Rituximab for first line chronic lymphocytic leukaemia
Supplementary Clarification Question

The ERG has requested that the PSA be updated to take into account structural uncertainty related to survival in light of the fact that the latest available clinical evidence has not demonstrated statistically significant differences in overall survival between the two arms.

Roche fully acknowledges the uncertainty surrounding overall survival and how it is often a common problem among many oncology randomised control trials where PFS and not overall survival is the primary endpoint. This issue is further accentuated in diseases which have a relatively long natural history such as CLL.

At the interim (which became the final and main) analysis of CLL-8, with a median follow-up of 20.7 months, the statistical analysis found a significant overall survival benefit in favour of the R-FC arm (p=0.0427). However, because the majority of CLL patients were alive at this stage, a marginal p-value for overall survival should be interpreted cautiously. With the subsequent snapshot analyses referred to by the ERG (a further 4-5 months of follow-up), the p-value for overall survival becomes statistically non-significant. Five months is a very short time period in the natural history of CLL, and the fact that the p-value has become non-significant merely highlights that assessing overall survival benefits at early stages of follow-up is difficult, not that a perceived benefit has disappeared.

Roche has accepted this issue as a limitation of the existing evidence base and attempted to address this using the appropriate methods as recommended by NICE within both its original submission and clarification letter:

1) Probabilistic Sensitivity Analysis
The monthly probability of death (from the progressed health state) was included in the PSA presented in the original Roche submission.

2) One-way sensitivity analysis
Secondly, the response to the clarification letter considered different mortality rates using large differences from the base case (+/- 50%) as one-way sensitivity analyses, which demonstrated that the base case ICER was robust to such changes.

3) Threshold Analysis
Finally we then presented an example of the predicted ICER in a scenario where mortality in the progressed health state for the rituximab arm was 315% greater than that for the comparator arm – the necessary increase required to remove completely any overall survival gain assumed in the rituximab arm of the model. The resulting ICER was approximately £30,366 per QALY gained.

Therefore even with no assumed differences in overall survival the ICER does not exceed £30,500. This exercise should only be considered one of mathematical exploration rather than of clinical plausibility as such an increase in mortality for the rituximab arm is not based on reason nor evidence.

To account for structural uncertainty within the PSA, as requested by the ERG, appears difficult to account for from a methods perspective. It is our understanding that PSA is designed to reflect parameter uncertainty and not structural uncertainty. Roche is more than happy to perform additional sensitivity analysis; however we would require more prescriptive instructions from the ERG.

We believe we have done everything we can to manage this uncertainty around overall survival benefit in our original submission and clarification letter and we hope that this evidence is sufficient to provide the case of clinical- and cost-effectiveness of rituximab in first line treatment of CLL.