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Application of Parametric Survival Model and Multinomial-Dirichlet Bayesian Model within a Multi-state Setup for Cost-Effectiveness Analysis of Two Alternative Chemotherapies for Patients with Chronic Lymphocytic Leukaemia

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Abstract

Estimation of transition probabilities between disease states and determination of length of stay in each state are two major concerns underlying the multi-state model based approach for cost-effectiveness analysis (CEA). The objective of this study is to apply and compare two different methods to estimate transition probabilities between three disease states *viz.*, progression-free, progression, and death, for performing CEA of chemoimmunotherapy, as compared to chemotherapy, for treating patients suffering from Lymphocytic Leukaemia. In the first method, we fit a parametric survival model to the events progression and death, and as an alternative approach, we fit a Multinomial- Dirichlet Bayesian model to the number of transitions between different states. In the first method a Weibull clock-forward time-inhomogeneous semi-markov model is used, while in the second method the transition probabilities are assumed to be time-independent and are estimated through simulations from their posterior distributions using MCMC implementation.

Results from both methods suggest that chemoimmunotherapy is cost-effective over chemotherapy. However, a comparison between the predictions of long term transitions from the two methods suggests that the method based on Weibull time-inhomogeneous semi-markov model provides more reliable estimates, especially when the time horizon of the study is long. Chemoimmunotherapy is cost effective when patients are willing to pay an additional cut off cost of around 13,000-15,000 GBP (by first method) for per unit additional gain in QALY.

Key words: ICER; Multi-state model; IPD reconstruction; Rituximab; Willingness to pay; Health economics; Total length of stay.

1. Introduction

Scientific comparison of alternative treatments for a disease, both in terms of desired outcome and costs, is imperative for optimal decision making in medical sciences. Cost-effectiveness analysis (CEA) is an important aspect of Health Economics and deals with the evaluation of cost per outcome gained. Outcome is usually defined in terms of survivability and hence, cost-effectiveness analysis evaluates both survival data and costs data simultaneously.

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Markov, semi-Markov and non-Markov multi-state models provide a comprehensive approach towards CEA of interventions for diseases for which discrete progression states can be defined based on certain clinical and pathological markers. Briggs and Sculpher (1998) provided a comprehensive structure of markov modelling for health economic evaluation and also discussed the importance of scrutinizing the Markovian assumption before estimating the transition probabilities. In a significant number of work based on Markov decision-analytic models in health economics, authors have preferred to obtain transition probabilities from published literature, refer Gharaibeh *et al*. (2015), Veldhuijzen *et al.* (2010), Lee *et al.* (2013), and Yeh *et al.* (2010). However, as the time horizon of the study from which published estimates are obtained is generally different from the time horizon of the study being conducted, these estimates are unlikely to act as reliable estimates of the true transition probabilities. This is due to the fact that, in most cases of disease progressions, transition probabilities are expected to be time dependent owing to the impact of changes in various covariates.

In the presence of individual patient data (IPD), parametric and semi-parametric survival models can be fitted to the survival data to estimate the transition probabilities of multi-state models. Exponential, Gamma, Weibull, Lognormal, and Generalized Gamma survival models are popularly found to be appropriate parametric options for the purpose of estimating transition probabilities, see for example Wu *et al.* (2014), Speight *et al.* (2006), Coon *et al.* (2010), and Diaby *et al.* (2013). Use of Cox proportional hazards models has been suggested by some authors, like Malehi *et al.* (2015) and Mihaylova *et al.* (2011) among others, especially when our interest also lies in estimating hazards associated with the covariates, given the validity of the proportional hazards assumption. Flexible semi-parametric survival models, like partitioned Cox models, can be adopted to allow for flexibility in case of violation of the proportional hazards assumption, refer Jackson *et al.* (2010) and Williams *et al.* (2017 b). Application of Bayesian parametric models to estimate the transition probabilities of multi state models has also been discussed to some extent in the literature of Health Economics; see for example Welton and Ades (2005) and Baio (2013).

In the absence of IPD, survival data can be reconstructed from published Kaplan-Meier (KM) curves by incorporating the published information about risk sets at different time points of the study. The method is discussed in detail by Hoyle and Henley (2011), Guyot *et al.* (2012), and Wan *et al.* (2015).

This paper aims to apply and compare two different methods to estimate transition probabilities between the three states of chronic lymphocytic leukaemia *viz.*, progression-free (PF), progression, and death, and carry out CEA of two types of chemotherapies used for treating patients. We have reconstructed survival data of two groups of patients suffering from chronic lymphocytic leukaemia; one group was treated with the combination of fludarabine and cyclophosphamide (chemotherapy group), and the other group was treated with the combination of fludarabine, cyclophosphamide, and rituximab (chemoimmunotherapy group). Transition probabilities between different states are estimated by fitting a a) time-inhomogeneous Weibull semi-markov model and b) Multinomial-Dirichlet Bayesian model for number of transitions. Quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) are calculated to compare the economic and survival utility of the two interventions.

2. Survival Data: Reconstruction of IPD

KM curves for overall survival (OS) and progression-free survival (PFS) for both chemotherapy and chemoimmunotherapy groups are obtained from the published work of Hallek *et al.* (2010) based on a randomized phase 3 trial of patients with chronic lymphocytic leukaemia. PFS is defined as the time between randomization and the date of the first documented disease progression, relapse, or death by any cause, and OS is defined as the time between randomization and the date of death from any cause; refer Roche (2008). Summary of the actual (published) data is shown in Table 1.

Enguage Digitizer software is used to extract coordinates from the four KM curves. The algorithm (R code) for reconstructing IPD from the extracted coordinates of KM curves developed by Guyot *et al.* (2012) is applied to reconstruct the survival data with right censoring for both treatment groups. KM curves based on actual data from Hallek *et al.* (2010) and those based on reconstructed data (with 95% confidence bounds) are shown in Figures 1 and 2 respectively. The *x*-axis in these curves represents time since the start of the study in months.

3. Methodology and Results

A three state multi-state model is conceived with possible transitions between states as described in Figure 3. An overview of the methodological structure of this study is outlined in Figure 4. A lifetime time horizon of 15 years is taken for base cost-effectiveness analyses as only 1.3% of the cohort are estimated to be surviving beyond this period as reported by Roche (2008). However, QALYs and ICERs have also been calculated for a time horizon of 20 years to evaluate the effect of choice of time horizon on QALYs and ICERs. This is necessary to account for the uncertainty underlying the choice of lifetime time horizon, see Jackson *et al.* (2017).

3.1. Estimation of transition probabilities of the multi-state model using parametric survival model

To start with, Gamma, Exponential, Weibull, Log-logistic, Log-normal, and Generalized Gamma survival models are fitted to the transitions data of both groups. Based on the Akaike Information Criterion (AIC), and size of confidence intervals, survival models with Weibull distribution for time to events (progression and death) are found to exhibit best fits for both chemotherapy and chemoimmunotherapy groups. AIC values of the fitted models are provided in Tables 2 and 3. Plots of estimated survival functions, along with corresponding confidence intervals and KM estimates, are presented in Appendix-A, Figures A.1 and A.2. A combination of R functions available in the packages ‘flexsurv’ by Jackson (2016) and ‘mstate’ by de Wreede *et al.* (2010) are used to obtain these results. The chosen Weibull model is a clock-forward time-inhomogeneous semi-markov model. This suggests that the transition probabilities are assumed to vary with time. As an illustration, estimated transition probability matrices at the times $t = 50$ months, $t = 100$ months, $t = 180$ months and $t = 240$ months from the start of the study ($t = 0$) are presented in Table 4 (for chemotherapy arm) and Table 5 (for chemoimmunotherapy arm). These transition probabilities, say, P_{rs}^{T}, $r = 1,2,3$, $s = 1,2,3$, and $T = 1,2,3\ldots$, represent the probability that a patient is in state s at time $t = T$, given that he/she was in state r at time $t = 0$. These transition probabilities are used to calculate expected total length of stay (TLOS) in each state s, when a patient starts from a

particular state r at time $t = 0$. TLOS matrices calculated for both groups, at 15 years' and 20 years' time horizon, are provided in Table 6.

3.2. Costs data

In both treatment regimes, some of the costs are fixed, while some of them are variable and depend on the length of the treatment. Cost of supportive care in PF state, cost of supportive care in progression, and cost of second-line and subsequent therapy are dependent on the duration of treatment/ care in the respective states and so, total expected costs under these heads have been calculated using estimated TLOS in the respective states. Monthly mean costs for these heads are obtained from Roche (2008). Expected total costs for the variable heads are calculated at discount rates of 3.5% and 5% per annum over the lengths of stay. Estimated mean total costs of both treatment regimes, and the expected cost incremental for chemoimmunotherapy with respect to chemotherapy, are shown in Table 7 (15 years time horizon) and Table 8 (20 years time horizon). Discount rate of 3.5% has been advised by the National Institute of Health and Care Excellence (NICE), UK, and discount rate of 5% is taken to analyze the sensitivity of the results towards the choice of discount rates. Remaining mean costs, which are not related to the length of stay in any state and are essentially fixed costs, are taken from Williams *et al.* (2017 a). Since a patient is not expected to go back to the PF state after entering progression state, it is safe to use the generic formula given in equation (1) to calculate discounted costs.

$$PV = \sum_i \frac{V_i}{(1+d)^i} \tag{1}$$

Here, d is per unit time discount rate, PV is present value of the total cost and V_i is actual cost incurred at i^{th} time point (with base period at $i = 0$).

3.3. QALY and ICER

For calculation of mean QALYs, utility values of 0.8 and 0.6 have been considered for the PF health state and the progression health state respectively; refer Roche (2008). QALYs are discounted at 3.5% and 5% rates, in concurrence with the rates of discount for costs, and using the formula given in equation (1) after replacing costs with lengths of stay. ICER, which represents the cost per unit increase in QALY, is calculated for each time horizon at both discount rates. Calculated values of discounted mean QALYs for both treatment groups, QALY incremental, cost incremental and ICERs are reported in Table 9. QALY incremental, cost incremental, and ICERs have been calculated taking chemotherapy as the base intervention. Figure 5 exhibits the cost-effectiveness plane, showing acceptability of the chemoimmunotherapy over chemotherapy at two different values of willingness to pay, *viz*. K = 15,000 GBP and K = 13,000 GBP, for a unit additional gain in QALY.

3.4. Estimation of transition probabilities of the multi-state model using Multinomial-Dirichlet Bayesian model

In this method, instead of getting into the realm of survival models, we define the observed number of transitions between states as a vector of random variables following Multinomial distribution and estimate the parameters under Bayesian framework using Dirichlet as the prior distribution; refer Baio (2013) and Welton and Ades (2005). Dirichlet

distribution is a conjugate prior for Multinomial distribution. The Multinomial- Dirichlet Bayesian model for our multi-state set up is defined as follows:

Notations:

$r_{st}^{(I)}$: Total number of observed transitions from state *s* to state *t* for intervention *I.*

$\lambda_{st}^{(I)}$: Transition probability from state *s* to state *t* for intervention *I.*

$n_s^{(I)}$: Total number of transitions from state *s* to all other states for intervention *I.*

$r_s^{(I)} = (r_{s1}^{(I)}, r_{s2}^{(I)}, r_{s3}^{(I)})$

$\lambda_s^{(I)} = (\lambda_{s1}^{(I)}, \lambda_{s2}^{(I)}, \lambda_{s3}^{(I)})$

Here, $s = 1, 2, 3$ and $I = 1, 2$.

$$r_s^{(I)} | \lambda_s^{(I)} \sim Multinomial(\lambda_s^{(I)}, n_s^{(I)})$$

$$= \frac{n_s^{(I)}}{r_{s1}^{(I)}! r_{s2}^{(I)}! r_{s3}^{(I)}!} {\lambda_{s1}^{(I)}}^{r_{s1}^{(I)}} {\lambda_{s2}^{(I)}}^{r_{s2}^{(I)}} {\lambda_{s3}^{(I)}}^{r_{s3}^{(I)}} \quad (2)$$

And prior distribution of the transition probabilities is defined as,

$$\lambda_s^{(I)} | \alpha^{(I)} \sim Dirichlet(\alpha_1^{(I)}, \alpha_2^{(I)}, \alpha_3^{(I)})$$

$$= \frac{\Gamma(\alpha_1^{(I)} + \alpha_2^{(I)} + \alpha_3^{(I)})}{\Gamma(\alpha_1^{(I)})\Gamma(\alpha_2^{(I)})\Gamma(\alpha_3^{(I)})} \lambda_{s1}^{(I)(\alpha_1^{(I)} - 1)} \lambda_{s2}^{(I)(\alpha_2^{(I)} - 1)} \lambda_{s3}^{(I)(\alpha_3^{(I)} - 1)} \quad (3)$$

Unknown parameter of the Multinomial distribution in (2) is nothing but the vector of transition probabilities from state *s* to all other states, whose prior distribution is defined by the Dirichlet distribution with density function given in (3). It should be noted that while specifying this model, the transition probabilities are assumed to be constant, *i.e.* independent of time, unlike in the case of previous method based on Weibull clock-forward semi-markov model. Markov Chain Monte Carlo (MCMC) method is implemented through JAGS (Just Another Gibbs Sampler) within R session for simulating posterior distributions of the vectors of transition probabilities. R and JAGS codes are adopted from Baio (2013), and implemented with necessary modifications, corrections and additions to estimate transition probabilities from their posterior realizations. Beyond this point, two approaches are implemented to carry out CEA.

In the first approach, CEA is performed using the function bcea( ) available in the R package 'BCEA'. In this method, ICERs are determined from vectors of cost incremental values and benefit incremental values calculated at all simulated values of the transition probabilities. Here, benefit is defined as the total number of time units (months) spent by patients in the first state, *i.e.* PF state; which is mathematically equal to the total number of patients in PF state summed over the entire time horizon. Calculations of costs and benefits are done at discount rates of 3.5% and 5% each. ICERs and Cost Effectiveness Acceptability Curves (CEACs) are obtained for time horizons of 15 and 20 years. Results at discount rates of 3.5% and 5% are presented in the Figures 6 and 7, respectively.

The second approach has been adopted to gain better insight into the comparative assessment between the Weibull semi-markov method and the Multinomial-Dirichlet

Bayesian method. Expected TLOS in each state and respective 95% confidence intervals are calculated on the basis of transition probabilities simulated from their posterior distribution. Further, at utility values of 0.8 for PF state and 0.6 for progression state, QALYs are obtained using TLOS matrices at 3.5% and 5% discount rates. Estimated time-independent probability transition matrices (with 95% CIs), and expected TLOS matrices, for both treatment groups, are provided in Tables 10 and 11 respectively.

4. Summary and Discussions

4.1. CEA based on Weibull semi-markov model

The estimated transition probability matrices based on Weibull semi-markov models for chemotherapy group and chemoimmunotherapy group exhibit notable differences in the probability of a patient in PF state to remain in the same state after a time interval $t\ (>0)$. A resultant major impact of this finding from the CEA point of view is the significant difference between the expected TLOS in the first state, PF, of the two intervention groups. PF state has maximum utility value among the three states and contributes the most to gain in QALYs. From Table 6, for time horizons of both 15 years and 20 years, the expected TLOS in the PF state for the chemoimmunotherapy group is around 52 months as opposed to that of just 35 months for the chemotherapy group; a difference of around 17 months. However, difference in the expected TLOS in the progression state between the two intervention groups is least prominent.

QALY results in Table 9 show additional/ incremental gains of 0.84 (d = 3.5%) and 0.94 (d = 5 %) QALYs for 15 years' time horizon, and of 0.79 (d = 3.5%) and 0.90 (d = 5%) QALYs for 20 years' time horizon, for the chemoimmunotherapy group over the chemotherapy group. At both discount rates, QALY incremental is lower and cost incremental is higher in case of 20 years' time horizon, as compared to those for 15 years' time horizon. As a result, the ICERs for 20 years' time horizon are on the higher side as compared to those for 15 years' time horizon. For a fixed time horizon, ICERs corresponding to the discount rate of 3.5% are significantly higher than those corresponding to the discount rate of 5%. It can also be noted that the ICERs are more sensitive towards the choice of discount rates (keeping time horizon fixed), than towards the choice of time horizon (keeping discount rate fixed). ICERs corresponding to 5% discount rate are below the willingness to pay line of K = 13,000 GBP, while both ICERs corresponding to 3.5% discount rate are above that line. At the willingness to pay of 15,000 GBP or more for a unit increase in QALY, choosing chemoimmunotherapy over chemotherapy accounts for an optimal decision as all the four points A,B,C and D lie below the line corresponding to K = 15,000 GBP (Figure 5).

4.2. CEA based on Multinomial- Dirichlet Bayesian model

First approach: Optimal decisions derived from this approach find chemoimmunotherapy to be cost-effective over chemotherapy for willingness to pay parameter more than or equal to around 227,000 GBP, for both time horizons, and 3.5% discount rate (Figure 6). At 5% discount rate, chemoimmunotherapy is cost-effective over chemotherapy if a patient is willing to pay around 306,000 GBP for an additional gain of QALY, for both 15 years' and 20 years' time horizons (Figure 7). In this case also, ICERs are found to be significantly sensitive towards the choice of discount rates, but not towards the

choice of time horizon. These values of ICERs are strikingly and absurdly higher than those obtained from the first method.

Second approach: As is apparent from the results reported in Table 11, the expected TLOS in the PF state are much higher and in progression state are unreliably low, raising speculations of wrong predictions. However, because of the drastic underestimation of TLOS in progression state and overestimation in PF state, the ICER comes out to be balanced. At 3.5% discount rate and for 15 years time horizon, while the cost incremental is approximately 11,560 GBP, QALY incremental is only 0.66, rendering ICER to around 17,515 GBP for one unit additional gain in QALY.

Another notable difference in these two approaches is that utility values have not been used for calculation of benefits in the first approach. Also, in the first approach, using the function bcea( ), the benefit incremental is calculated as difference in the total number of months spent by patients in PF state for the two intervention groups; which is equivalent to expected TLOS incremental in months in PF state. Thus, the first approach completely ignores the gain in utility because of stay in progression state. Extremely high ICER from the first approach suggests that the difference in expected number months spent by patients in PF state is very small and does not capture the actual difference in gain in QALY between the two groups.

4.3. Comparing predictions from the two models

As the study involves long lifetime time horizons, accuracy of prediction of transitions is of utmost importance for conducting CEA. Remarkable differences in the results of QALYs and ICERs obtained from the two methods suggest that at least one of them may not be reliable. To compare and examine the predictions from the two methods, graphs of estimated proportion of patients in each state at different time points (virtual follow-up times) are plotted for both intervention groups (Figures 8 and 9). From the graphs in Figure 8, pertaining to first method, we can see that only few patients are expected to remain in PF state till around 150 months in chemotherapy group, and till 180 months in chemoimmunotherapy group. While based on the transition probabilities of the second method, it is apparent from the graphs in Figure 9 that more than 25% of patients are expected to live even after 180 months in both intervention groups. This is in clear contrast with the observed survival data and the contradiction can be visualized easily on comparing the original KM curves in Figure 1with the graphs in Figure 9. However, we can safely claim that the shapes of the graphs in Figure 8 conform to those of the original KM curves till the observed time period of 5 years (or 60 months). According to the KM curves, at the end of 60 months, around 25% patients in chemotherapy group and 40% patients in chemoimmunotherapy group were free of progression (*i.e.* in PF state), while around 60% patients in chemotherapy group and more than 50% patients in chemoimmunotherapy group were still alive. Around same proportions are depicted by the patient proportion graphs based on Weibull time-inhomogeneous semi-markov model.

Failure of the Multinomial-Dirichlet Bayesian model in this study can be attributed to the assumption of time-homogeneous (or constant) transition probabilities over the entire time horizon of the study. In a long-term study, transition probabilities from a state to other states are expected to change with time, especially when patients stay in the state for a longer duration. So, it is safe to conclude that this method, or any other method with the assumption of constant transition probabilities, should be avoided for CEA in long-term studies.

For further comparison, plots of estimated transition probabilities against time for the two methods are provided in Appendix-B (Figures B.1 and B.2).

5. Conclusion

We have applied two different methods for analyzing cost-effectiveness of chemoimmunotherapy over chemotherapy for treating patients with chronic lymphocytic leukaemia. Although results from both methods find chemoimmunotherapy to be cost effective over chemotherapy, values of QALYs and ICERs from the Weibull time-inhomogeneous semi-markov model are found to be more reliable. To be precise, chemoimmunotherapy is cost effective over chemotherapy if the patients are willing to pay around 15,000 GBP or more for a unit additional gain in QALY. Also, it can be inferred from the results that administration of chemoimmunotherapy in place of chemotherapy is expected to result in a patient to stay for a much longer period (over a year on an average) in the PF state, which is the state of highest utility.

For one-way sensitivity analysis of cost-effectiveness towards the choice of lifetime time horizon and the choice of discount rate, analyses are carried out for two different lifetime time horizons and at two different discount rates for cost and QALY calculations. Results from both models confirm that ICERs are more sensitive towards the choice of discount rate than the choice of lifetime time horizon. This suggests that discount rate should be chosen carefully after consulting relevant economic parameters of the region of study to avoid biased and misleading results.

Since a reconstructed data has been used for the analyses, the data consists of only survival times for the events progression and death, and no information is available on covariates and factors affecting survivability. Inclusion of data on covariates, like pathological and clinical factors, demographic variables *etc.*, will make such cost-effectiveness studies more comprehensive and informative.

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TABLES AND FIGURES

Table 1: Summary of original data

Total no. of patients enrolled: 817	**Chemotherapy Group**	**Chemoimmunotherapy Group**
Total assigned to group	409	408
Lost to follow up	40	14
No. of PFS events observed	227	162
No. of death events observed	86	65
Total follow-up period	5 year	5 years

Source: *Hallek et al.* (2010)

Table 2: Chemotherapy data fit

Distribution	**AIC**
Exponential	2597.634
Gamma	2597.693
Weibull	2585.173
Log-logistic	2600.635
Log-normal	2620.277
Generalized Gamma	2596.533

Table 3: Chemoimmunotherapy data fit

Distribution	**AIC**
Exponential	3286.647
Gamma	3281.338
Weibull	3269.976
Log-logistic	3287.074
Log-normal	3323.709
Generalized Gamma	3280.407

Table 4: Chemotherapy—estimated transition probabilities (and 95% confidence intervals))

At t = 1 month	**Progression Free**	**Progression**	**Death**
Progression Free	0.990 (0.984; 0.993)	0.006 (0.004; 0.009)	0.004 (0.003; 0.007)
Progression	0	0.997 (0.995; 0.998)	0.003 (0.002; 0.005)
Death	0	0	1
At t= 50 months	**Progression Free**	**Progression**	**Death**
Progression Free	0.237 (0.192; 0.277)	0.348 (0.295; 0.399)	0.415 (0.365; 0.476)
Progression	0	0.658 (0.574; 0.726)	0.342 (0.274; 0.426)
Death	0	0	1
At t= 180 months	**Progression Free**	**Progression**	**Death**
Progression Free	0.001 (0; 0.003)	0.101 (0.043; 0.174)	0.898 (0.824; 0.957)
Progression	0	0.123 (0.05; 0.215)	0.877 (0.785; 0.950)
Death	0	0	1

At t= 240 months	**Progression Free**	**Progression**	**Death**
Progression Free	0	0.041 (0.011; 0.093)	0.959 (0.907; 0.989)
Progression	0	0.049 (0.012; 0.115)	0.951 (0.885; 0.988)
Death	0	0	1

Table 5: Chemoimmunotherapy—estimated transition probabilities (and 95% confidence intervals)

At t= 1 month	**Progression Free**	**Progression**	**Death**
Progression Free	0.994 (0.99; 0.997)	0.003 (0.002; 0.005)	0.003 (0.001; 0.005)
Progression	0	0.998 (0.996; 0.999)	0.002 (0.001; 0.004)
Death	0	0	1
At t= 50 months	**Progression Free**	**Progression**	**Death**
Progression Free	0.425 (0.371; 0.469)	0.253 (0.211; 0.304)	0.322 (0.277; 0.375)
Progression	0	0.705 (0.613; 0.779)	0.295 (0.221; 0.387)
Death	0	0	1
At t= 180 months	**Progression Free**	**Progression**	**Death**
Progression Free	0.012 (0.003; 0.032)	0.138 (0.061; 0.230)	0.850 (0.748; 0.933)
Progression	0	0.166 (0.063; 0.296)	0.834 (0.704; 0.937)
Death	0	0	1
At t= 240 months	**Progression Free**	**Progression**	**Death**
Progression Free	0.002 (0; 0.009)	0.065 (0.014; 0.143)	0.933 (0.853; 0.986)
Progression	0	0.074 (0.013; 0.174)	0.926 (0.826; 0.987)
Death	0	0	1

Table 6: Expected total length of stay in months (and 95% confidence intervals)

Chemotherapy 15-Year Horizon=180 months	**Progression Free**	**Progression**	**Death**
Progression Free	34.80 (31.74; 38.08)	41.66 (31.80; 51.73)	103.54 (92.78; 114.25)
Progression	0	85.14 (70.64; 99.43)	94.86 (80.57; 109.36)
Death	0	0	180
Chemotherapy 20-Year Horizon=240 months	**Progression Free**	**Progression**	**Death**
Progression Free	34.81 (31.56; 38.45)	45.67 (33.24; 59.04)	159.52 (145.35; 73.57)
Progression	0	90.01 (71.29; 108.45)	149.99 (131.55; 168.71)
Death	0	0	240
Chemoimmunotherapy 15-Year Horizon=180 months	**Progression Free**	**Progression**	**Death**
Progression Free	51.92 (46.25; 57.51)	37.48 (27.47; 47.48)	90.60 (79.56; 102.46)
Progression	0	93.52 (76.61; 108.83)	86.48 (71.17; 103.39)
Death	0	0	180
Chemoimmunotherapy 20-Year Horizon=240 months	**Progression Free**	**Progression**	**Death**
Progression Free	52.24 (46.28; 59.46)	43.38 (30.90; 58.34)	144.38 (127.39; 160.44)
Progression	0	100.40 (78.68; 122.97)	139.60 (117.03; 161.32)
Death	0	0	240

Table 7: Mean costs (in GBP) for 15-year lifetime time horizon

Cost Head	Chemoimmunotherapy		Chemotherapy		Incremental (*d*=3.5%)	Incremental (*d*=5%)
	Mean total cost (*d*=3.5%)	Mean total cost (*d*=5%)	Mean total cost (*d*=3.5%)	Mean total cost (*d*=5%)		
Mean cost of PFS	**18645.28**	**18605.12**	**6650.10**	**6634.65**	**11995.18**	**11970.47**
Costs of rituximab	10113	10113	0	0	10113	10113
Administration costs of rituximab	1224	1224	0	0	1224	1224
Cost of fludarabine	2776	2776	2790	2790	−14	−14
Administration costs of fludarabine	1109	1109	1115	1115	− 6	− 6
Costs of cyclophosphamide	21	21	22	22	−1	−1
Administration costs of cyclophosphamide	1109	1109	1115	1115	− 6	− 6
*Cost of supportive care in PFS	1061.28	1021.12	741.10	725.65	320.18	295.47
Cost of bone marrow transplantation	592	592	360	360	232	232
Cost of blood transfusions	640	640	507	507	133	133
Mean cost of progression	**7329.60**	**7178.44**	**8061.20**	**7893.01**	**− 731.60**	**− 714.57**
*Cost of supportive care in progression	1802.04	1764.88	1981.91	1940.56	− 179.87	− 175.68
*Cost of second-line & subsequent therapy	5527.55	5413.56	6079.28	5952.45	− 551.73	− 538.89
Mean total cost	**25974.88**	**25783.57**	**14711.30**	**14527.66**	**11263.58**	**11255.90**
*Calculated and discounted with respect to the total length of stay in the given state						

Table 8: Mean costs (in GBP) for 20-year lifetime time horizon

Cost Head	Chemoimmunotherapy		Chemotherapy		Incremental (*d*=3.5%)	Incremental (*d*=5%)
	Mean total cost (*d*=3.5%)	Mean total cost (*d*=5%)	Mean total cost (*d*=3.5%)	Mean total cost (*d*=5%)		
Mean cost of PFS	**18648.36**	**18611.09**	**6650.10**	**6634.65**	**11998.26**	**11976.45**
Costs of rituximab	10113	10113	0	0	10113	10113
Administration costs of rituximab	1224	1224	0	0	1224	1224
Cost of fludarabine	2776	2776	2790	2790	−14	−14
Administration costs of fludarabine	1109	1109	1115	1115	− 6	− 6
Costs of cyclophosphamide	21	21	22	22	− 1	− 1
Administration costs of cyclophosphamide	1109	1109	1115	1115	− 6	− 6
*Cost of supportive care in PFS	1064.36	1027.09	741.10	725.65	323.26	301.45
Cost of bone marrow transplantation	592	592	360	360	232	232
Cost of blood transfusions	640	640	507	507	133	133

Mean cost of progression	**8377.23**	**8160.49**	**8769.82**	**8547.54**	**− 392.60**	**− 387.05**
*Cost of supportive care in progression	2059.61	2006.33	2156.14	2101.49	− 96.52	− 95.16
*Cost of second-line & subsequent therapy	6317.61	6154.16	6613.69	6446.06	− 296.07	− 291.89
Mean Total cost	**27025.58**	**26771.58**	**15419.92**	**15182.19**	**11605.66**	**11589.39**

*Calculated and discounted with respect to the total length of stay in the given state

Table 9: QALYs and ICERs (in GBP/ QALY)

State	**15-year Horizon**		**20-year Horizon**	
	***d* = 3.5%**	***d* = 5%**	***d* = 3.5%**	***d* = 5%**
Gain in QALY for a patient in PF state at randomization−chemotherapy				
Progression Free	2.25	2.22	2.25	2.22
Progression	2	1.97	2.18	2.14
Death	0	0	0	0
Total QALY	4.25	4.19	4.43	4.36
Gain in QALY for a patient in PF state at randomization−chemoimmunotherapy				
Progression Free	3.28	3.20	3.29	3.22
Progression	1.81	1.78	2.08	2.04
Death	0	0	0	0
Total QALY	5.09	4.98	5.37	5.26
QALY Incremental	0.84	0.94	0.79	0.90
Cost Incremental	11263.58	11255.90	11605.66	11589.39
ICER	13409.02	11974.37	14690.71	12877.10

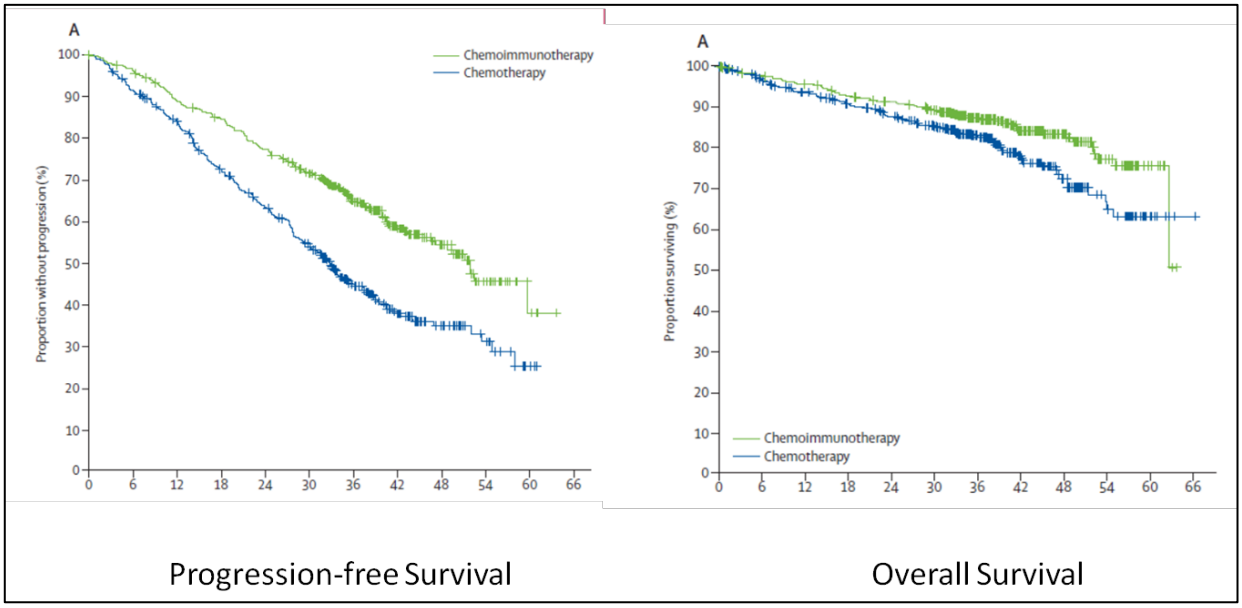
Table 10: Bayesian model—estimated transition probabilities (with 95% confidence limits)

Chemotherapy	**Progression Free**	**Progression**	**Death**
Progression Free	0.99 (0.977; 0.998)	0.01 (0.002; 0.023)	0
Progression	0	0.794 (0.401; 0.0.993)	0.206(0.007; 0.599)
Death	0	0	1
Chemoimmunotherapy	**Progression Free**	**Progression**	**Death**
Progression Free	0.993 (0.982; 0.998)	0.007 (0.002; 0.018)	0
Progression	0	0.798 (0.414; 0.993)	0.202 (0.007; 0.586)
Death	0	0	1

Table 11: Bayesian model—expected total length of stay in each state for 15-year lifetime time horizon (in months)

Chemotherapy	**Progression Free**	**Progression**	**Death**
Progression Free	90.91 (72.97; 145.91)	10.17 (2.45; 56.33)	78.92 (61.29; 127)
Progression	0	15.40 (3.30; 102.15)	164.60 (160.12; 178.33)
Death	0	0	180
Chemoimmunotherapy	**Progression Free**	**Progression**	**Death**
Progression Free	106.70 (85.76; 157.38)	8.54 (2.11; 45.74)	64.77 (44.11; 118.99)
Progression	0	15.54 (3.32; 103.76)	164.46 (160.12; 178.29)
Death	0	0	180

Figure 1: Kaplan-Meier curves used for data reconstruction



Source: *Hallek et al.* (2010)

Figure 2: Kaplan-Meier curves from reconstructed data

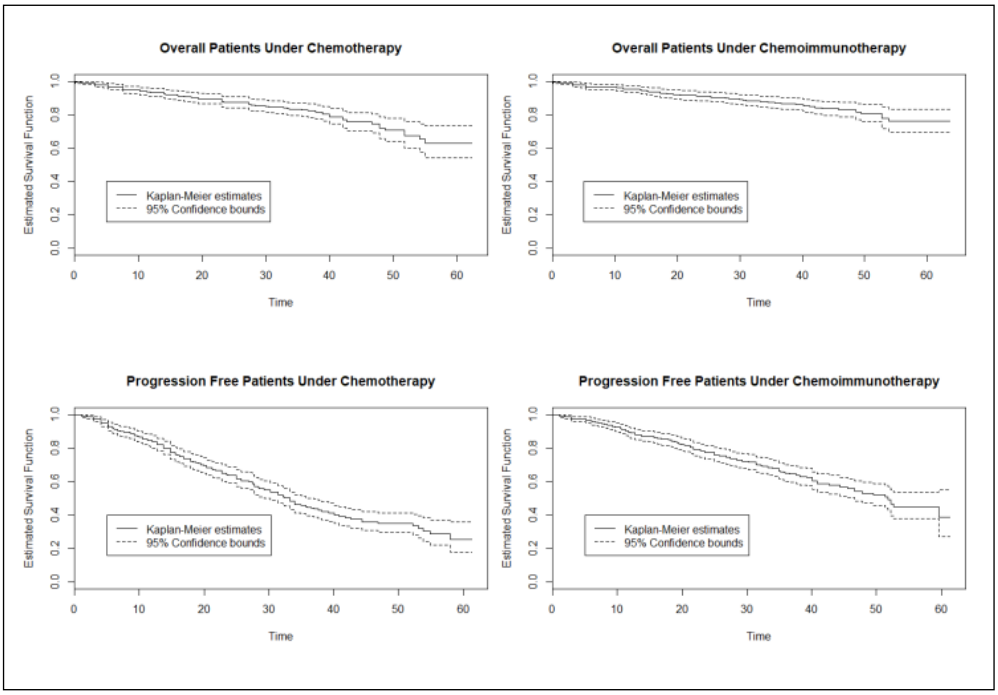


Figure 3: Transition map between three states of the multi-state model

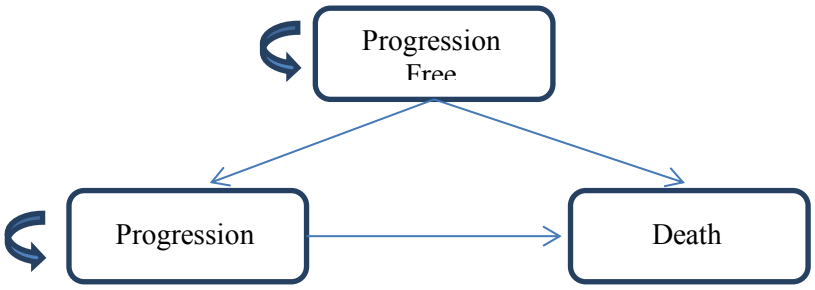


Figure 4: Methodological structure

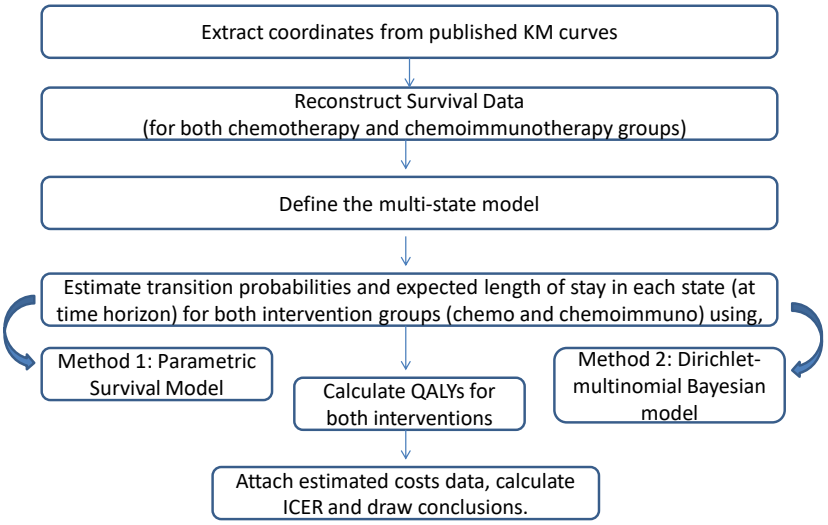


Figure 5: Cost-effectiveness plane from the first method

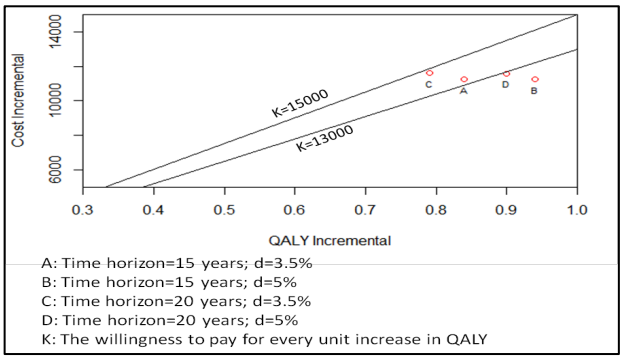
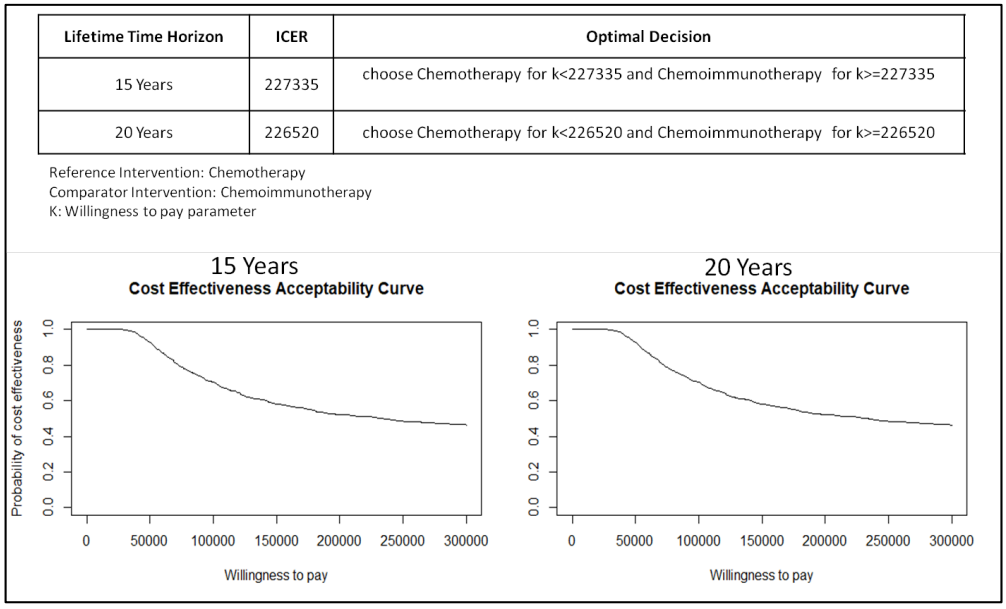


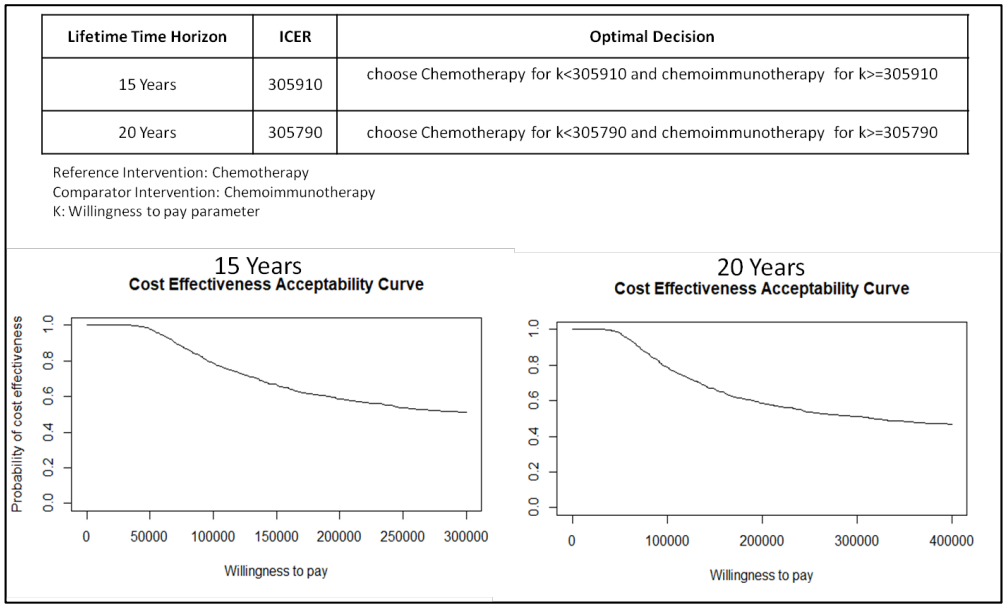
Figure 6: Results of Bayesian cost-effectiveness analysis using BCEA (d = 3.5%)



Lifetime Time Horizon	ICER	Optimal Decision
15 Years	227335	choose Chemotherapy for k<227335 and Chemoimmunotherapy for k>=227335
20 Years	226520	choose Chemotherapy for k<226520 and Chemoimmunotherapy for k>=226520

Reference Intervention: Chemotherapy
Comparator Intervention: Chemoimmunotherapy
K: Willingness to pay parameter

Figure 7: Results of Bayesian cost-effectiveness analysis using BCEA (d = 5%)



Lifetime Time Horizon	ICER	Optimal Decision
15 Years	305910	choose Chemotherapy for k<305910 and chemoimmunotherapy for k>=305910
20 Years	305790	choose Chemotherapy for k<305790 and chemoimmunotherapy for k>=305790

Reference Intervention: Chemotherapy
Comparator Intervention: Chemoimmunotherapy
K: Willingness to pay parameter

Figure 8: Proportion of patients expected to be in each state at different virtual follow-up time points—Weibull time-inhomogeneous semi-markov model

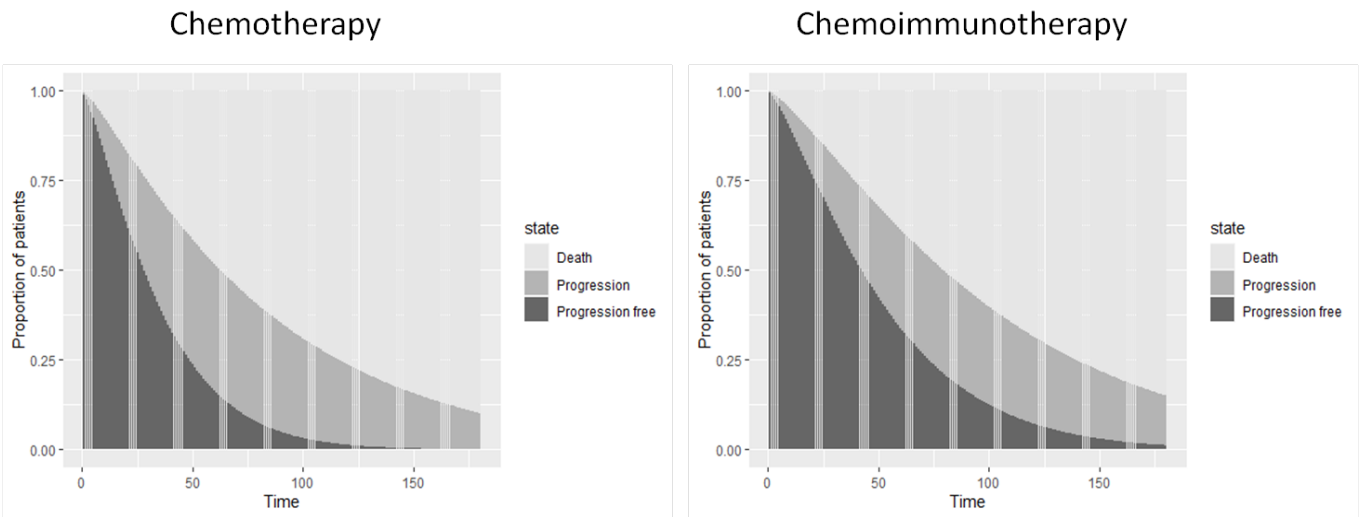
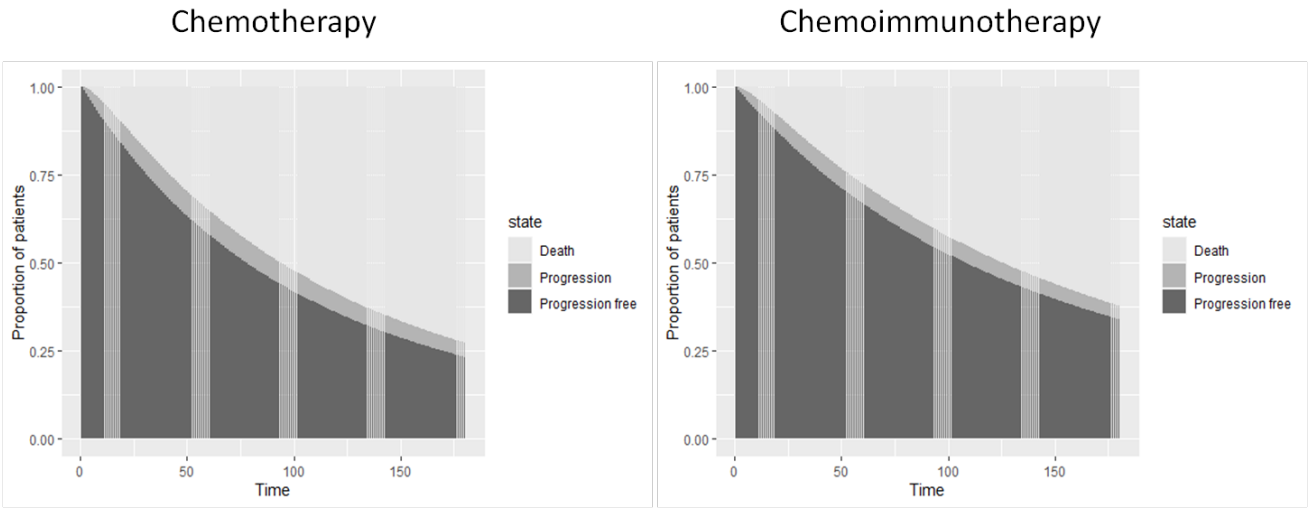


Figure 9: Proportion of patients expected to be in each state at different virtual follow-up time points—Multinomial-Dirichlet Bayesian model



Appendix-A

Figure A.1: Estimated survival functions of fitted models—Chemotherapy group

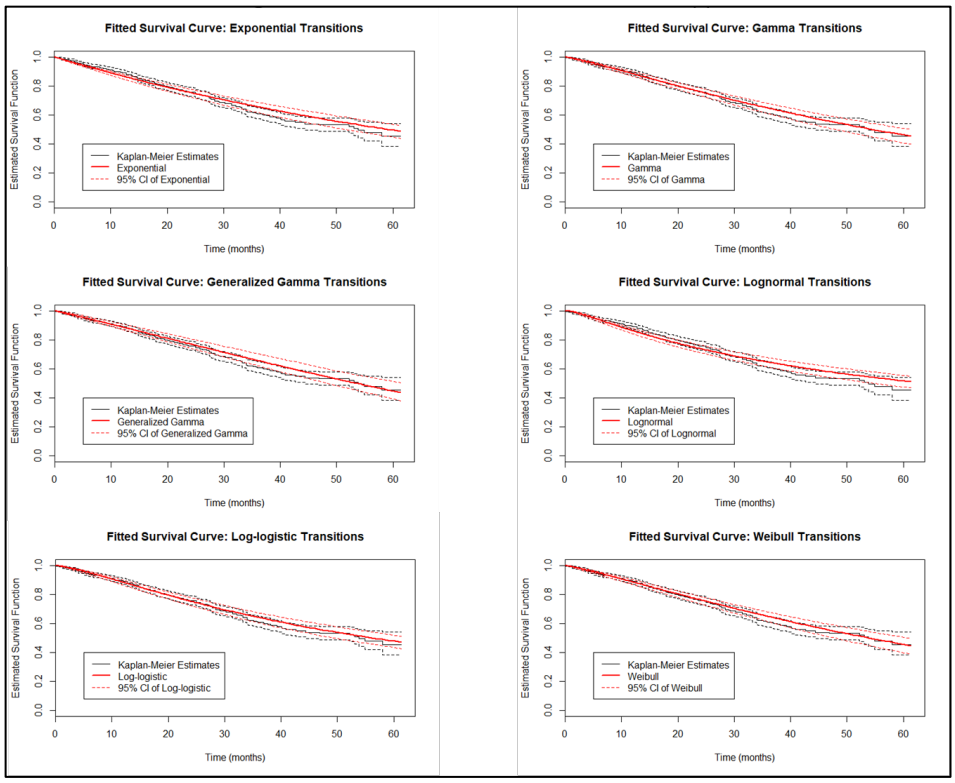
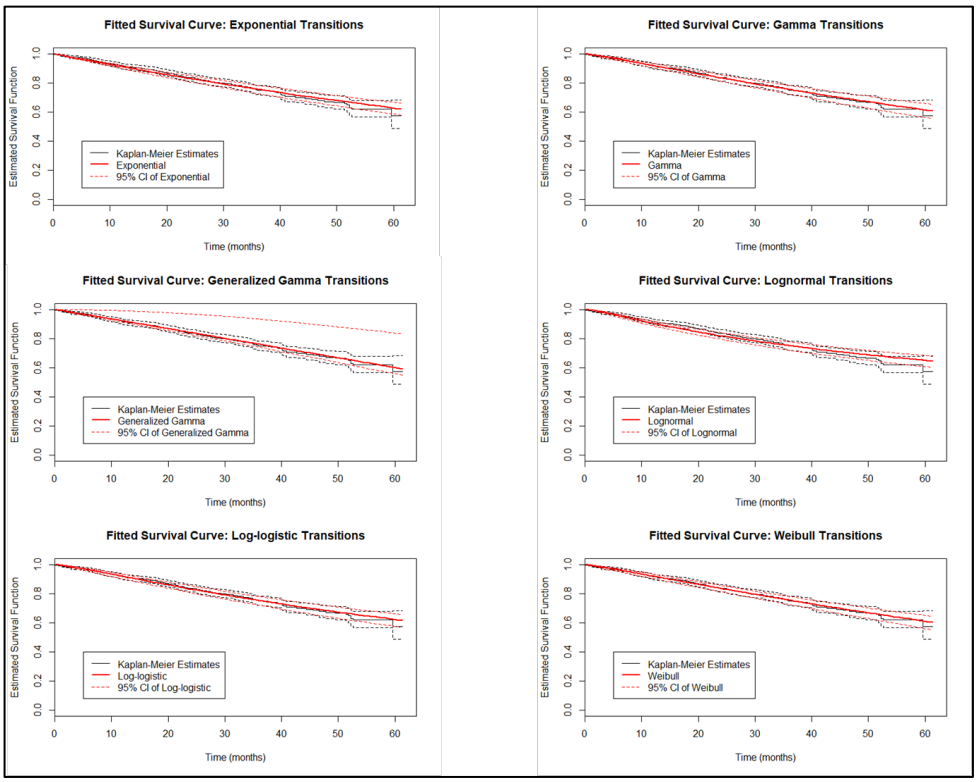


Figure A.2: Estimated survival functions of fitted models—Chemoimmunotherapy group



Appendix-B

Figure B.1: Transition probabilities plotted against time—Weibull semi-markov model

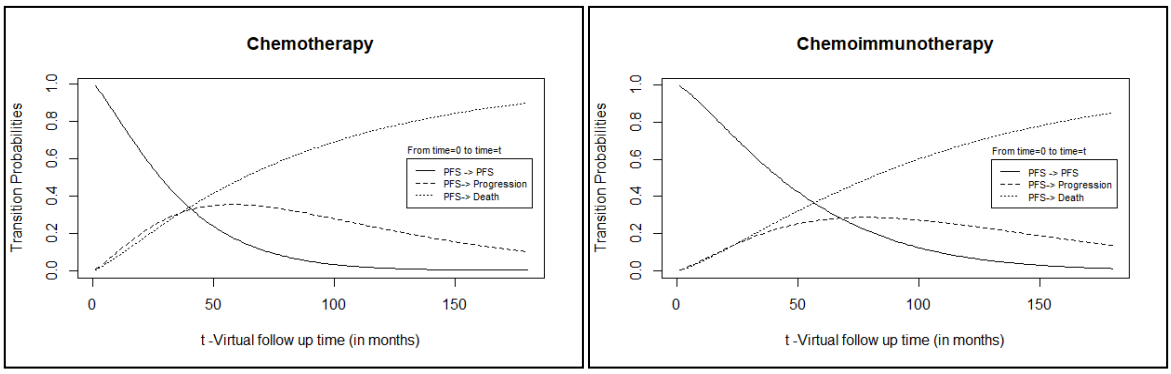


Figure B.2: Transition probabilities plotted against time—Multinomial-Dirichlet Bayesian model