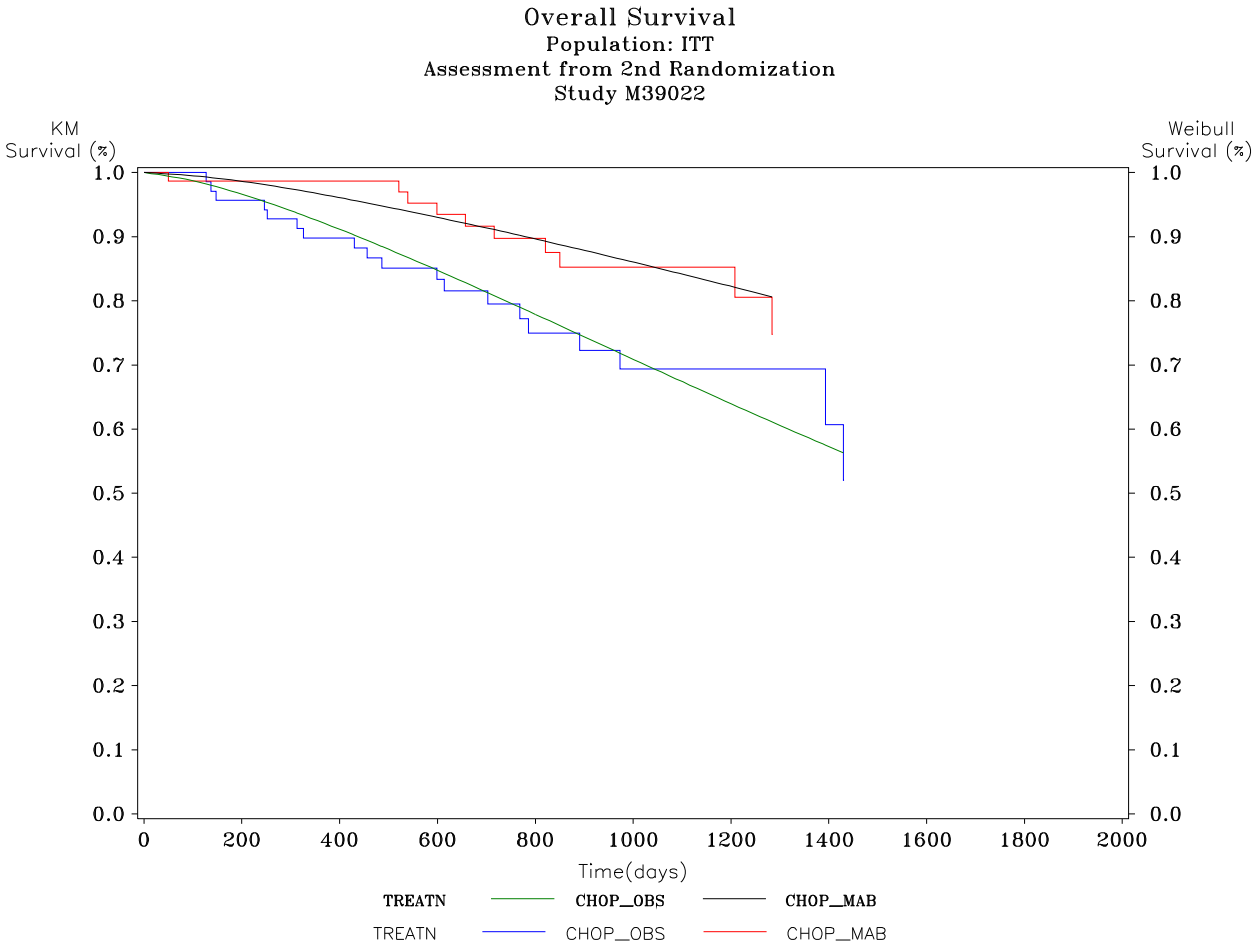
Note: The Gompertz model failed to converge for R-CHOP + (MabThera vs. Observation) and CHOP + (MabThera vs. Observeration) and therefore was dismissed due t o being too poor a fit

The AIC and BIC statistics are two alternative measures of measuring the goodness for fit, with the number closer to zero representing the best fit of the data. In six of the eight scenarios for Overall Survival and PFS, the exponential (as highlighted) was the best fit of the data and therefore selected for the event-free excluded scenario.

Graphical overlay of Kaplan Meier data and Extrapolated Curves for CHOP-R and CHOP-O patients

As requested the graphical plot of the alternative fitted curves to the RCT data are presented below.

Weibull Overall Survival – CHOP,O and CHOP,R



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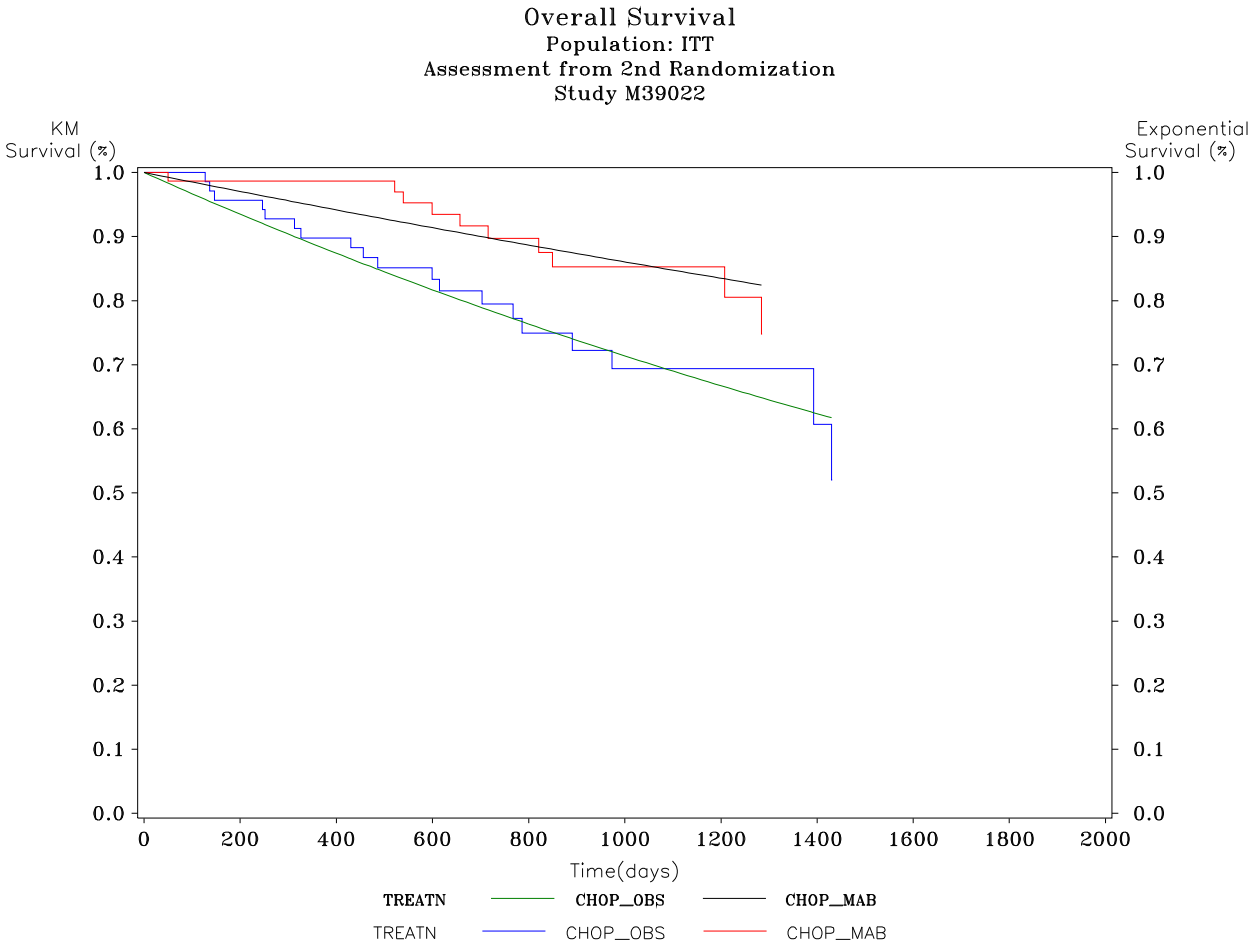
Exponential Overall Survival– CHOP,O and CHOP,R



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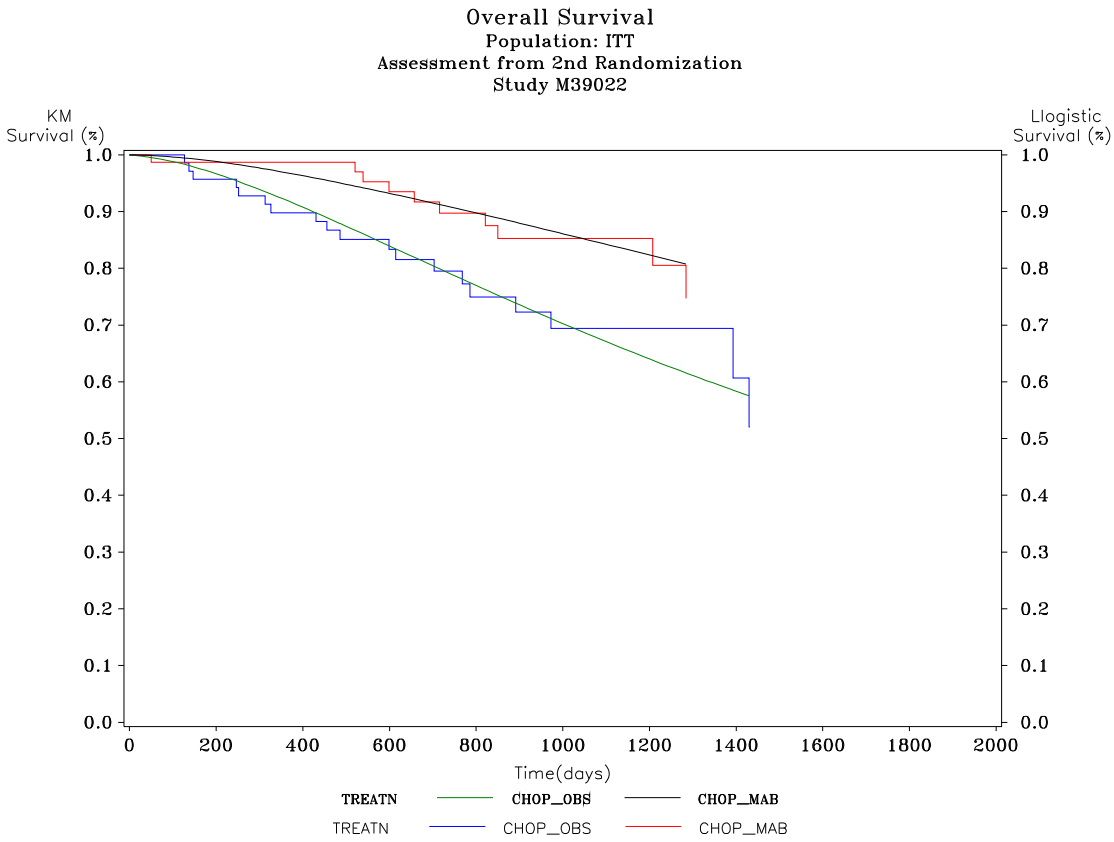
Log Logistic Overall Survival– CHOP,O and CHOP,R



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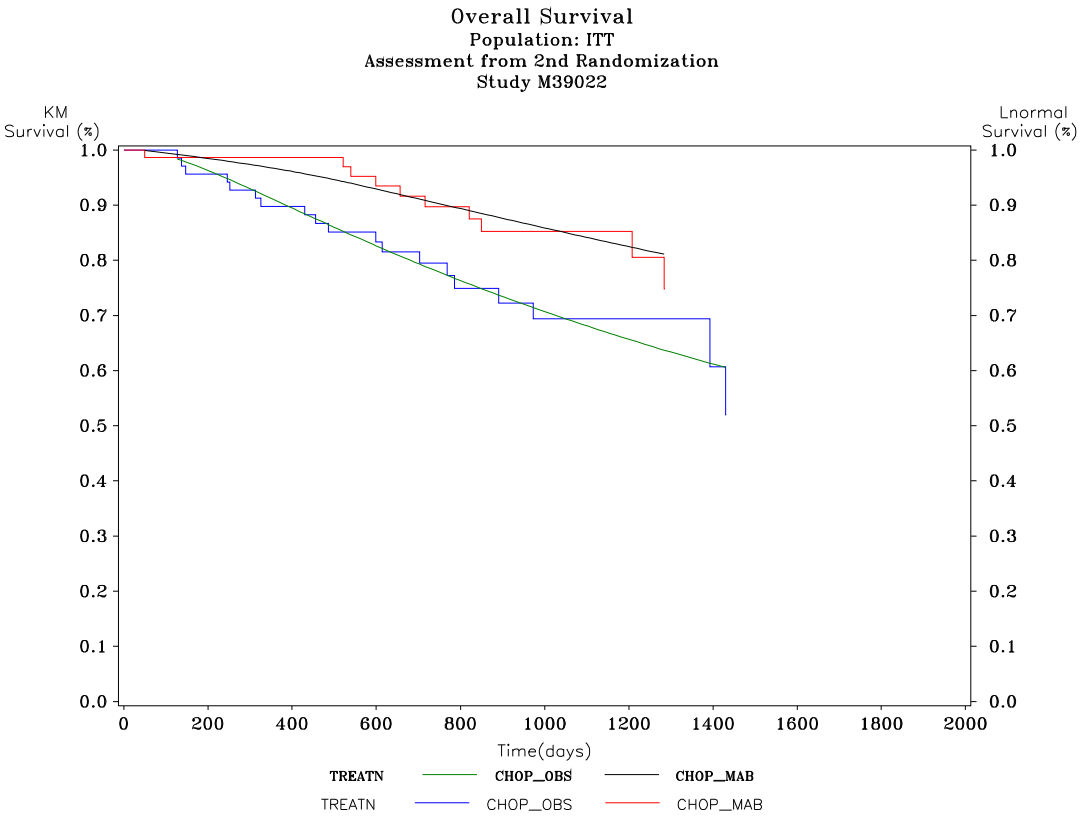
Log Normal PFS– CHOP,O and CHOP,R



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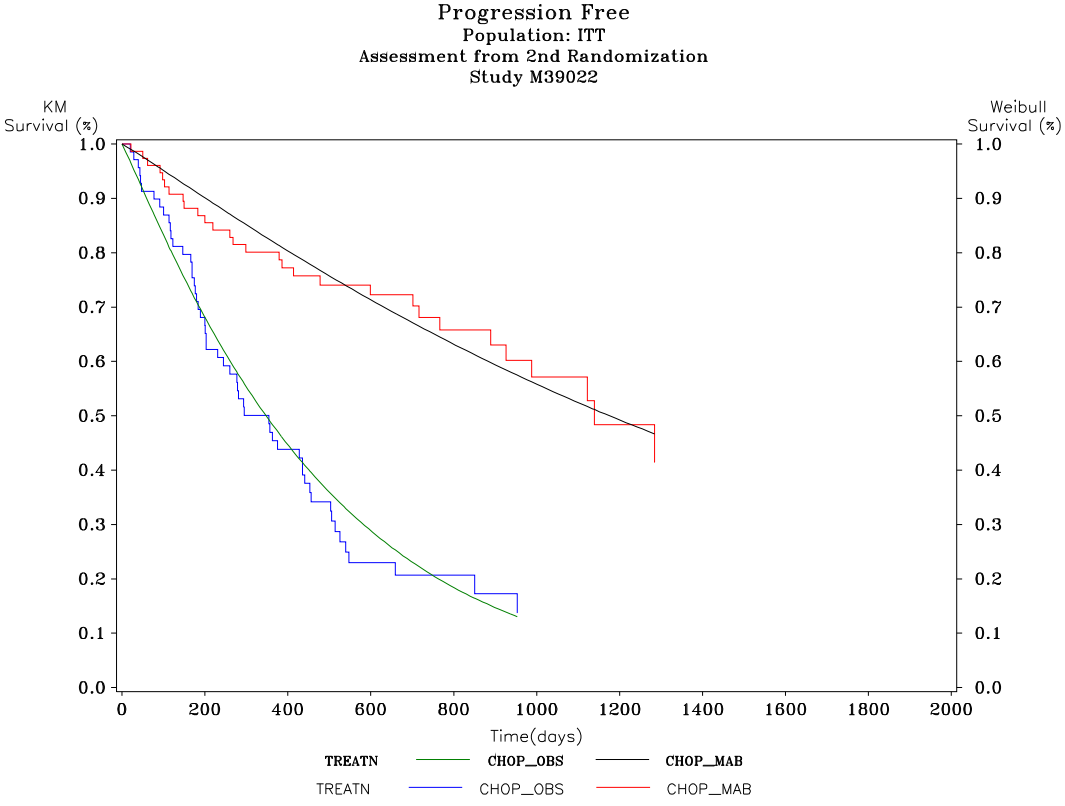
Weibull PFS– CHOP,O and CHOP,R– CHOP,O and CHOP,R



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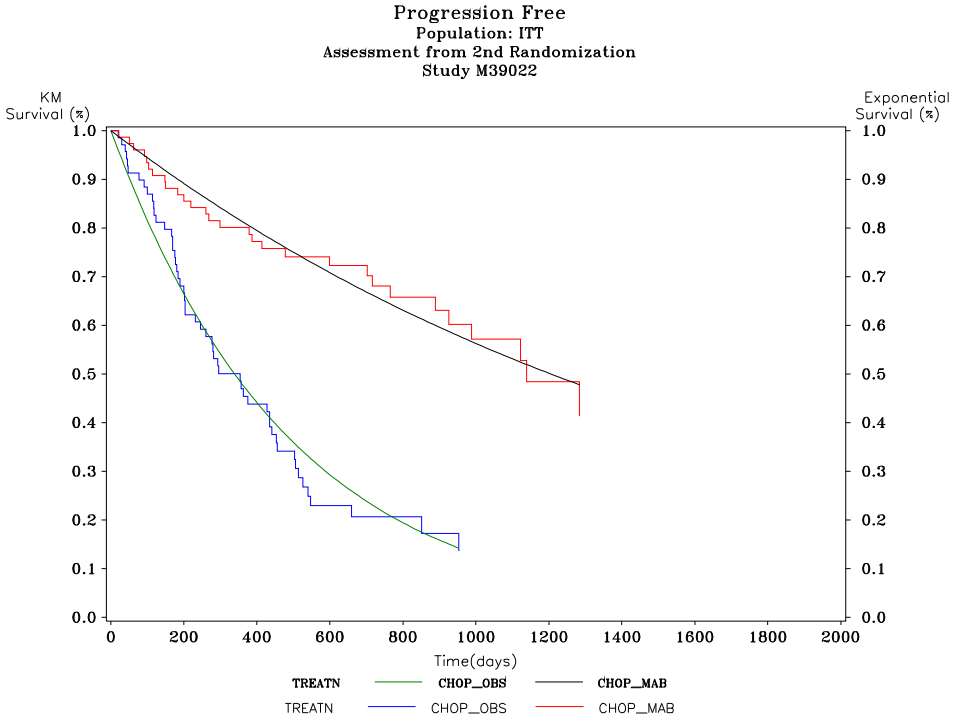
Exponential PFS– CHOP,O and CHOP,R



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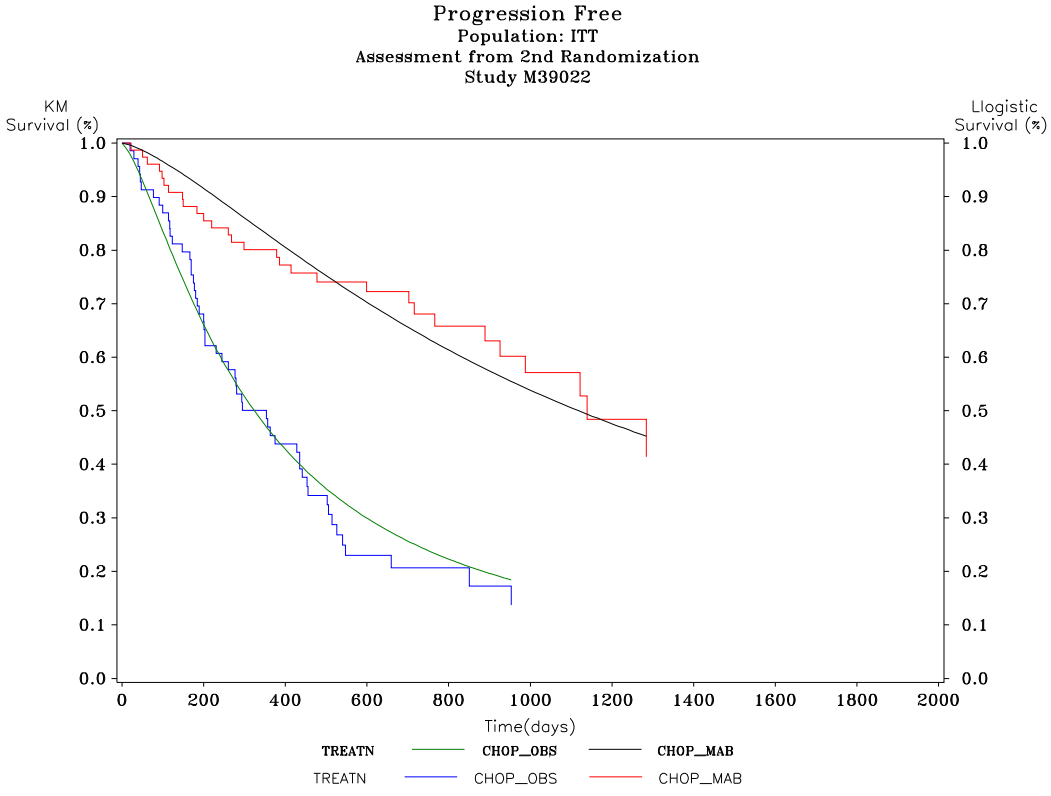
Log Logistic PFS– CHOP,O and CHOP,R



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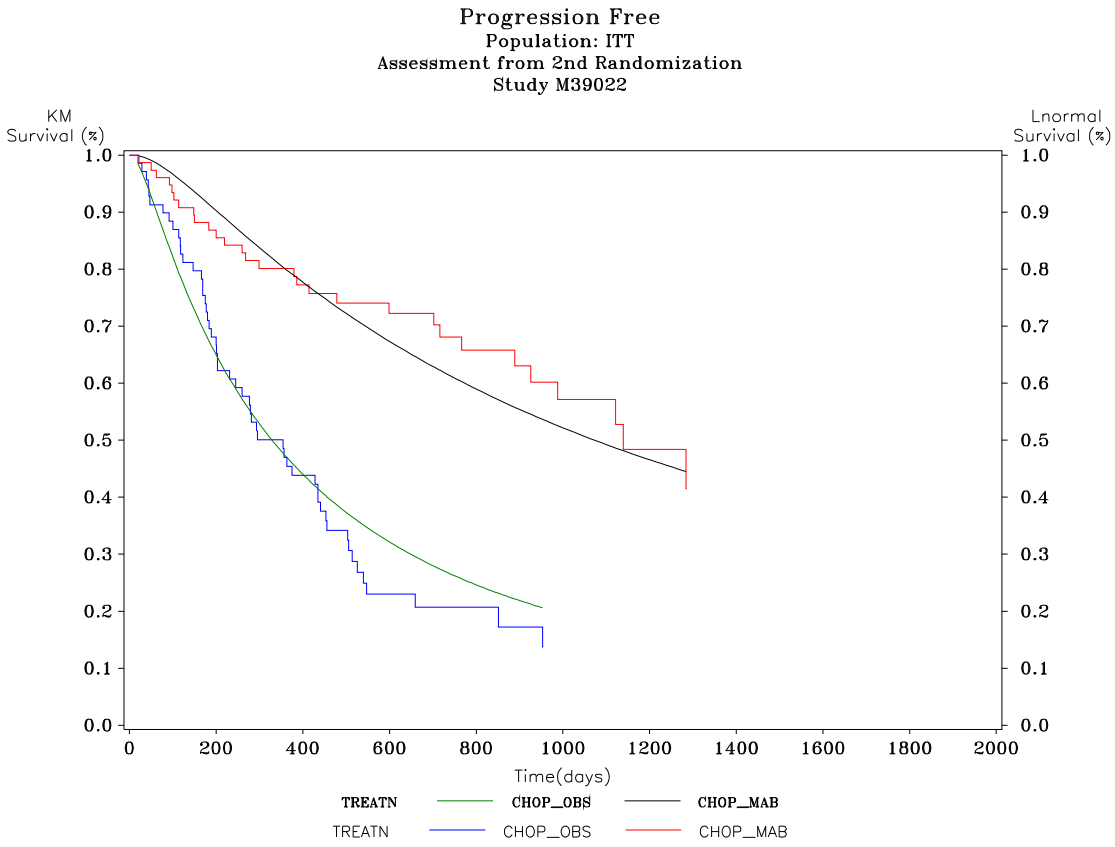
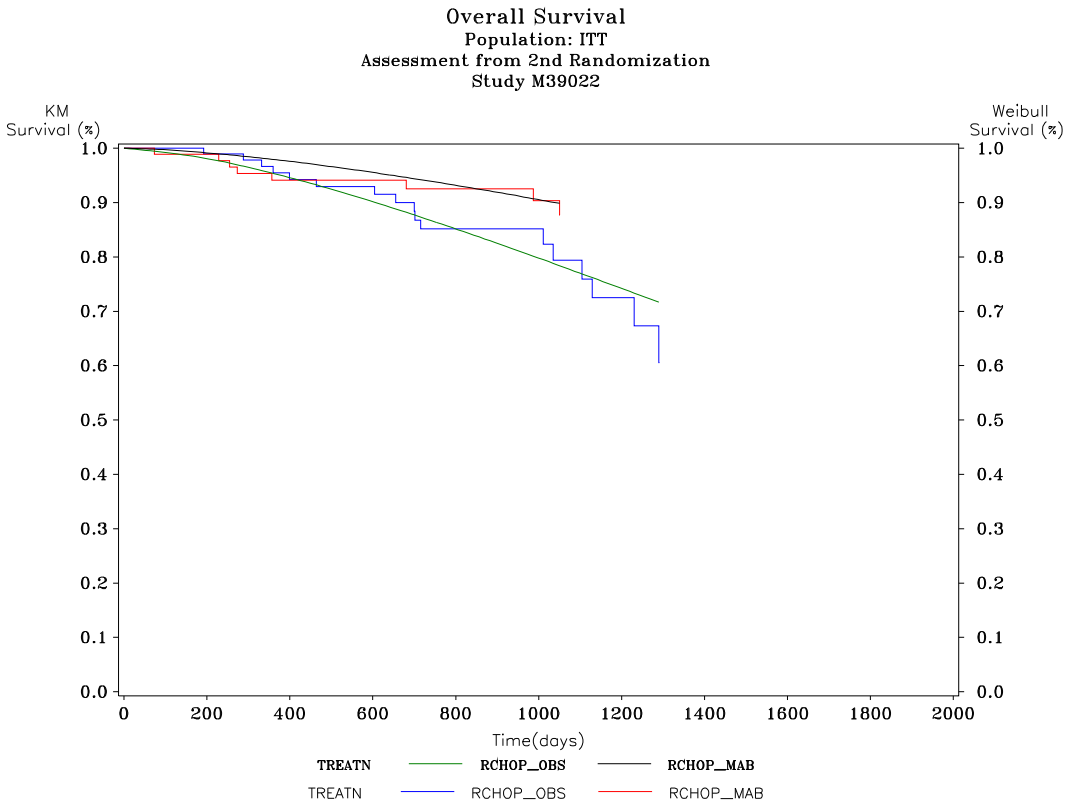
Log-Normal PFS– CHOP,O and CHOP,R

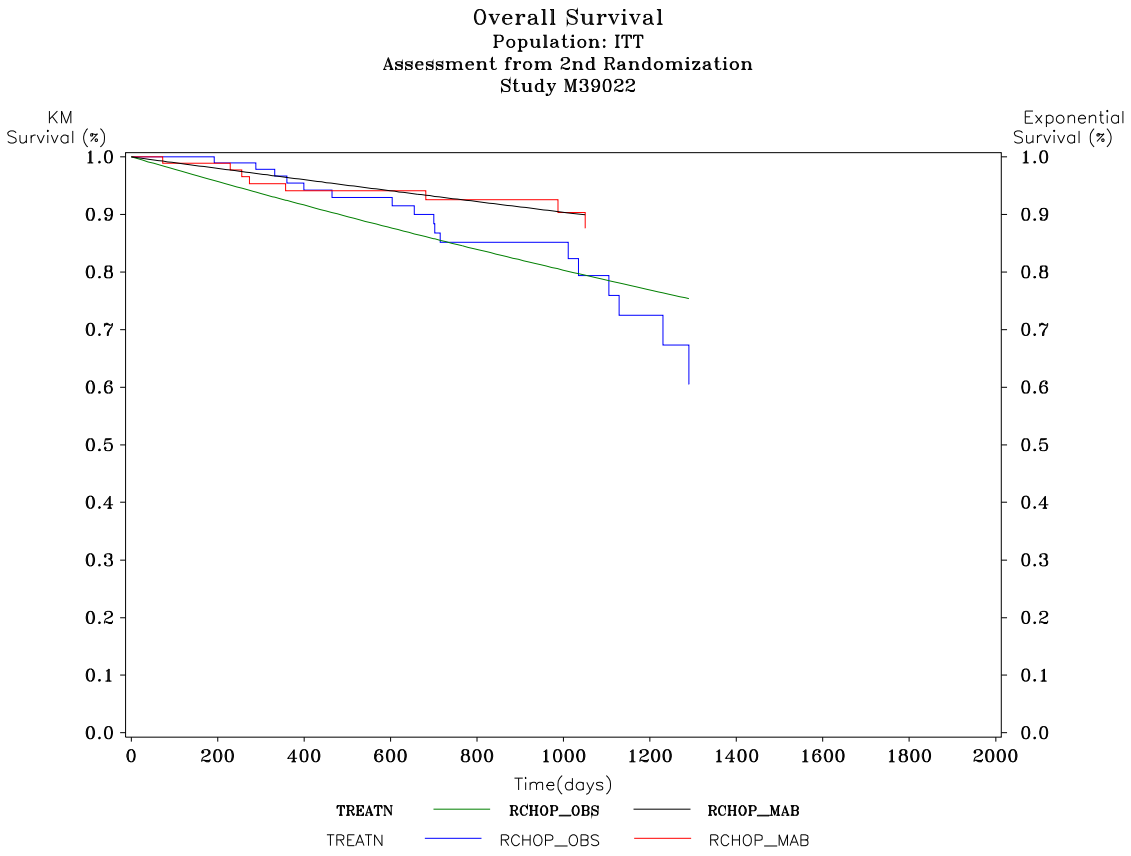


Graphical overlay of Kaplan Meier data and Extrapolated Curves for RCHOP- R and RCHOP – O patients

Weibull Overall Survival – RCHOP-R and RCHOP-O



Exponential Overall Survival – RCHOP-R and RCHOP-O



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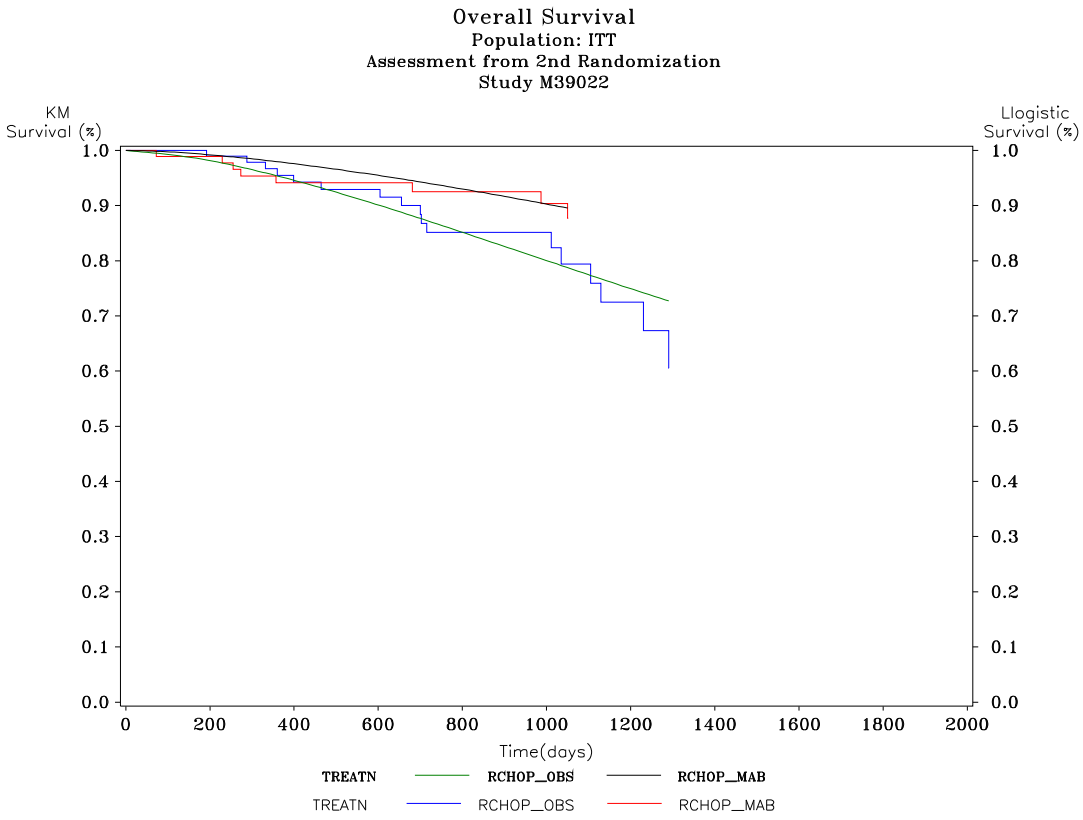
Log Logistic Overall Survival – RCHOP-R and RCHOP-O



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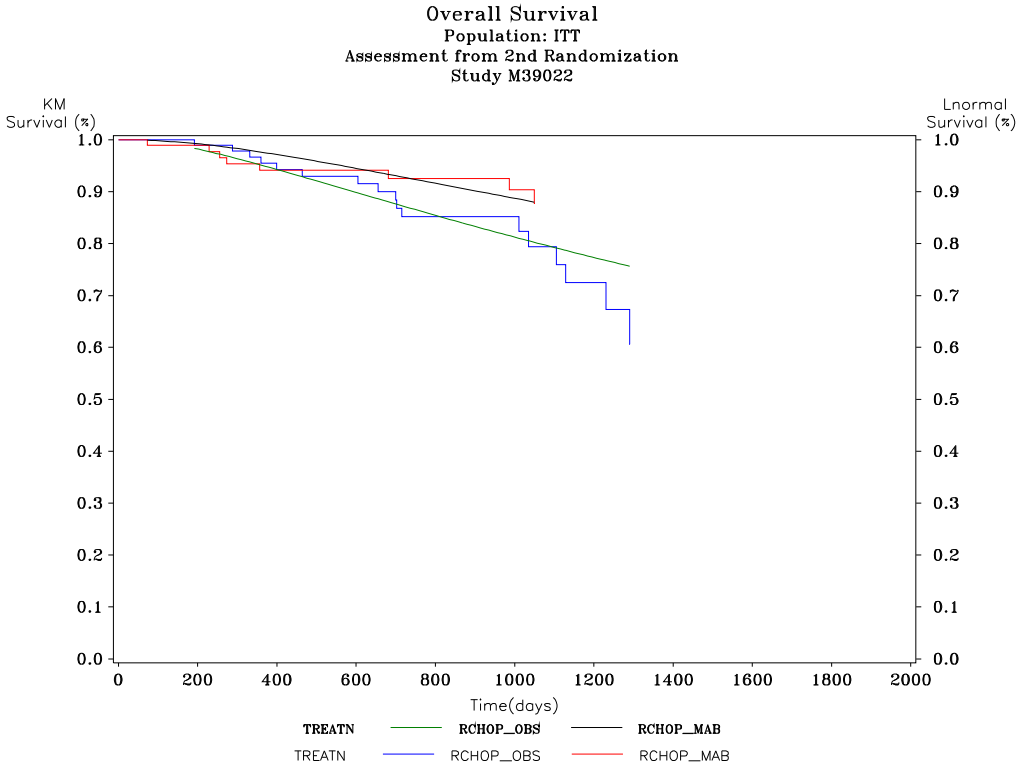
Log Normal Overall Survival – RCHOP-R and RCHOP-O



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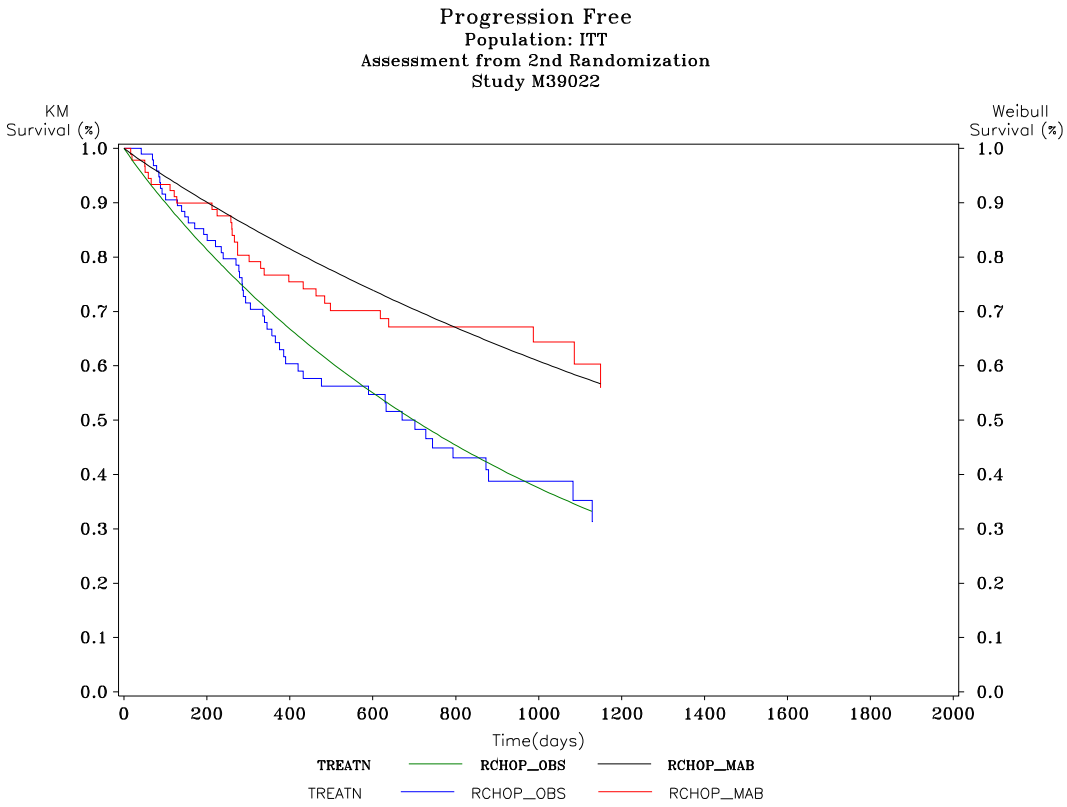
Weibull Progression Free Survival – RCHOP-R and RCHOP-O



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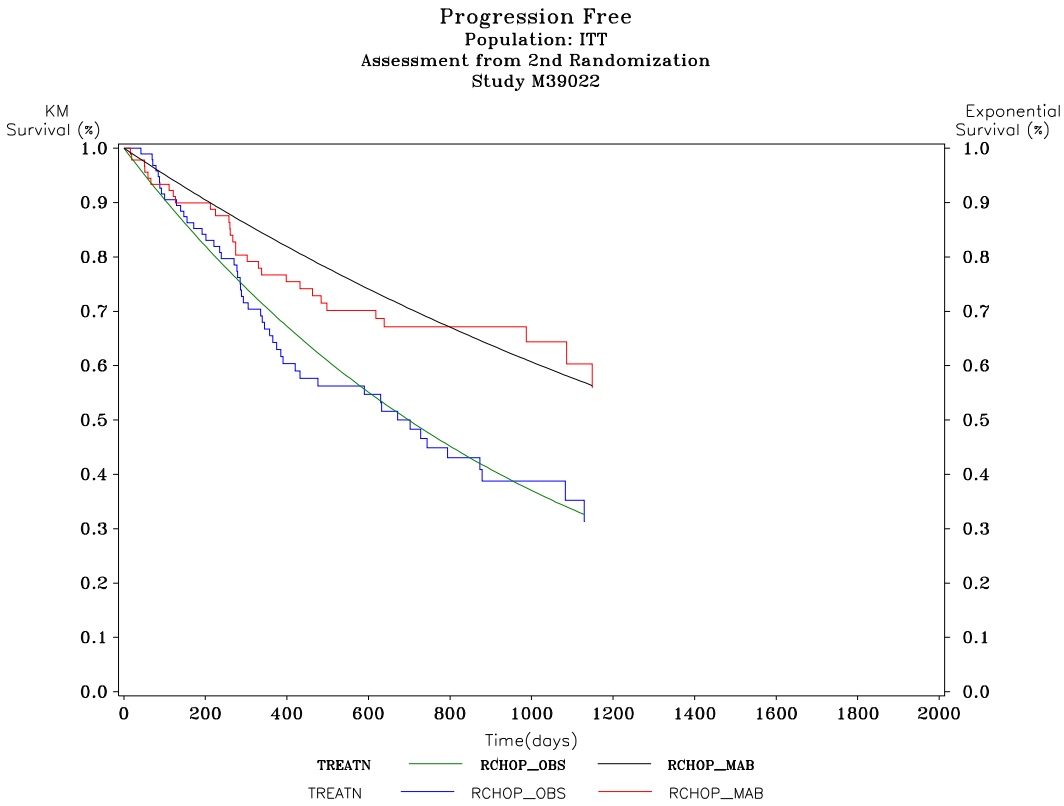
Exponential Progression Free Survival – RCHOP-R and RCHOP-O



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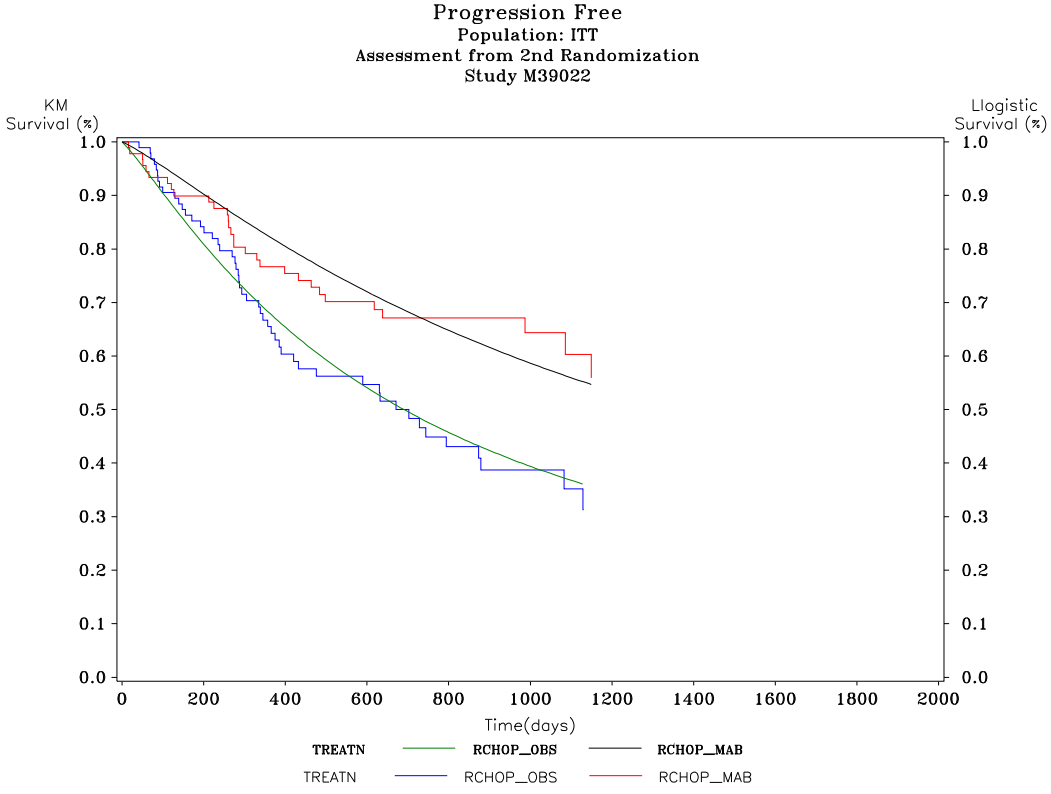
Log Logistic Progression Free Survival – RCHOP-R and RCHOP-O



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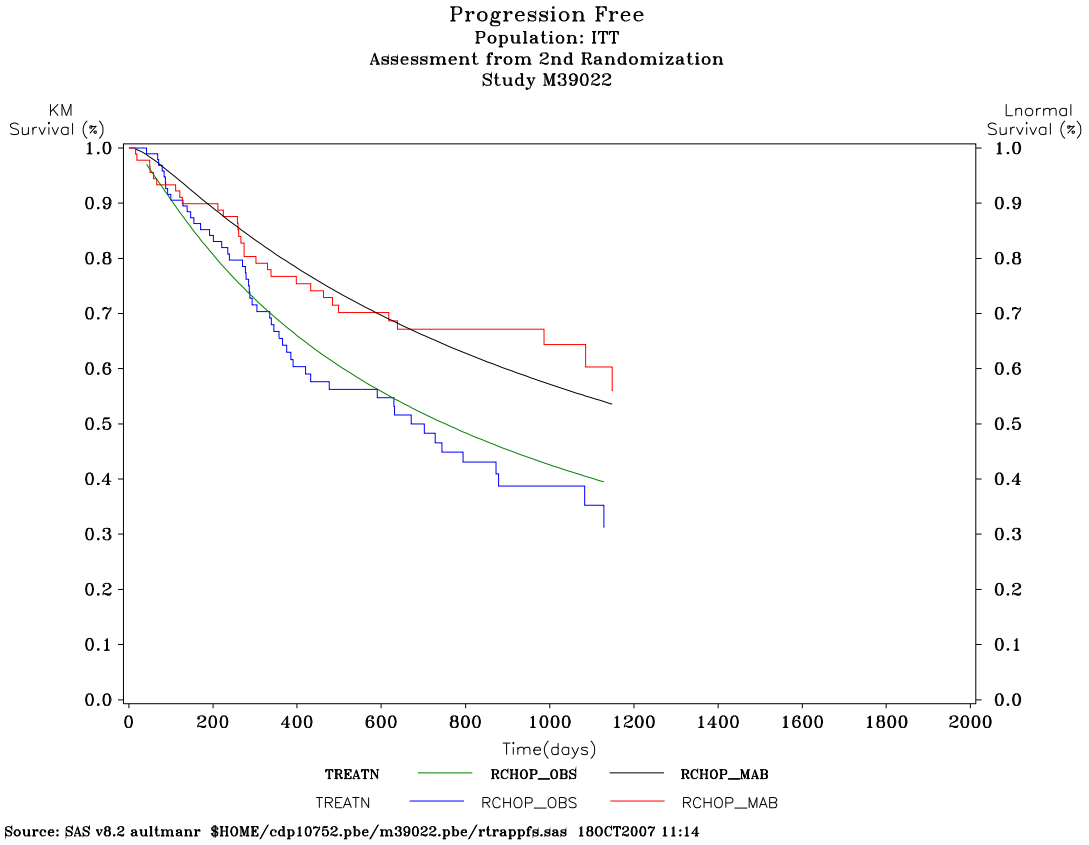
Log Normal Progression Free Survival – RCHOP-R and RCHOP-O



From the above analysis of the goodness of fit statistic (AIC) and visual inspection of the graphical overlay above, the exponential function was considered the optimal curve for the Kaplan Meier data when excluding the event-free period of the Kaplan Meier curve.

The impact upon the ICER is illustrated above in question 1 for the scenario when the event-free period is excluded (Exponential and Weibull)

3. Sensitivity analysis of fitting models to patient groups independently as well as in pairs using common parameters

The response to question 4 below provides strong statistical evidence for the use of a proportional hazard assumption for the survival analysis, based specifically upon RCT data, as requested within the ACD. This provides a justification for the same shape parametric function applied within the Roche base case economic model.

However to fully address the Appraisal Committee's request, independent curve fitting has also been undertaken to evaluate its impact upon both the projected clinical benefits and ICER of rituximab dual therapy.

The goodness of fit results for each independent curve fitting exercise is illustrated in the table below:

Table 4: AIC Goodness of Fit Statistics for Independent Curve Fitting (event free excluded)

		BIC		AIC	
Treatment	**Distribution**	**OS**	**PFS**	**OS**	**PFS**
R-CHOP + R	Exponential	-36.73	-98.14	-36.48	-97.89
	Log Logistic	-38.96	-98.85	-38.45	-98.34
	Log Normal	-38.72	-98.22	-38.21	-97.71
	Weibull	-38.99	-99.38	-38.48	-98.87
	Gompertz	NC	NC	NC	NC
CHOP + R	Exponential	-36.57	-83.18	-36.40	-83.02
	Log Logistic	-37.41	-85.46	-37.08	-85.13
	Log Normal	-38.33	-85.17	-38.00	-84.84
	Weibull	-37.36	-85.34	-37.03	-85.01
	Gompertz	NC	NC	NC	NC
R-CHOP + O	Exponential	-53.07	-116.68	-52.78	-116.38
	Log Logistic	-51.14	-116.65	-50.56	-116.07
	Log Normal	-51.05	-115.44	-50.46	-114.85
	Weibull	-51.11	-118.70	-50.53	-118.11
	Gompertz	NC	NC	NC	NC
CHOP + O	Exponential	-56.47	-99.20	-56.35	-99.08
	Log Logistic	-57.61	-98.53	-57.38	-98.30
	Log Normal	-57.27	-98.85	-57.03	-98.62
	Weibull	-57.67	-100.83	-57.43	-100.59
	Gompertz	NC	NC	NC	NC

The function with the best goodness of fit when the assumption of proportional hazards is relaxed is the exponential function for the comparators relating to the dual therapy decision problem. The impact of applying the best fitting independent shaped curve upon the dual therapy ICER is illustrated in the table below for both the exponential and Weibull curves

Table 5: Dual Therapy ICER of independent shaped curves using truncated data

Kaplan Meier Data	Parametric Function	ICER; Rituximab Dual Therapy
Event Free excluded, truncated	Independent Weibull	£15,775
Event Free excluded, truncated	Independent Exponential	£16,183

The use of independent curve fitting therefore reduces the estimated ICER for dual therapy rituximab compared to single use maintenance by approximately £8,000. The Independent exponential ICER has the same value as the proportional hazard exponential ICER reported above, as relaxing the proportional hazard assumption allows flexibility in the shape parameter. However, the exponential curve has a fixed shape parameter of 1, therefore the assumption of independence would not affect the subsequent exponential curve estimation.

4. If a proportional hazards model is assumed, justification should be provided based on RCT data

Progression Free Survival

The assumption of proportional hazards (PH) is initially assessed by looking for clear evidence of significant deviation in the diagnostic plots from the LIFETEST procedure in the statistical software SAS. In general the diagnostic plot "The Negative Log of Survival by Time" should be linear with intercept zero if the underlying assumption of an exponential is correct, however this has been shown to be somewhat unreliable. When there is sufficient cause to believe that the underlying assumption of PH has been violated, then a further investigation is performed on the various residual plots of the COX Proportional Hazards model (Therneau, Schoenfeld, Lin); they are:

- The deviance residual; a transformation of the Martingale residuals to achieve a more symmetric distribution
- The Schoenfeld residuals
- The Score residuals
- The Martingale residuals.

Index plots of these residuals are useful when assessing the proportional hazard assumption and have been found to be more reliable than the diagnostic plots from the Kaplan-Meier analysis.

The Martingale residual can be interpreted as the difference between the observed and expected number of deaths (Collett). These residuals highlight individuals who, on the basis of the assumed model have died too soon or lived too long. Large negative residuals correspond to individuals who have a longer survival time than what the model would predict given the included covariates. Conversely, residuals close to 1 are observed when individuals have unexpectedly short survival time from what the model would have predicted. A large number of patients with large residuals in absolute value will require further scrutiny. The Martingales are skewed and are at times difficult to interpret thus the Deviance residuals, a symmetric transformation of the Martingale residuals, are preferred due to their ease in identifying outliers. If the residuals are randomly spread about zero then the fit of the model can be assumed to be correct and the assumption of proportional hazards reasonable.

The deviance plots as well as the experimental simulation suggest that the assumption of proportional hazards has not been violated and that further use of this assumption in modelling the data parametrically is reasonable.

Overall Survival

Assessment of proportional hazards with respect to overall survival was carried out in a similar manner as progression free survival. A small number of patients (N=52) with positive Martingales close to one and their reason for prematurely terminating is presented in the table below. Patients with a value above 0.6 were considered outliers and were further scrutinized. The maximum number of patients in a given treatment arm was 17 which occurred in the two maintenance observation (R-CHOP – Observation and CHOP – Observation) arms. The follow up for overall survival was immature as the median had not

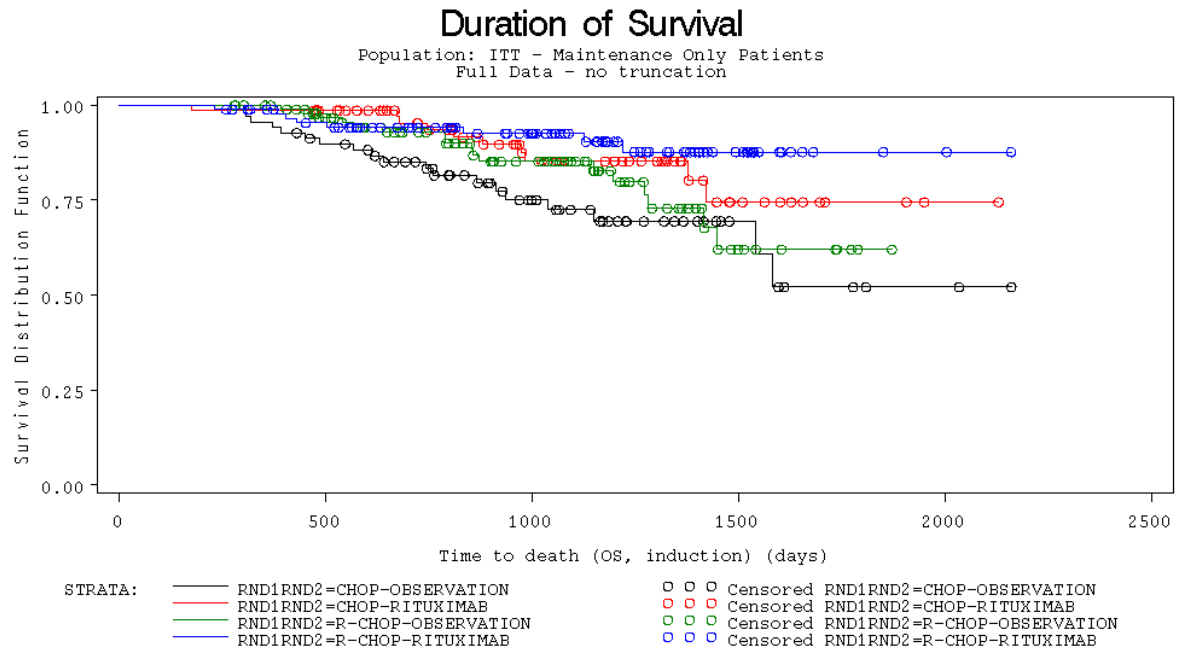
been reached at the time of the analysis. The deviance index plot along with the simulation plot suggests that there is a small deviation present; however because of the small number of patients, their influence on the proportional hazards assumption is considered to be minor. The number of patients in each treatment arm is insufficient to allow for a further stratification of the data. Secondly if the assumption of proportional hazard is relaxed for overall survival and not for progression free survival, then the risk increases for having more patients in progression free than are alive.

Thus it was decided that the assumption of proportional hazards had not been violated and so parametric extrapolation assuming same shape parameter was carried out for the original Roche model.

Charts illustrating the tests of the proportional hazard assumption are included in Appendix 2.

5. Sensitivity analysis of fitting models to all available data and patient data limited to 1500 days

Additional analysis has been performed to evaluate the impact on the extrapolated curves if ,all of the Kaplan Meier data is included and not truncated to 1,500 days, as originally performed by Roche.



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As illustrated in the diagram above, it was originally decided to truncate the analysis at 1,500 days to avoid any potential bias in the observed flat tails of the KM data.

The following analysis examines the impact upon goodness of fit, the selection of the optimal curve and subsequent clinical benefits and ICERs of using the un-truncated Kaplan Meier data illustrated in the figure above.

The AIC and graphical plots of the un-truncated curve extrapolations are included in Appendix 3. The AIC analysis demonstrates that the exponential curve remains the best fitting curve when the un-truncated Kaplan Meier data is utilised. The following table illustrates the impact on the projected overall survival when un-truncated Kaplan Meier data is utilised compared to truncated data.

Table 6: Comparison of estimated Overall Survival with and without truncation

Treatment Strategy	Mean Overall Survival Truncated Data	Mean Overall Survival Un-truncated Data	Difference
CHOP – observation	6.35	6.40	+0.05
RCHOP – observation	7.63	7.67	+0.04
CHOP – maintenance	7.42	7.48	+0.06
RCHOP – maintenance	8.24	8.29	+0.05

Intuitively when un-truncated data is utilised there is a small increase in the estimated overall survival through capturing the effect of the long tails of the KM data. However these changes are both small in absolute terms and have a similar impact across each intervention. Consequently the impact on the ICER of the use of truncated or un-truncated data is very small increase of less than £400, as illustrated in the table below.

Table 7: Impact upon Dual Therapy ICER of truncation at 1500 days

Kaplan Meier Data	ICER with truncation	ICER without truncation
Event-free period excluded, independence, exponential function	£16,183	£16,512

6. Sensitivity analysis should include the effects of varying the time horizons and varying the assumed duration of treatment benefit, within the range 1500 days to 30 years.

Our responses to questions 1 to 5 above illustrate a large range of possible base case ICERs for rituximab dual therapy. Therefore, the requested sensitivity analysis has only been performed on a selective number of scenarios. The highest, lowest and Roche recommended base case estimates are consequently reported in order to provide the Appraisal Committee with a broad cross-section of ICERs.

The following table illustrates the impact on the ICER of varying the treatment benefit and time horizon from 3 or 4 years to 30 years as requested. Since the model structure does not readily allow a precise estimate at 1,500 days, 3 years (1095 days) and 4 years (1,460 days) was modelled for treatment benefit and time horizon respectively.

Table 8: One-Way Sensitivity Analysis of rituximab ICER for treatment benefits and time horizon of included costs and benefits

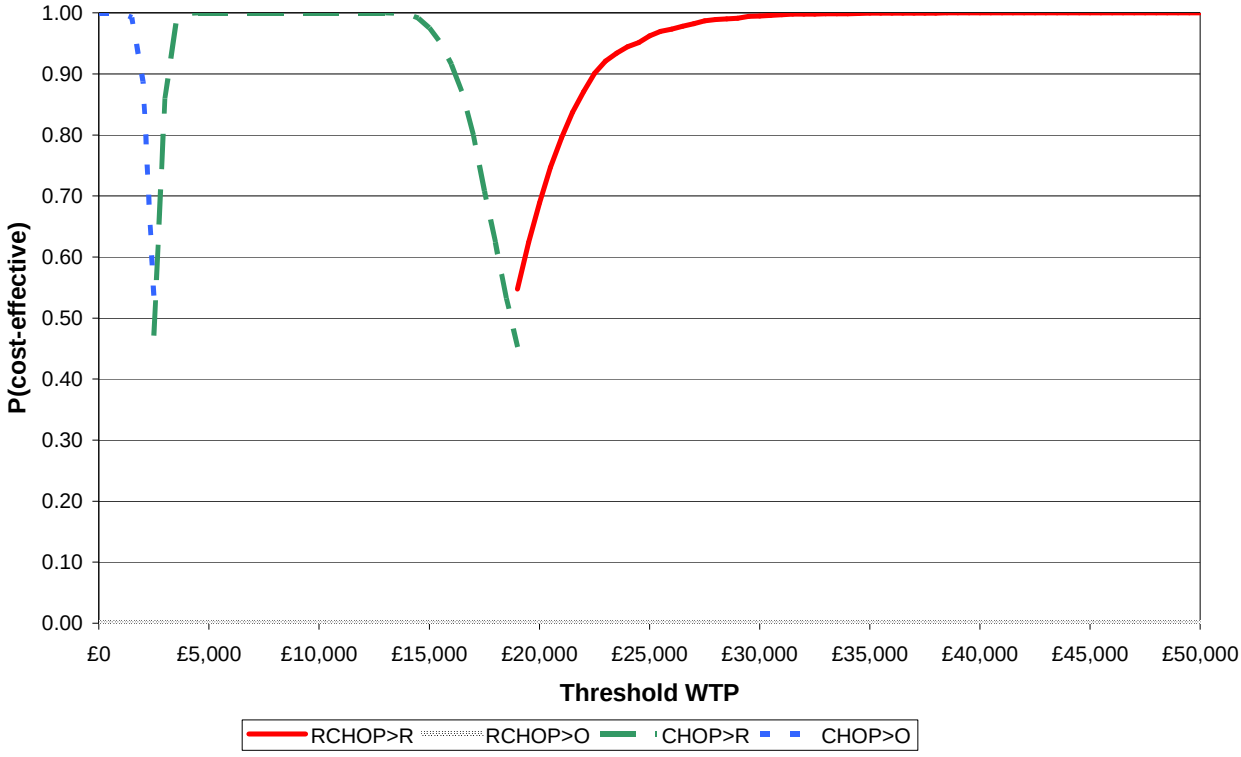
Model Version	ICER	Treatment Benefit		Time Horizon	
		3 years	30 years	4 years	30 years
Weibull Proportional Hazard (event free excluded)	£21,379	£34,232	£9,303	£56,503	£21,379
Independent Curve Fitting (event-free excluded)	£16,183	£23,972	£8,636	£57,874	£16,183
Un-truncated Data	£16,512	£24,051	£9,065	£58,927	£16,512

The ICERs relating to a 4 year time horizon are higher compared to the similar truncated ERG analysis of £43,000 as the ERG use actual Kaplan Meier data for 1,500 days, whereas the above 4 year analysis uses 2 year Kaplan Meier data and 2 year extrapolated curves, generating a different incremental clinical benefit.

Again Roche would stress to the Appraisal Committee that to evaluate an ICER over a time horizon of less than 30 years is not in-keeping with good economic evaluation practice or NICE reference case requirements. Also considering the EORTC study demonstrates a treatment benefit up to 1500 days (4.11 years) the shortened treatment benefit of only 3 years (1095 days) is also inappropriate.

7. Presentation of the results of probabilistic sensitivity analysis should include CEACs for pairwise comparisons and CEAFs for comparisons of multiple strategies. Comparisons of particular interest are single use of rituximab at induction or for maintenance versus no use and dual use of rituximab at induction and maintenance versus single use either for induction or maintenance.

Figure 1: Cost Effectiveness Acceptability Frontier



The above figure illustrates the cost effectiveness acceptability frontier for the available treatment strategies. For this updated PSA, the highest base case ICER from the additional analysis above was selected (£21,379) in order to be conservative in the assumed base case ICER of rituximab dual therapy.

Probabilsitic and not deterministic estimates of the mean ICER were used to construct the above CEAF. The RCHOP followed by observation strategy is excluded as it is dominated at both the mean and probabilistic mean values of the ICER.

The CEAF illustrates that at any threshold above £18,710 the RCHOP – R treatment strategy is the most appropriate and cost effective treatment option.

Table 9: Net Benefit of treatment strategies relative to CHOP only (deterministic estimates)

Rituximab Strategy	Incremental Cost	Incremental QALY	ICER	Net benefit per Patient			
				£20,000 threshold		£30,000 threshold	
				NMB	NHB	NMB	NHB
SCENARIO ONE: Proportional hazard, event free excluded, Weibull							
Induction Only	£4,721	0.674	£7,009	£8,750	0.438	£15,486	0.52
R Maintenance Only	£3,300	0.743	£4,440	£11,564	0.579	£18,996	0.63
Induction and	£12,290	1.16	£10,561	£10,984	0.549	£22,622	0.75

Maintenance							
SCEANRIO TWO: Independent curves, event free excluded, exponential							
Induction Only	£5,728	0.981	£5,841	£13,884	0.694	£23,691	0.79
Maintenance Only	£2,902	0.904	£3,210	£15,180	0.759	£24,222	0.81
Induction and Maintenance	£12,532	1.50	£8,359	£17,452	0.873	£32,444	1.08

As requested during the recent teleconference with the technical team at NICE, to help further manage decision uncertainty, table 1 in the ERG supplementary report (10th September, 2007) has been reproduced following the further analysis in section one. Two of the various curve fitting scenarios presented in section one are illustrated for the committee's consideration in Table 9. One scenario based on the basecase ICER of dual therapy of £21,379 and a second on the base case ICER of £16,183.

Only when the highest basecase ICER is selected from section one and a cost effectiveness threshold of £20,000 is assumed does the decision rule based upon net benefit indicate dual therapy rituximab is not cost effective.

Section Two: Response to Appraisal Consultation Document

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

Roche believes that the ACD does not adequately consider several key pieces of evidence which presently compromise the validity of some of the recommendations made. It appears to Roche that some important evidence was not taken into account in the formulation of the ACD. This evidence is listed below:

a) Alternative survival analysis provided by Roche in response to the ERG clarification letter

Several of the questions raised in section 4.14 of the ACD can be addressed through reference to the further analysis provided by Roche within our response to the ERG clarification letter. For example, the ACD fails to acknowledge the analysis presented in tables 1 and 2 of the Roche clarification letter. This analysis illustrates that the selected Weibull curve by Roche generated the smallest incremental clinical benefit for rituximab dual therapy, thus utilizing any other curve would lead to increased clinical benefit and a reduced ICER for rituximab dual therapy. The ACD fails to give reference to this important evidence when evaluating the appropriateness of the Roche estimates of the long term clinical benefits of rituximab.

b) Actual RCT reported post progression treatments / costs

Section 4.7 of the ACD states how the Appraisal Committee: "*thought that it was appropriate to calculate costs at progression by aggregating treatments into categories, and it agreed with the ERG's assumptions as to how these would vary across the treatment strategies*". Roche consider this a step down in the hierarchy of evidence presented to the Appraisal Committee. The original Roche submission made available the actual treatments received post progression within the EORTC study for each arm. Costing data captured from within the RCT of interest is traditionally seen as the optimum source of resource use and costing evidence. Had Roche not utilised this evidence and adopted the more arbitrary non-evidence based approach, undoubtedly this would have raised criticism by the Appraisal Committee.

2 WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE

a) Inaccurate representation of event-free period within Roche economic model

Section 4.8 of the ACD states:

"*It noted that there was no initial zero-hazard period modelled, but there was a protocol-driven event-free period in the data. The Committee agreed that including an event-free period could change the goodness-of-fit of any distribution fitted to trial data and influence the outcome of the cost-effectiveness analysis*"

The Roche economic model, as outlined in the original Roche submission (page 98, Roche STA submission) utilises the actual Kaplan Meier data direct from the EORTC study for the first 2 years of the model. The extrapolated curves are only utilised beyond this time horizon. Consequently for the ACD to state that an event-free period was not modelled is both incorrect and misleading.

This event-free period was also included when estimating the extrapolated curves in the original Roche economic model. However for sensitivity analysis, the extrapolated curves have since been estimated and subsequent ICER reported when this event-free (zero hazard) period is excluded. The analysis in section one above confirms that the significance of this event-free period is very small when estimating both the extrapolated curves and the ICER for dual therapy rituximab.

b) Inaccurate representation of assumed treatment benefit within Roche economic model

Section 4.9 of the ACD reports that:

"*the Committee considered that assuming proportional hazards from data over the RCT follow-up period and then extrapolating parametric models beyond the trial period, would assume that the treatment benefit observed in the trial would persist over the duration of the extrapolation. The Committee concluded that the manufacturer's approach to survival modelling could overestimate the clinical and cost effectiveness of rituximab*"

The ACD fails to give reference to the fact the Roche economic model assumes no treatment benefit for rituximab after 5 years (with further sensitivity analysis further curtailing this to 2 years). As evidence within the Roche response to the ERG clarification letter clearly indicates, firstly alternative parametric curves generated a higher incremental clinical benefit than the selected curve and secondly the treatment benefit was not assumed over the entire duration of the economic model. Consequently Roche considers the above statement within the ACD both incorrect and misleading in relation to the survival analysis by Roche. The *under*-estimation of clinical benefits could equally apply based upon the evidence presented to the committee.

c) Inaccurate representation of relationship between post progression treatments and outcomes

One of the main reasons that the Appraisal Committee rejected the trial-based evidence of drug treatment upon disease progression relates to the claim that the economic model does not capture the subsequent outcomes related to these specific treatment distributions.

Considering the Kaplan Meier overall survival data utilised within both the economic model

and for the purposes of curve estimation will reflect the treatments actually utilised within the trial post progression, this reasoning for rejecting the trial based costs appears flawed.

d) Reasons why £43,000 ICER is uncertain are incompletely reported within ACD

As illustrated in the introduction to section 1 above, the main reason the ICER for rituximab dual therapy exceeds £30,000 in the ERG's analysis is through the use of Kaplan Meier data only and the rejection of any curve extrapolation, a conventional requirement in order to estimate the lifetime costs and benefits of an intervention as set out in the Guide to Methods of Technology Appraisal.

However section 4.12 of the ACD reports that: "*the committee thought this high ICER could indicate that this strategy is not cost effective, but was aware that the limited availability of data for the ERG's probabilistic sensitivity analysis comparing the cost effectiveness of multiple strategies made this analysis uncertain"*.

The ACD implies that the absence of suitable PSA is the reason for uncertainty around the high ICER, when the ERG selection of survival data is clearly the primary reason for the high ICER and subsequent uncertainty.

3 WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS

Whilst we welcome the positive endorsement of aspects of the rituximab license, Roche does not believe that all of the provisional recommendations provide a suitable basis for the preparation of guidance to the NHS.

Firstly they currently fail to recommend the most clinically effective treatment strategy for follicular lymphoma patients, despite this being demonstrated to be cost effective compared to current standard of care, as confirmed within the conclusion of the ERG report. The only rationale presented for ignoring this fact is the assertion in section 4.11 of the ACD that maintenance therapy was considered the clinical priority and therefore will become standard of care following this appraisal. However one could equally argue that following this appraisal dual therapy should become the new standard of care as it is cost effective compared to current standard of care (no rituximab use).

Secondly the current guidance being based inappropriately upon an estimated ICER of £43,000 for dual therapy, does not take a lifetime time horizon and thus adequately consider the potential longer term benefits of rituximab. Consequently, current guidance is based on utilizing analyses which are inconsistent with NICE's own Guide to Methods of Technology Appraisal and its reference case methods.

4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

No further comments

We hope that our feedback is helpful to the Appraisal Committee in its subsequent deliberations.

Yours sincerely,

Appendix 1 – Goodness of Fit statistics and subsequent clinical benefits assessed for original Roche base case.

Table 1: Estimated Clinical Benefit of dual therapy stratified by selected curve (event-free period included)

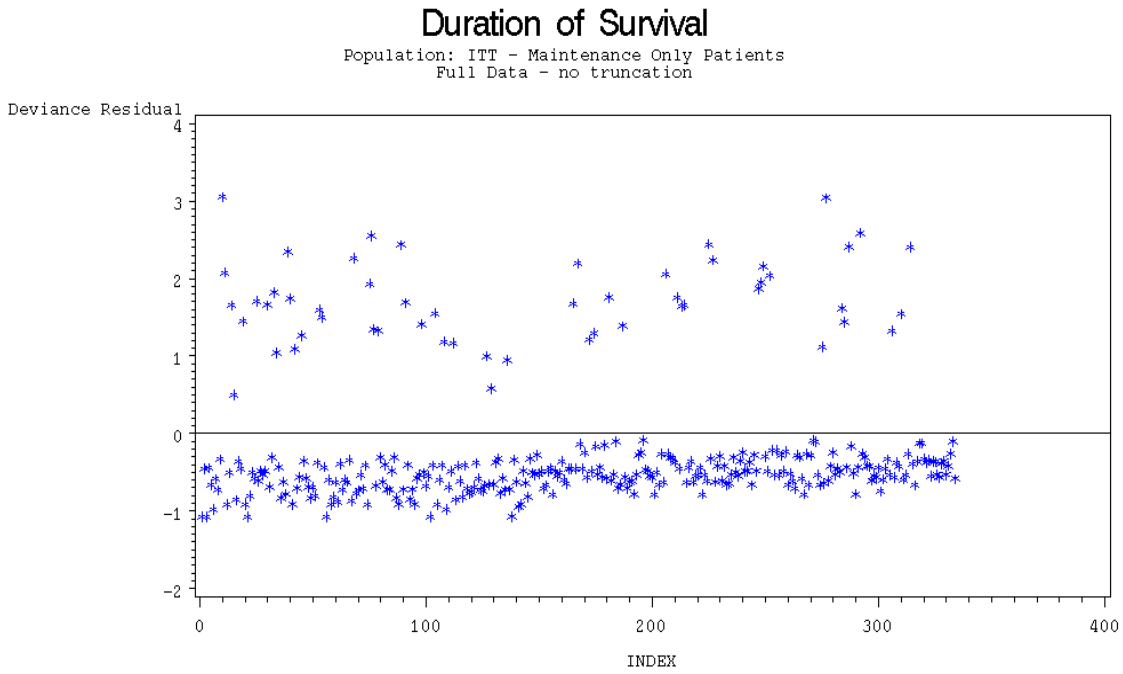
Treatment arm	OS				PFS			
	Weibull	**Log-Normal**	**Log-Logistic**	**Exponential**	**Weibull**	**Log-Normal**	**Log-Logistic**	**Exponential**
4 arm	(days)				(days)			
RCHOP-R v's CHOP-R	**198.62**	327.54	225.04	1,225.44	**263.37**	472.41	461.43	312.87

Table 2: Summary of Goodness of Fit by Treatment Comparators and Distribution (Table 22 of the original Roche submission)

		BIC		AIC	
Treatment	**Distribution**	**OS**	**PFS**	**OS**	**PFS**
R-CHOP + (MabThera or Observation)	Exponential	-84.198	-185.837	-83.577	-185.216
	Log Logistic	-80.533	-178.553	-79.291	-177.311
	Log Normal	-80.828	-175.544	-79.587	-174.302
	Weibull	-80.326	-182.102	-79.085	-180.860
	Gompertz	NC	NC	NC	NC
CHOP + (MabThera or Observation)	Exponential	-84.669	-155.935	-84.181	-155.446
	Log Logistic	-82.061	-143.607	-81.084	-142.631
	Log Normal	-81.279	-142.960	-80.302	-141.984
	Weibull	-82.641	-147.304	-81.664	-146.327
	Gompertz	NC	NC	NC	NC
CHOP_ vs. R-CHOP_ (Non Responders)	Exponential	-143.739	-191.087	-143.301	-190.650
	Log Logistic	-146.031	-190.965	-145.156	-190.090
	Log Normal	-147.376	-191.320	-146.501	-190.444
	Weibull	-146.144	-193.401	-145.269	-192.526
	Gompertz	NC	NC	NC	NC

Note: The Gompertz model failed to converge for R-CHOP + (MabThera vs. Observation) and CHOP + (MabThera vs. Observeration)

Appendix 2: Test of Proportional Hazard Assumption



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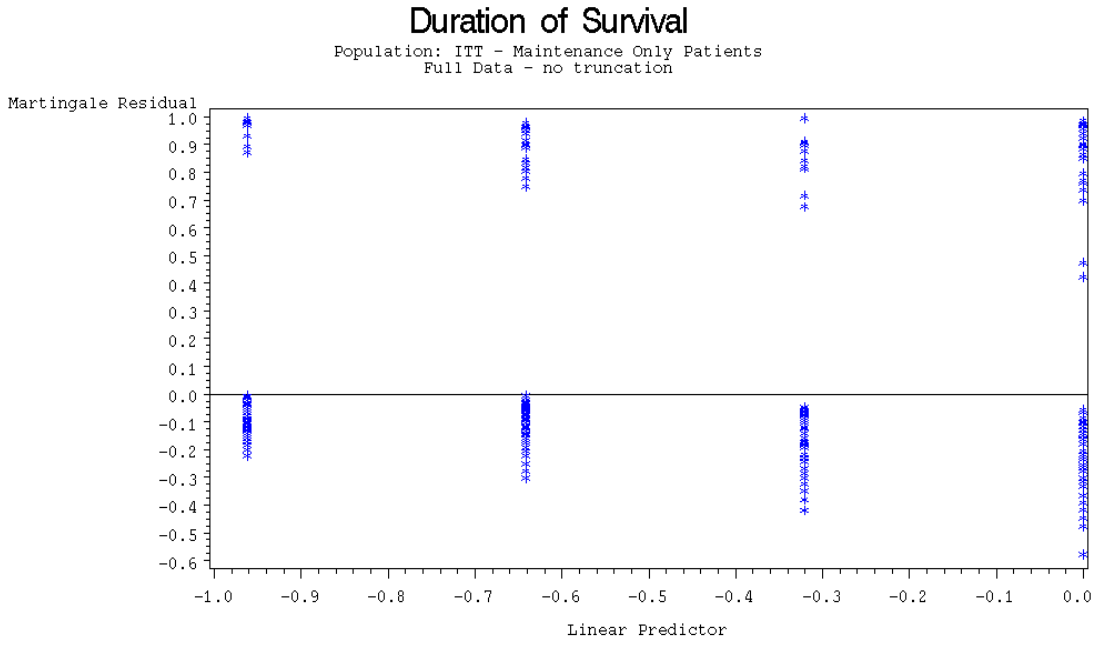

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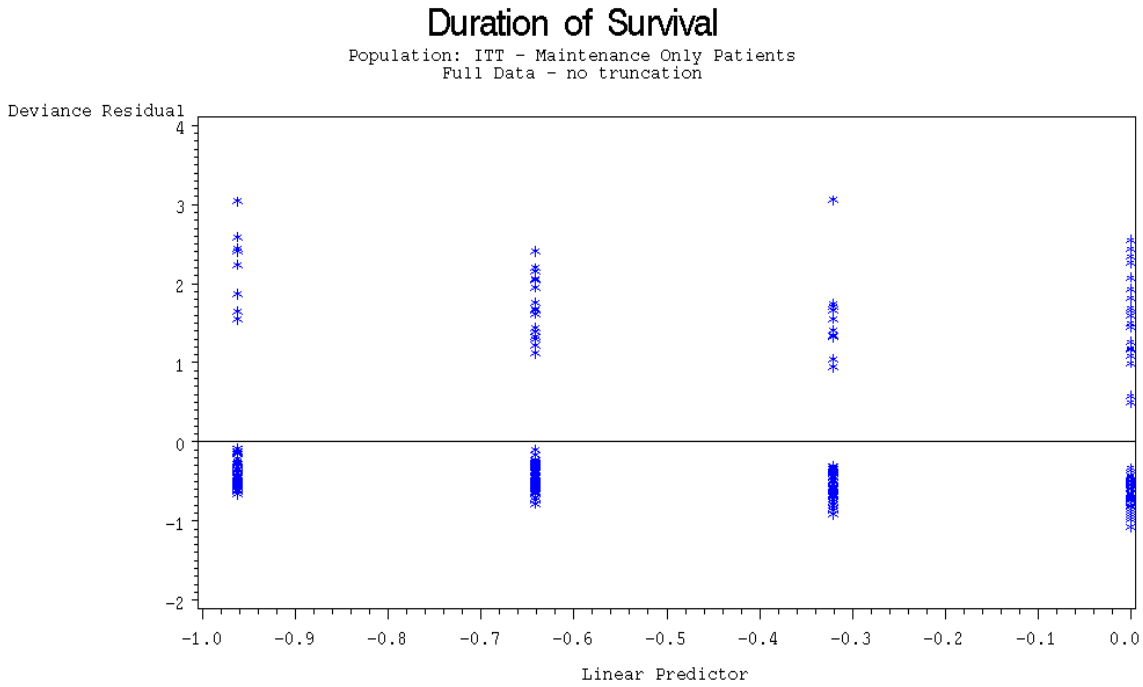

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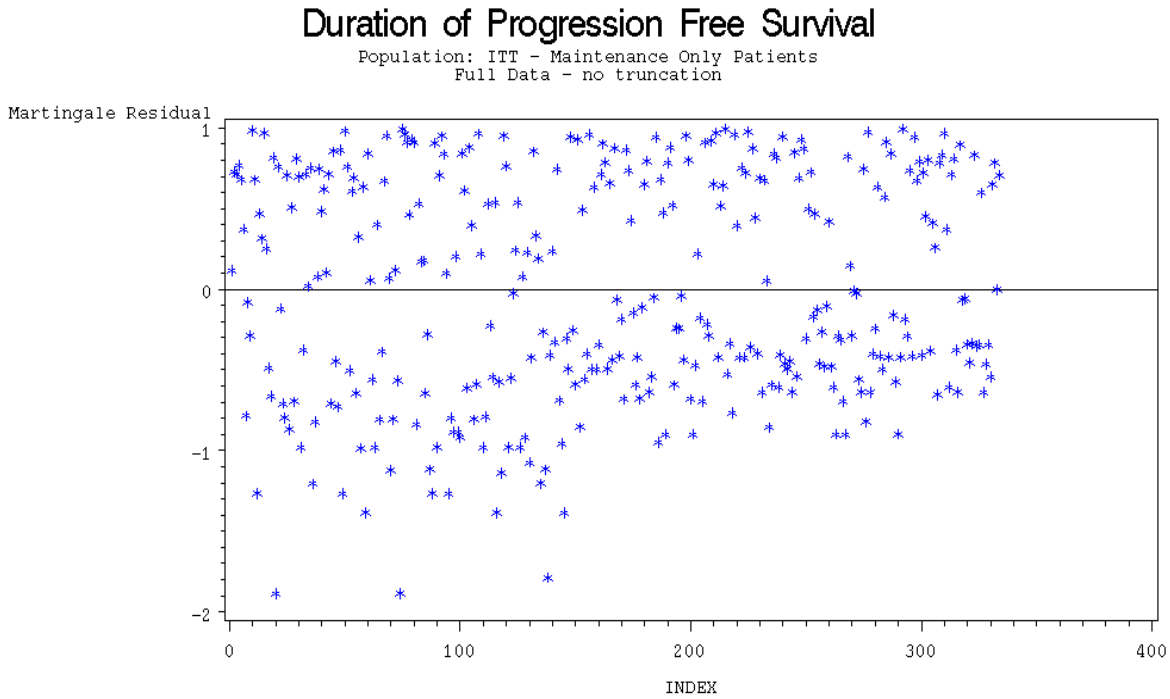

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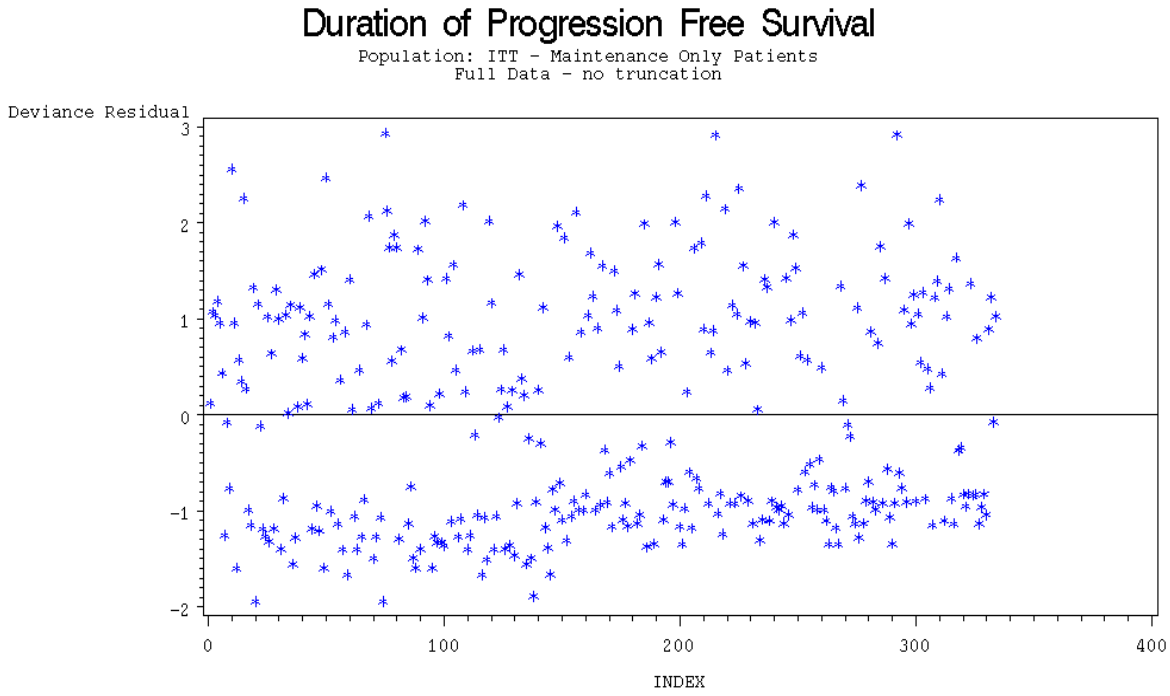

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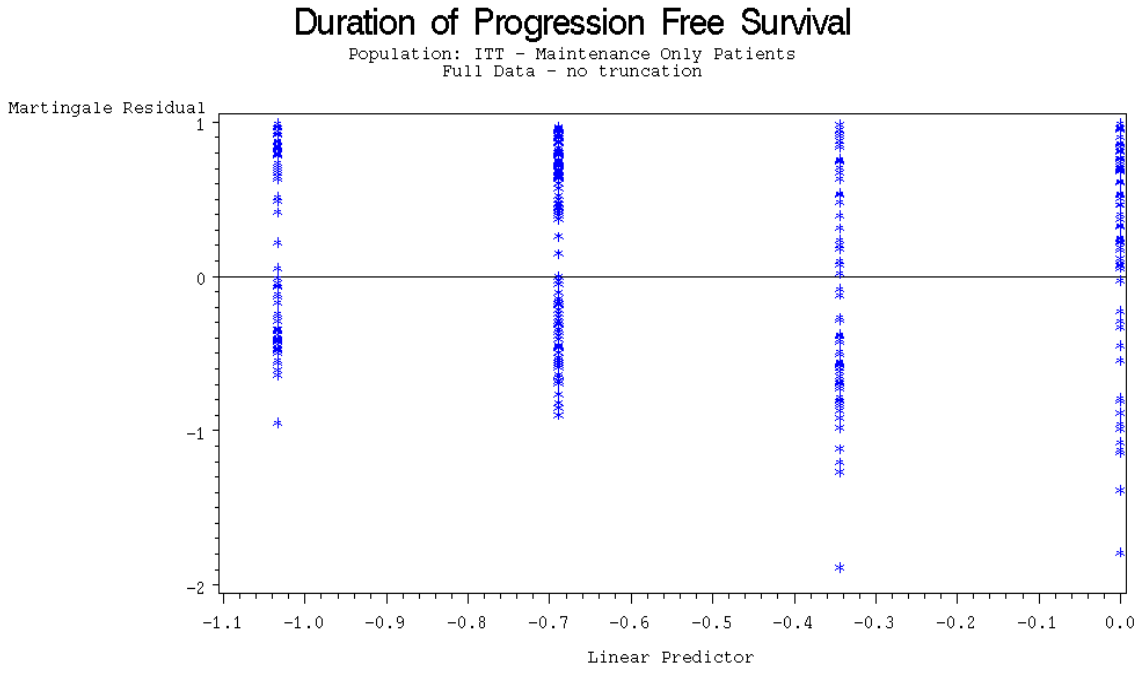

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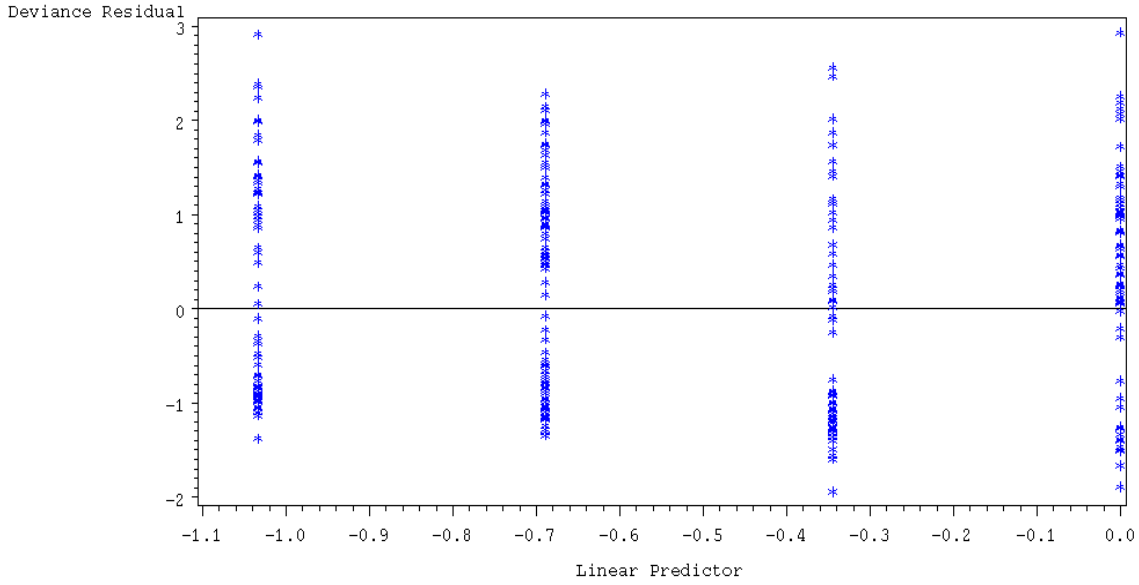
Duration of Progression Free Survival

Population: ITT - Maintenance Only Patients
Full Data - no truncation



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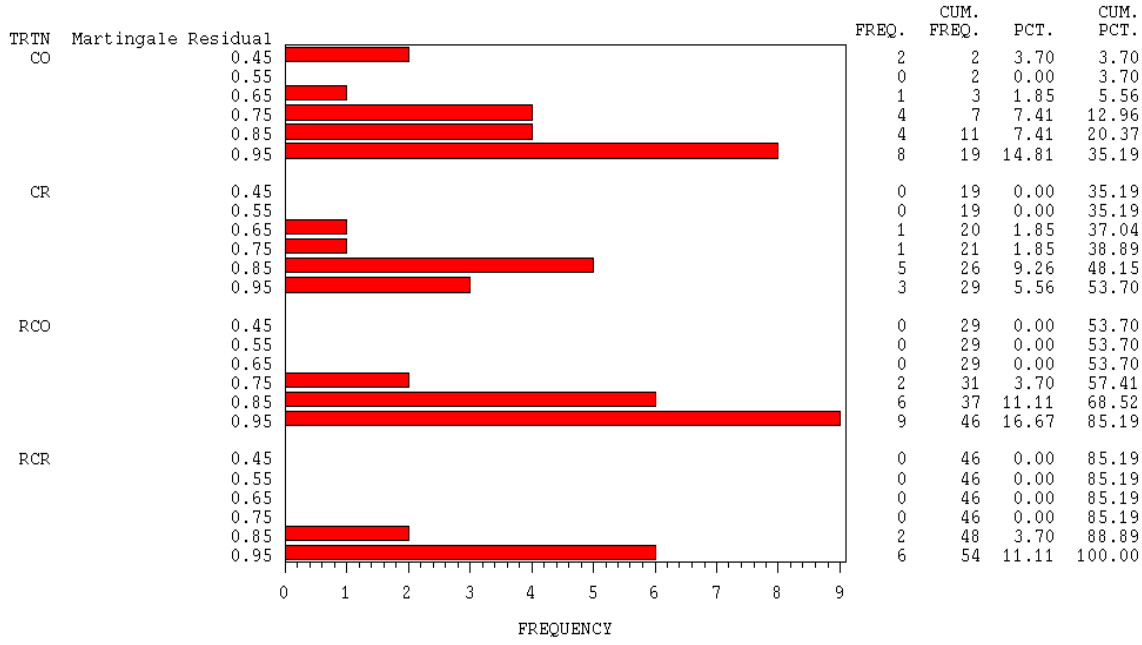
Nr of Patients with Positive Martingales by Treatment



TRTN	Martingale Residual	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
CO	0.45	2	2	3.70	3.70
	0.55	0	2	0.00	3.70
	0.65	1	3	1.85	5.56
	0.75	4	7	7.41	12.96
	0.85	4	11	7.41	20.37
	0.95	8	19	14.81	35.19
CR	0.45	0	19	0.00	35.19
	0.55	0	19	0.00	35.19
	0.65	1	20	1.85	37.04
	0.75	1	21	1.85	38.89
	0.85	5	26	9.26	48.15
	0.95	3	29	5.56	53.70
RCO	0.45	0	29	0.00	53.70
	0.55	0	29	0.00	53.70
	0.65	0	29	0.00	53.70
	0.75	2	31	3.70	57.41
	0.85	6	37	11.11	68.52
	0.95	9	46	16.67	85.19
RCR	0.45	0	46	0.00	85.19
	0.55	0	46	0.00	85.19
	0.65	0	46	0.00	85.19
	0.75	0	46	0.00	85.19
	0.85	2	48	3.70	88.89
	0.95	6	54	11.11	100.00

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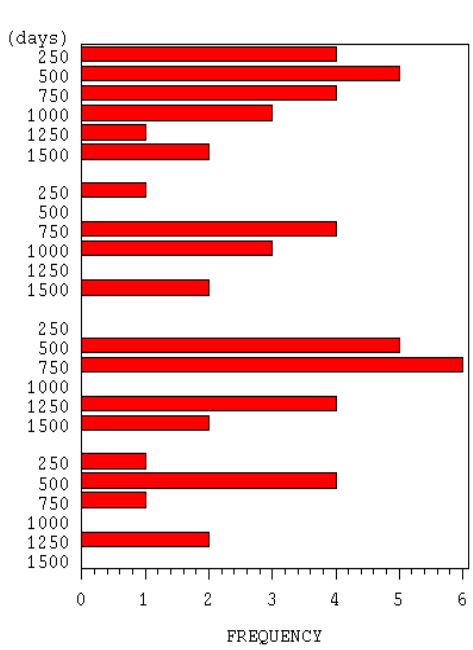
Distribution of Survival Time for Patients with Positive Martingales by Treatment

TRTN	Time to death (OS, induction) (days)	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
CO	250	4	4	7.41	7.41
	500	5	9	9.26	16.67
	750	4	13	7.41	24.07
	1000	3	16	5.56	29.63
	1250	1	17	1.85	31.48
	1500	2	19	3.70	35.19
CR	250	1	20	1.85	37.04
	500	0	20	0.00	37.04
	750	4	24	7.41	44.44
	1000	3	27	5.56	50.00
	1250	0	27	0.00	50.00
	1500	2	29	3.70	53.70
RCO	250	0	29	0.00	53.70
	500	5	34	9.26	62.96
	750	6	40	11.11	74.07
	1000	0	40	0.00	74.07
	1250	4	44	7.41	81.48
	1500	2	46	3.70	85.19
RCR	250	1	47	1.85	87.04
	500	4	51	7.41	94.44
	750	1	52	1.85	96.30
	1000	0	52	0.00	96.30
	1250	2	54	3.70	100.00
	1500	0	54	0.00	100.00



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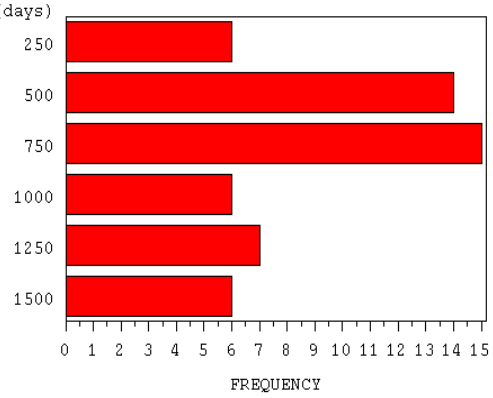
Distribution of Survival Time for Patients with Positive Martingales

Time to death (OS, induction) (days)	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
250	6	6	11.11	11.11
500	14	20	25.93	37.04
750	15	35	27.78	64.81
1000	6	41	11.11	75.93
1250	7	48	12.96	88.89
1500	6	54	11.11	100.00



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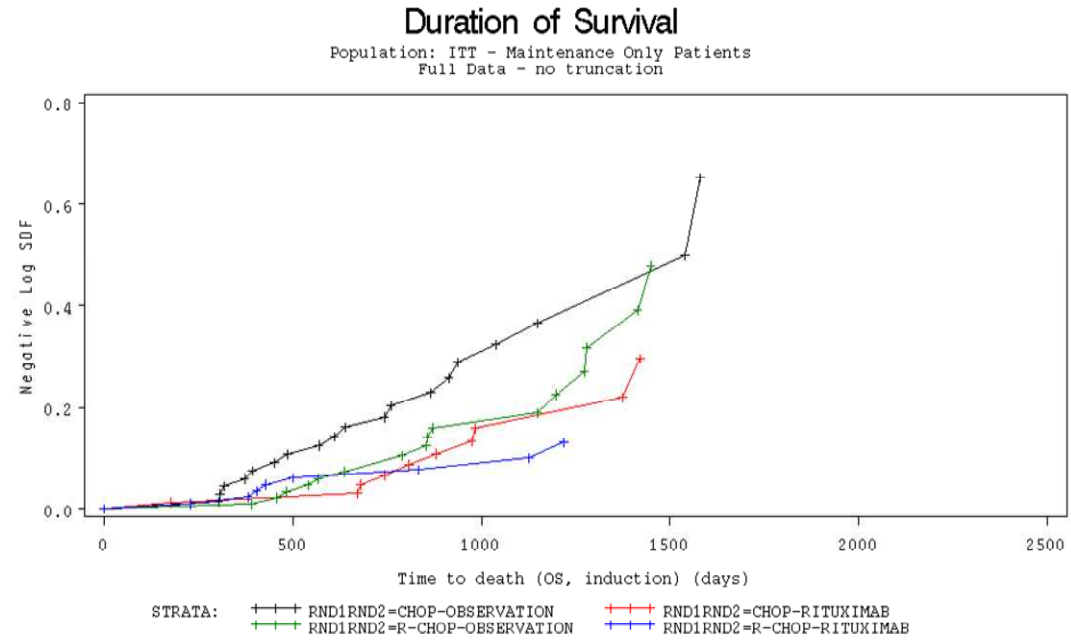

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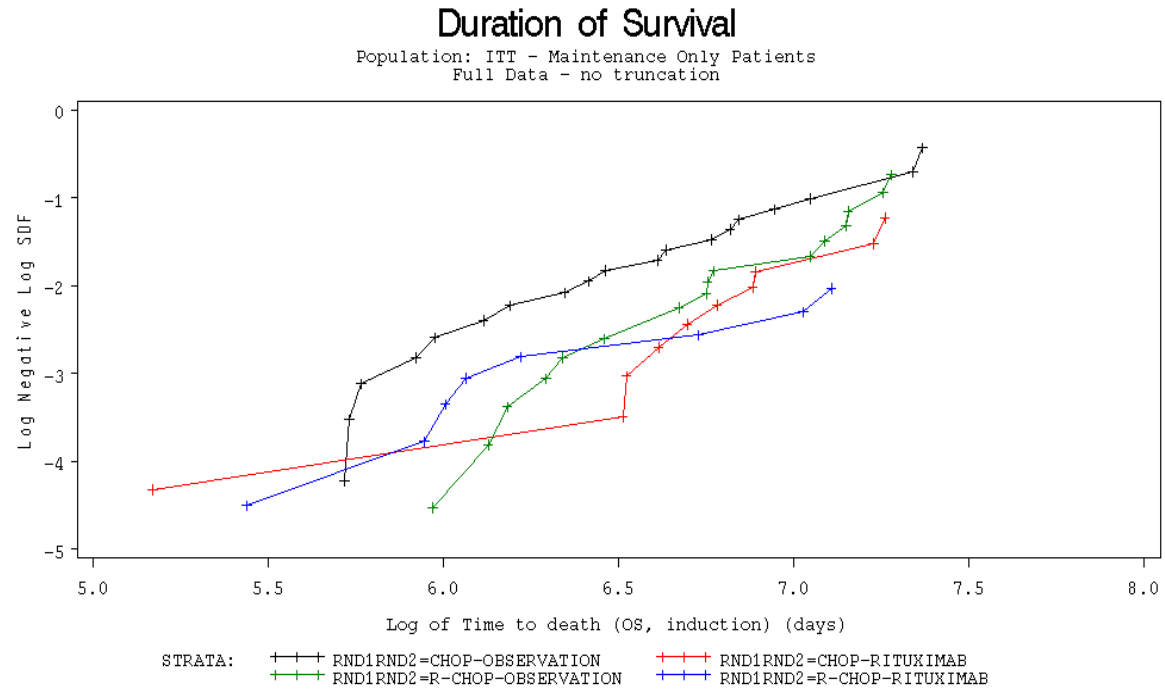

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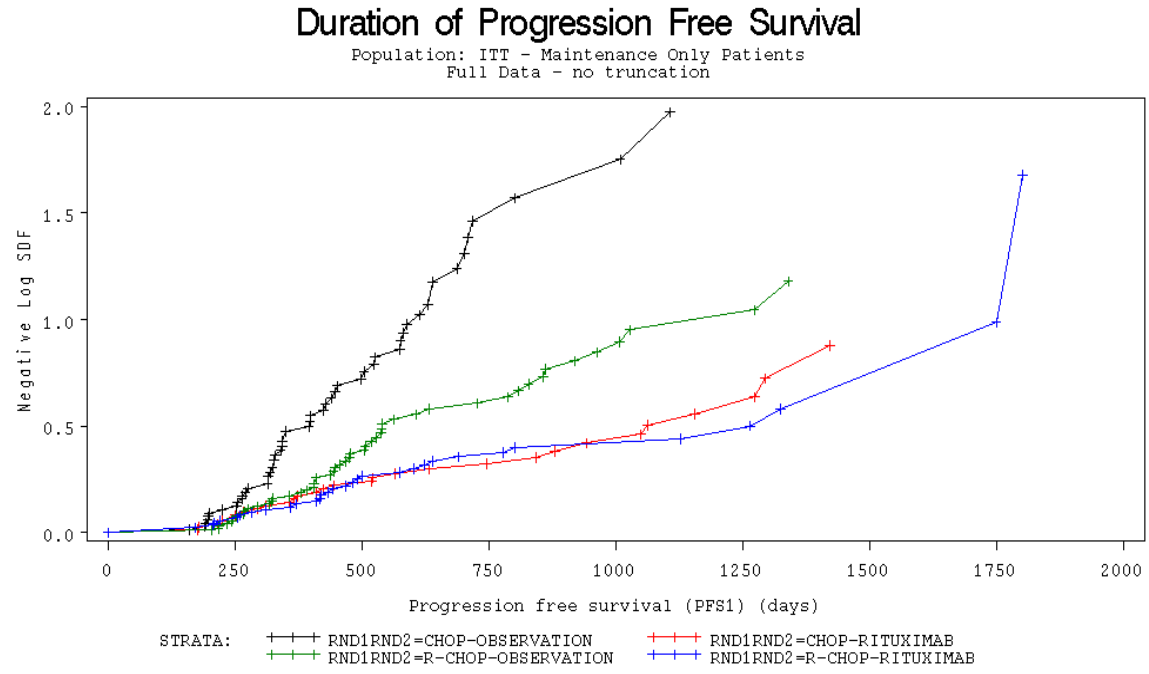

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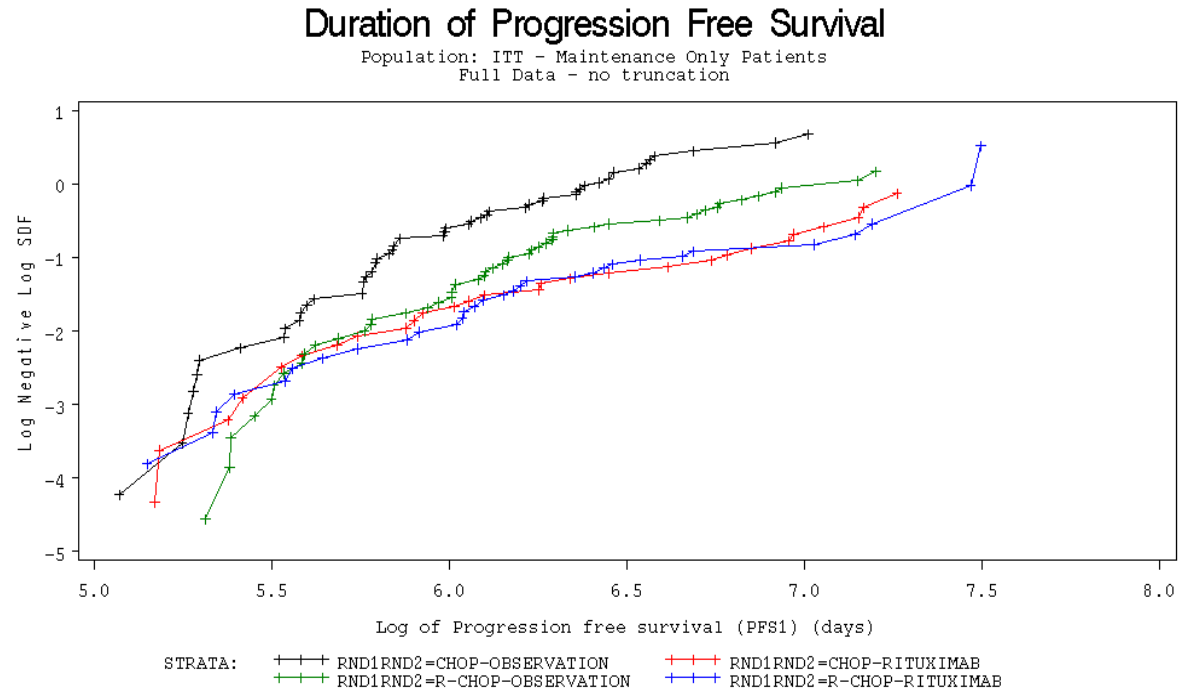

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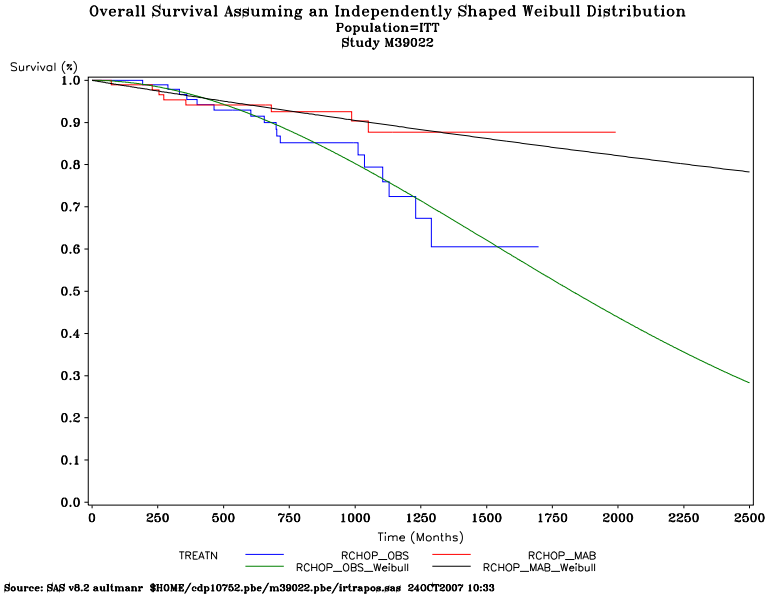
Appendix 3 Goodness of Fit statistics and graphical plots for Un-truncated Kaplan Meier data (independent curves, event-free excluded)

Table 1: AIC goodness of fit statistics – (un-truncated, event free, independent)

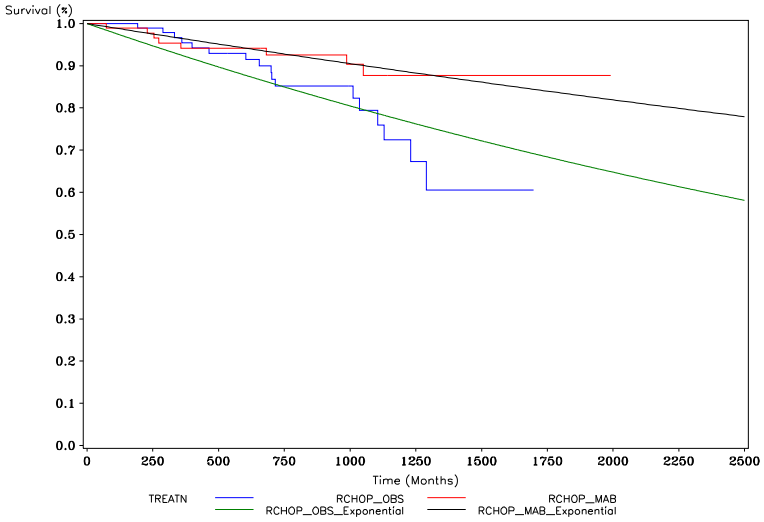
		BIC		AIC	
Treatment	**Distribution**	**OS**	**PFS**	**OS**	**PFS**
R-CHOP + R	Exponential	-36.83	-98.73	-36.58	-98.48
	Log Logistic	-39.05	-100.50	-38.54	-99.96
	Log Normal	-38.79	-100.15	-38.38	-99.64
	Weibull	-39.09	-100.52	-38.58	-100.01
	Gompertz	NC	NC	NC	NC
CHOP + R	Exponential	-36.73	-83.43	-36.56	-83.27
	Log Logistic	-37.72	-85.63	-37.39	-85.30
	Log Normal	-38.52	-85.32	-38.19	-84.99
	Weibull	-37.72	-85.58	-37.38	-85.25
	Gompertz	NC	NC	NC	NC
R-CHOP + O	Exponential	-53.21	-116.76	-52.92	-116.47
	Log Logistic	-51.48	-116.72	-50.90	-116.13
	Log Normal	-51.31	-115.50	-50.73	-114.91
	Weibull	-51.54	-118.80	-50.96	-118.22
	Gompertz	NC	NC	NC	NC
CHOP + O	Exponential	-58.87	-99.27	-56.75	-99.15
	Log Logistic	-58.10	-98.57	-57.86	-98.33
	Log Normal	-57.67	-98.89	-57.43	-98.66
	Weibull	-58.30	-100.92	-58.06	-100.69
	Gompertz	NC	NC	NC	NC

For the decision problem of interest the AIC and BIC statistics illustrate that the exponential curve is the best fitting function for the un-truncated Kaplan Meier data.

Graphical plots – un-truncated Kaplan Meier



Overall Survival Assuming an Independently Shaped Exponential Distribution
Population=ITT
Study M39022



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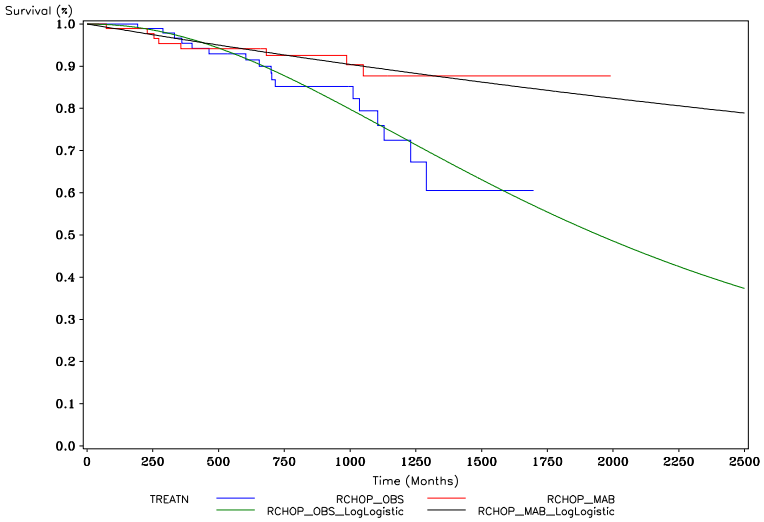
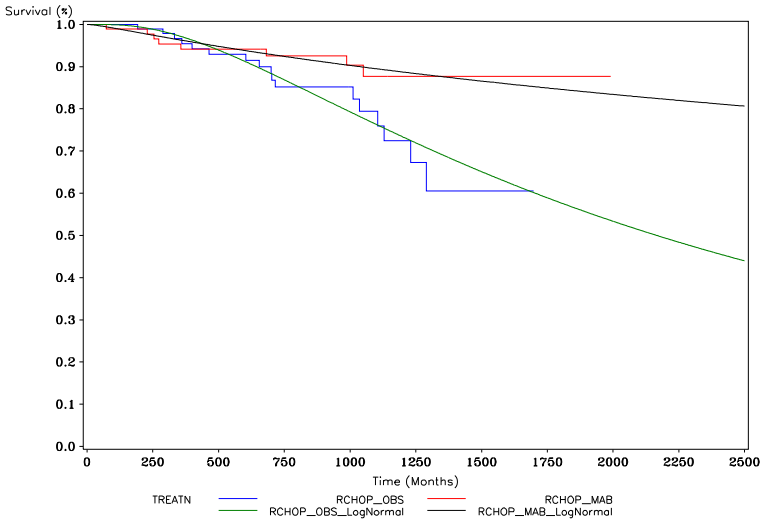
Overall Survival Assuming an Independently Shaped Llogistic Distribution
Population=ITT
Study M39022



Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/irtrapos.sas 24OCT2007 10:33

Overall Survival Assuming an Independently Shaped Lnormal Distribution
Population=ITT
Study M39022



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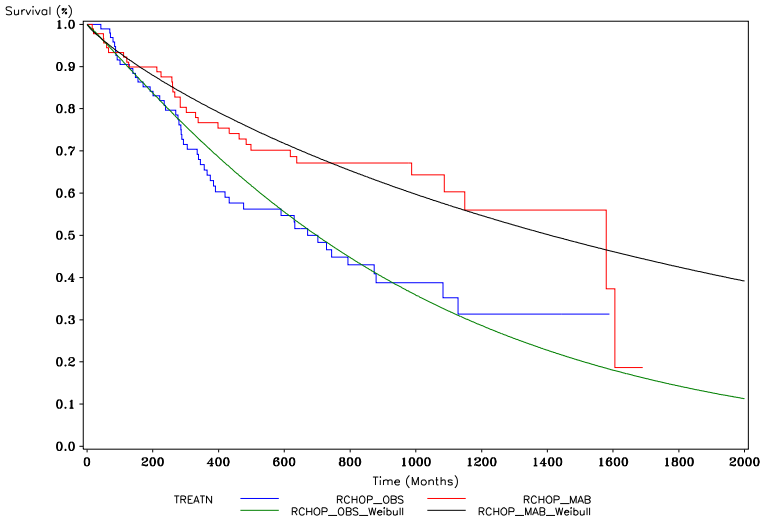
Progression Free Survival Assuming an Independently Shaped Weibull Distribution
Population=ITT
Study M39022



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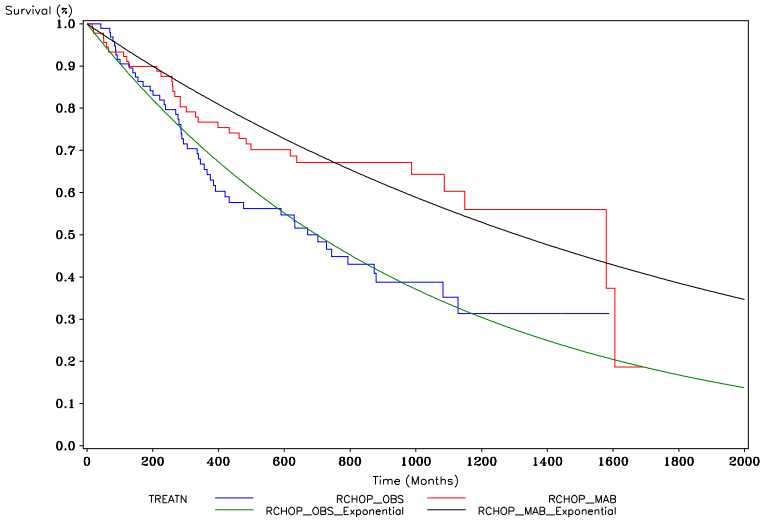
Progression Free Survival Assuming an Independently Shaped Exponential Distribution
Population=ITT
Study M39022



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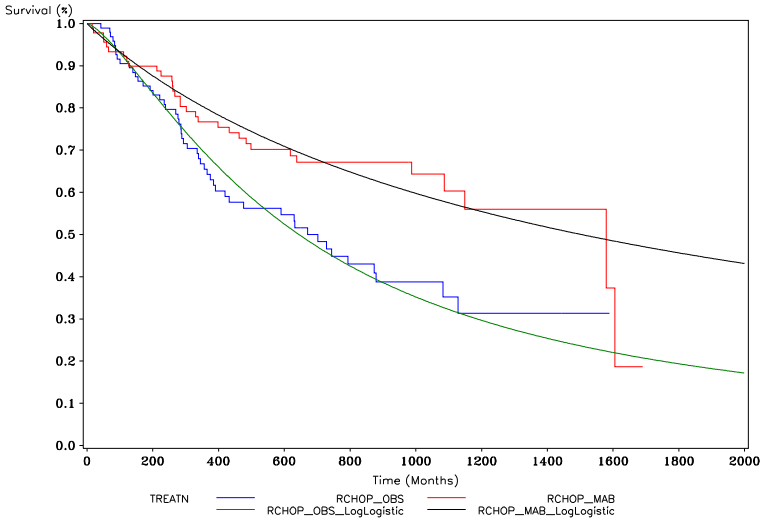
Progression Free Survival Assuming an Independently Shaped Llogistic Distribution
Population=ITT
Study M39022



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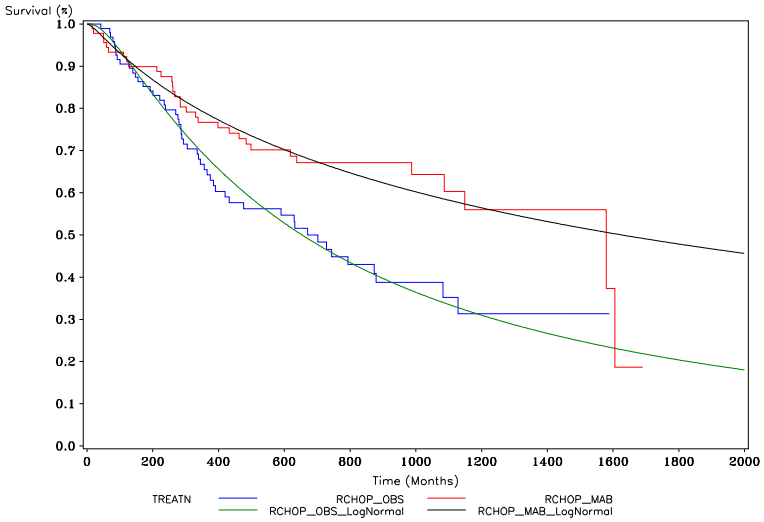
Progression Free Survival Assuming an Independently Shaped Lnormal Distribution
Population=ITT
Study M39022



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