TECHNICAL APPENDIX 2:

Calculation of mean survival and life-time extrapolation for economic evaluation

In order to perform an economic evaluation of the EMR 62 202-006 trial, the difference in mean progression free survival (PFS) and overall survival (OS) between Erbitux + Radiotherapy (ERT) and Radiotherapy (RT) was required. As is often the case, the pre-defined time-to-event end-points of the trial were reported as medians rather than means. Therefore, a post-hoc analysis was performed to estimate mean PFS and OS times for ERT and RT for the study period. Furthermore, median length of follow-up in the trial was 3.8 years and given that significantly more patients in the ERT than RT arm were alive at the data cut-off point, a longer time horizon is required in order not to bias the economic model against ERT. Therefore, PFS and OS were extrapolated to a life-time horizon. This process is described below.

Each patient has a time for overall and progression-free survival recorded in the trial dataset. Where these values are censored, it is necessary to impute estimates for the actual progression free and overall survival time. These estimates can be imputed from a parametric survival model fitted to the trial data.

Standard survival analysis methods assume that there is a non-zero probability that the event of interest will be observed in a finite follow-up time. However the STATA® (StataCorp LP, Texas) command “cureregr”, enables the estimation of parametric survival curves that allow for the assumption that an estimable fraction of individuals are cured, that is for whom the event of interest will never occur, with the remaining individuals subject to a process which leads to the event of interest after a time generated by a standard survival process. This model can be written:

$$P(T > t) = S(t) = \pi_c + (1 - \pi_c) \times S_{nc}(t)$$

That is, the overall probability of survival beyond any time, t, is the sum of the cured fraction, π_c, and the remaining fraction weighted by the survival probability for those who are not cured, $S_{nc}(t)$. The latter is a conditional survival function which has all the properties of a standard survival probability. This model has been studied extensively (Yin et al, 2005).

The parametric models for the non-cured survival function available for analysis using the mixture model include Weibull, log-normal, logistic, gamma and exponential. While the goodness-of-fit, based on the log-likelihood statistic and the Akaike information criterion – twice the difference between the number of parameters in the model and the log-likelihood for the model – were similar across most of these models, the log-normal model was chosen on the grounds that it is frequently used to model cancer data, which commonly features an increase followed by a decrease in the hazard function over time. This model has a long history in head and neck cancer epidemiology, starting with publications from the 1940s (Boag, 1949).

While the mixture cure model was suitable to estimate the fraction of cured and non-cured patients up to the end of follow-up, it was recognised that there was no mechanism incorporated to discount the survival of the cured patients, who in theory would live indefinitely. In order to model a more realistic scenario, it was decided to apply a different survival probability distribution to the probability of being cured. This was done via a standard life-table, as no suitable distribution of lifetimes for cured cancer patients was available. A life-table of life-expectancy for UK males (http://www.gad.gov.uk/Life_Tables/docs/wltukm0103.xls) from the (UK) Government Actuary's department was used. This was converted from year-to-year to month-to-month survival probabilities by linear interpolation.

Further, in order to induce a compromised life-expectancy in the cured group of patients, a proportional hazard of 2.786 was applied to the life-table survival probabilities, which was derived as follows. Pignon et al (2000) published a meta-analysis based on individual patient data that compared the overall survival for patients with SCCHN treated with either radiotherapy alone or chemoradiotherapy. Overall survival curves were published (**Figure 2**, page 952) from 0-10 years. A straight line of best fit was estimated from the curves to the estimated point of intercept with the time axis. This line was placed between the estimated survival curves for the two treatment groups, to obtain a mean hazard across the two groups. From two time points - 5 years of follow-up (survival probability of 0.35) and intercept at 19 years (survival probability approximately 0) - the mean hazard rate was estimated by the negative gradient (slope) of the line (-(-0.36)/14 ≈ 0.0257) divided by the survival probability at each year, pooled across years from 5 to 19. The pooled estimate was 1.167 × 10-1.

Therefore the estimated hazard ratio was 2.786 (=1.167× 10-1/ 4.188 × 10-2).

Note that an assumption of this approach is that patients from the meta-analysis cohort (Pignon et al, 2000) are considered cured after 5 years.

Thus the final model from which imputations for censored survival times were drawn was

$$P(T > t) = S(t) = \pi_c \times S_{lt}(t)^{2.786} + (1 - \pi_c) \times S_{nc}(t),$$

where $S_{lt}(t)$ is the unadjusted estimated life-table survival probability for a patient who is cured from head and neck cancer.

In order to emulate the age-group of the trial cohort, the initial survival time was set to 57 years, the mean age of the cohort at the start of the trial.

Complete overall survival times were imputed for each censored observation using this model.

The imputation of PFS times was also based on a log-normal mixture cure model, with the cured fraction also discounted in the manner described above. Note that therefore the PFS model is a time to progression or death model not just a time to progression model.

In order to ensure that there is no contradiction between the imputed PFS times and the OS times, where patients are assumed to have been cured ($S_{nc}(t) \to 0$), the OS times are set to be equal to the PFS times. In addition all other imputed times for PFS were checked for consistency against the corresponding overall survival (OS) times, and were re-estimated when found to be greater.

Reference List

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