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Reply to the NICE assessment report of 'The clinical and cost-effectiveness of bortezomib and thalidomide for the first-line treatment of multiple myeloma'

Response from the MRC Myeloma IX Trial Management Group and Clinical Trials Research Unit, University of Leeds

Review of the assessment report shows that the Assessment Group has paid particular attention to two French IFM studies comparing MPT versus MP, and a single study comparing MP Velcade with MP. Disappointingly, this seems to be at the expense of the large UK MRC Myeloma IX study comparing Cyclophosphamide, Thalidomide, and Dexamethasone (CTDa), with MP.

We provided the assessment group with a large body of data, comprising a total of 849 patients (the largest of all the studies), treated with CTDa in comparison to MP. This comparison was carried out in a group of patients unsuitable for ASCT, the group for which this treatment will be used in the UK. This is a well carried out study for which there is also cytogenetic sub-group data available.

On the basis that a maintenance question was also asked, the assessment report only includes response and toxicity data from the Myeloma IX trial and ignores the progression free survival, overall survival and time to progression data that were submitted. We contend that this is the wrong approach for a number of reasons. The 2 X 2 trial design is an effective recognised way of carrying out trials and to dismiss the data simply because it had this design is inappropriate. The MRC Myeloma IX study is by far the largest of the studies that have addressed this issue, and it gives important information about how to manage the group of patients that will be treated in this fashion in the UK. To develop this point further, one of the IFM studies was in a group that may be transplanted in the UK, and the other is an extremely fit, relatively young, population, as witnessed by their very long survival; this is not representative of patients treated in this fashion in the UK. The bortezomib comparison also suffers from the same limitations and the patients entered into that study are not the same as would be treated with a novel alkylating agent and steroid combination in the UK. [redacted]. This is not a randomised comparison, but no 'head to head' based comparison with ASCT exists in these poorer prognosis patients and may well never do so.

The Myeloma IX data set includes 163 patients randomised to receive no maintenance, 163 randomised to receive maintenance thalidomide, and 523 patients who did not undergo maintenance randomisation, and hence includes a large sub-group who did not receive maintenance therapy. We were not made aware by the assessment group that the majority of trial data would be ignored on the grounds of the maintenance randomisation, and we would be happy to provide data in a format that would permit a sub-group analysis to be performed.

We also provided the assessment group with Health Related Quality of Life data (EQ5D and EORTC-QLQ-C30) for the 778 patients who consented to the Quality of Life component of the trial. However, none of these data have been included in the Assessment Report, on the grounds that the HRQoL outcomes did not meet the inclusion criteria, for reasons which have not been communicated to us. Our data reveal interesting changes in QoL sub-scales, related

to the response rates to initial chemotherapy, but these findings have not been made available in the Assessment Report.

Regarding the cost-effectiveness analysis, it is clear that the elevated cost per QALY associated with CTDa is not due to the treatment, because CTDa and MPT are equivalent in terms of clinical effectiveness, delivery and toxicity, but rather because the Myeloma IX trial was conducted in poor performance status patients, representative of the UK patient population who will receive this treatment, in contrast to the selected patients included in the other studies.

[redacted]. In fact, the sub-set analysis is particularly informative in this elderly poor performance group of patients who are unsuitable for autologous stem cell transplantation.

We show interesting therapeutic benefits for patients treated with the amino bisphosphonate zoledronic acid, compared to the oral first generation, bisphosphonate clodronate. [redacted]

Based on the experience of many clinicians, CTDa has become a very widely used and trusted "standard" regimen, in the wake of the MRC Myeloma IX Trial. In conclusion, we would encourage the Review Panel to pay more attention to the Myeloma IX data, which is robust, was generated in the UK, is relevant to the group treated in the UK and does not reflect a selected group of good performance status patients. Simply to ignore the largest data set because it used a 2X2 factorial design seems highly inappropriate and could compromise therapeutic decisions for patients in the UK. We would be delighted to continue to cooperate with NICE in their consideration of the Myeloma IX data and share the results of our further analyses.

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On behalf of the MRC Myeloma IX Trial Management Group