Parameters for curve fits

Rituximab for the treatment of relapsed/refractory CLL. This is a confidential document about work in progress before submission of the ERG report. It is written with the intention of clarifying data from the submission.

[redacted]

The ERG requested information about parameters for the parametric fits described in the manufacturer's submission (page 198) as follows:

B1. Survival curves are described on page p198 of the submission. It would be helpful for the ERG if a single table were constructed defining:

i) the S(t) function for each of the parametric fits shown on page 198

ii) the parameter values corresponding to each fit that was used for the economic model (base case and sensitivity analyses)

The manufacturer's response to i) was to copy and paste information from various documents. This response was not particularly helpful because there are several variants of the equations that describe the parametric functions and it was not clear if those described matched up to the parameter provided.

The manufacturer's response to ii) was:

These have all been provided explicitly in Appendix 1.

Unfortunately the requested parameters were embedded amongst a very large number of input values for the economic model making their identification and extraction time-consuming. Also, the provided parameters were incomplete and in several instances clearly incorrect. The table below lists the different curve fits, the parameters required for each, what we were given in the submission and what would have liked to have seen. In summary, only the exponential function parameters were supplied as requested. For the other distributions (lognormal, weibull, loglogistic, gompertz and gamma) there was insufficient information to continue, with some of the parameters identical and others missing.

GROUP	Parametric distribution	Paramenters supplied in Appendix 1	Expected parameters	Comment
FC	Exponential	Lambda 0.021538853	Lambda	Supplied as expected
FC-R	Exponential	Lambda 0.032648063	Lambda	
FC	Lognormal	Lambda 0.019089139 Lambda 3.03372945 Gamma 1.26999224	Mu & sigma	Three parameters supplied; two given same label; one parameter (0.0190891349) does not make sense.
FC-R	Lognormal	Lambda 3.43910477	Mu & sigma	Only one parameter supplied. Useless.
FC	Weibull	Gamma 1.168851232	Shape & scale parameters	Gamma value is identical for FC and FC-R to 9 decimal places. Only one parameter supplied for FC .
FC-R	Weibull	Gamma 1.168851232 Lambda 0.012247453	Shape & scale parameters	
FC	Loglogistic	Lambda 0.012562418 Gamma 1.439731176	Shape & scale parameters	Supplied as expected
FC-R	Loglogistic	Lambda 0.007234917 Gamma 1.26999224	Shape & scale parameters	The gamma parameter is the same as that provided above for lognormal FC
FC	Gompertz	Lambda 0.028526053 Gamma 0.009632453	Shape & scale parameters	The gamma value is identical for FC and FC-R to 9 decimal places.
FC-R	Gompertz	Lambda 0.018423665 Gamma 0.009632453	Shape & scale parameters	
FC	Gamma	*	Parameters for generalised gamma distribution	
FC-R	Gamma			

* In view of the errors noted and the large number of parameters for the gamma distribution listed by the manufacturer and the general lack of clarity the ERG have not extracted these values.

If the ERG were given the PFS data (investigator assessment), the ERG could independently obtain their own parametric fits. Unfortunately the ERG were unable to identify a listing of this information in the full trial report supplied. The submitted model did have a spread sheet named “KM PFS”; however in this sheet the data was conflated so that only monthly values were provided, also this sheet apparently contains a half cycle correction.

In short the ERG are presently unable [a] to test the biological plausibility of all the PFS extrapolations used in the manufacturer’s economic modelling; [b] to make a comparison of the relative advantage of FC-R versus FC delivered by the various parametric models; [c] to effectively compare the investigator and the independent assessments of PFS that were undertaken during the REACH trial.

We request that the parameters are supplied with the utmost urgency so we can conduct this work. We feel this is very important as we suspect that the results could affect the cost effectiveness results considerably (but we’re not sure at the moment as we can’t check).