Single Technology Appraisal – Lenalidomide for multiple myeloma

Balance of Responses to Additional Questions from Evidence Review Group [8 August, 2008]

Additional errors / queries on lenalidomide model

All comments below refer to the updated Excel models: "REMM-Model prior relapses v2-0-0.xls" and "REMM-Model prior Thalidomide use v2-0-0.xls" received by PenTAG on 7th August 2008.

Calculation of overall survival

1. We agree with the calculation of progression-free survival for all drugs in columns Q, R and S in all the "Patient file" worksheets. However, we are concerned about the calculation of overall survival for lenalidomide, dexamethasone and bortezomib in columns T, U and V in all the "Patient file" worksheets.

   In these columns, overall survival is calculated for each of 3 cases for each patient record: 1: death has been recorded and the patient took lenalidomide in the RCT, 2: death has been recorded and the patient took dexamethasone in the RCT, and 3: death has not been recorded. In the first two cases, it appears that progression-free survival has been double-counted. For example, in the file "REMM-Model prior relapses v2-0-0.xls", worksheet "PD Patient File 1st" for the first patient, overall survival is calculated as "Follow up time in the trial" (15.44 * 30) + "Time of Progression" (157) = 620 days. However, it would seem more appropriate to calculate overall survival as simply 15.44 * 30 = 463 days.

   In the third case above, the calculation takes no account of the observed follow-up time. For example, for the 4th patient in the same worksheet, "PD Patient File 1st", in the calculation of overall survival, no account is taken of the fact that the patient has survived to at least 14.6 months.

   Finally, we believe that columns AH, AK and AN are supposed to represent post-progression survival. However, all three columns reference the follow-up time. It seems more appropriate to reference the time from progression until the time of follow-up.

   We believe that the above issues are connected to the fact that there appears to be a discrepancy in the median overall survival for lenalidomide between the model and the two RCTs. For 1 prior therapy, the modelled median overall survival for lenalidomide is approximately 3.9 years, whereas it is quoted as 3.25 in the pooled RCTs (p92 Celgene report).

Response: The equations that are used to estimate the PPS in the patient files (in both model files) are updated to:

- *Resolve double counting of TTP and follow-up times.*
  - *for patients who progressed in the trial, the actual time is used if they are assigned the same treatment as in the trial. Same occurs for PPS.*
  - *If they did not die in the trial this is estimated in the model accounting for the trial follow-up time*

    - *if they are assigned to a different treatment than what they received in the trial, the times are estimated taking into account their times in the clinical trial*
- *In response to the observation that the modelled median overall survival for lenalidomide patients with one prior therapy is higher tan reported in the pooled RCT data. It is important to note that the pooled RCT median OS was estimated by Kaplan-Meier methods, and therefore, consideration should be given the proportion of patients who had died at the time of analysis. By definition, a true median OS is only reached when the middle (50th percentile) patient has died. Until such a time is reached when 50% are dead in each sub-group of each arm in the trial, it is possible for the estimated median OS to continue to increase. The fewer patients that had died in each arm of each sub-group the more likely that the true (50th percentile) median will increase. Therefore, it is important to note that fewer patients who received only one prior therapy and were treated with Len/dex compared with Dex had died at the time of this OS analysis ([redacted]). The proportion dead in the Len/Dex arm ([redacted]) is some way off the 50th percentile and so the Len/dex OS is more likely to increase further than the Dex OS.*

% best response for prior thalidomide

2. There appears to be an inconsistency in the % patients best response for prior thalidomide.

   Specifically, the % best response used in the model (and quoted on "Treatment Efficacy" worksheet in the thalidomide model) are very different to the values in Tables 39 and 40 of Celgene's report. However, the % best response in the model are more similar to the values quoted in Table 11 Appendix 5. However, this table does not break down the % best response by 1 prior and > 1 prior therapy, therefore we cannot check the values in the model accurately.

Response: The references in the Summary tab have been corrected to resolve the issue

Dexamethasone overall survival

3. Celgene adjust dexamethasone post-progression survival in the model to achieve the following modelled median overall survival for dexamethasone;

   - 1 prior therapy: median [redacted]
   - >1 prior : median [redacted]

   These figures are cited in Celgene's report on p123 and Table 69 of Appendix 8.

   However, for dexamethasone in the 1 prior with thalidomide and >1 prior with thalidomide, we cannot see in Celgene's report what median dexamethasone overall survival is being modelled. In the prior thalidomide Excel model, Celgene state that they are aiming for 16.2 months for both the 1 prior with thalidomide and the >1 prior with thalidomide. This is stated in cell B28 in both the "Death 1prior the. Group" and "Death 2prior the. Group" worksheets. Can Celgene

confirm that this figure of 16.2 months is correct ? If so, please can they produce a table such as Table 69 in Appendix 8 ?

We further note that for the >1 prior with thalidomide, the model actually estimates a median overall survival for dexamethasone of approximately 10.5, not 16.2. We would be grateful if Celgene can resolve this issue.

Response: In the model, dexamethasone post-progression survival is adjusted to achieve the [redacted] *median overall survival, for one and 2 or more prior therapies respectively, estimated from MRC equations for patients with characteristics of those of the dexamethasone patients in the trials. The required calibration factors that are derived for these groups include patients with both prior thalidomide and no prior thalidomide, are directly used in the "patients with prior thalidomide" analyses. The modeled overall survival for this subgroup with prior thalidomide was driven by the characteristics of the patients considered and response profiles. There was not a separate targeted median overall survival for this group.*