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3rd December 2013

[redacted]
[redacted], [redacted] [redacted] 15th October, 2013
Bortezomib for Induction therapy in Multiple Myeloma
National Institute for Health and Clinical Excellence

Dear [redacted],

Re: ACD : Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation

We write in response to the above document, on behalf of the UK Myeloma Forum, and the Royal College of Pathologists.

<u>The analysis by the ERG</u>

1. We understand that the results of the mixed treatment comparisons (MTC) initially carried out by the manufacturer were noted to be subject to substantial uncertainty, hence were not used for the economic modeling. We were therefore surprised to find that, at the meeting, the ERG presented results of comparisons across different trials, without adjusting for trial design or study populations! We also noted that in such comparisons (Tables 16, 17and 18 in the Pre-meeting briefing document), the costs for CTD consistently came out *lower* than those for TD. This was pointed out during the meeting, and no explanation was forthcoming. We conclude that any exploratory ICERs using CTD as the base case based on these calculations must be intrinsically flawed.
2. We are concerned that the committee have elected to uphold the conclusions from the ERG's scenario analysis using data from Alvares et al to inform long term survival. We are surprised that the report from the meeting failed to mention our comment on the use of the Alvares data to model long term survival. We pointed out that the Alvares study, being a retrospective study, analysed survival by CR and less than CR rates only *in those patients who were evaluable at 3 months post-transplant (n=260).* The whole study population was 383 (median age of 54 years), of whom only 282 proceeded to a stem cell transplant (and 260 survived to be evauable at 3 months). The group of patients who received a transplant and survived to be analysed for response at 3 months post-transplant are therefore a highly selected group, with obviously a better prognosis. They are not representative of the group of patient who, at the time of starting induction therapy, are considered candidates for intensive therapy (stem cell transplantation). We know from the recent MRC Myeloma IX study that only 67% of such patients eventually go on to receive a transplant. Furthermore, the patients included in the Alvares study

were diagnosed between 1985 and 2004, which seems contemporaneous with the Myeloma VII study, which the ERG considered to be too old!

Comment on the Appraisal meeting 15th October

We were disappointed that a considerable proportion of the meeting was devoted to a discussion of process, and of the appropriateness of the modeling assumptions, with consequently less opportunity to discuss the clinical need and effectiveness of bortezomib-containing regimens in general in this patient group. We were also disappointed to note that our point regarding the un-suitability of the Alvares data for modeling survival was not minuted, and have re-iterated that point above, in our comment on the ACD.

We are pleased however, to note that the committee has understood that we, as physicians, feel that bortezomib-containing regimens are a valuable treatment option for this patient group, although there is no specific preference for a triplet regimen incorporating thalidomide (see below).

Comment on the Scope

We were disappointed and surprised to learn that the scope of the health economic analysis (and hence of the Appraisal) had been altered since the scoping workshop that we had attended, such that only VTD was being assessed for cost-effectiveness. We feel that restricting the appraisal of cost effectiveness to the VTD regimen and excluding the VD regimen from the base case analysis is at odds with clinical practice. The majority of physicians using a bortezomib regimen in this setting would use it in combination with Dexamethasone, and sometimes, a third agent, but this would not necessarily be thalidomide. In particular, for patients not suitable for thalidomide, we may use a combination with cyclophosphamide. The meeting Chair indeed commented that such a combination would be regarded favourably from the financial point of view. Restricting the base case analysis to the VTD regimen not only increases the cost and makes the treatment less competitive, it will force physicians into using a regimen that may be more intensive and/or toxic than other bortezomib regimens with which we have far more experience.

Clinical Practice in the UK

The most widely used regimen for treating patients with newly diagnosed multiple myeloma in the UK is CTD, which is an oral regimen that produces disease free survival that is comparable to the traditional VAD-type protocols (Myeloma IX study, Morgan et al, 2011). With the recent licensing of bortezomib, we have a real opportunity to improve on the results of frontline treatment for this group of patients; the progression free survival of patients on the bortezomib arms in the GIMEMA, PETHEMA and IFM studies (36 months – not reached) is superior to that reported for patients receiving CTD (Myeloma IX, 27 months), albeit with the limitations of comparing across studies. As we pointed out at the meeting, the real benefit may lie in getting more of these patients to a stem cell transplant. The availability of bortezomib for frontline therapy will be a significant advance in the therapy of these patients.

Request for further analyses

We realize that the Committee has requested the manufacturer to carry out further analyses including an indirect comparison between bortezomib in combination with dexamethasone compared with CTD, and compared with another comparator, in situations where a thalidomide containing regimen is not suitable. We welcome this request, as we believe it reflects the

Committee's intention to more fully understand the real clinical benefit of the technology in this patient setting. Hence we wish to point out that there are two groups of patients for whom we feel it is vital to have access to a bortezomib containing regimen for induction therapy prior to stem cell transplantation. Firstly, there is a group of patients for whom thalidomide is clinically unsuitable, eg with a high risk of VTE despite thromboprophylaxis, those intolerant of thalidomide, and those unable to comply with the pregnancy prevention programme. Secondly, there is a group of patients for whom bortezomib would be preferred on clinical grounds, because its relatively fast activity would help prevent irreversible organ damage. Examples of patients in this second group would be those at risk of renal failure from light chain kidney disease, and patients who require rapid tumour reduction because of the risks of hyperviscosity in association with coronary or cerebral vascular disease, or because of impending cord compression from an extradural tumour in the spine (where surgery or radiotherapy is not the preferred treatment because of multi-level disease). These patients may be those whose chances of getting to a stem cell transplant have previously been low, and for whom the availability of a bortezomib containing regimen may make all the difference. They would certainly not feature in the patient group reported by Alvares and co-workers.

We wish to conclude with 3 main points:

1. The analysis of the health economic benefits of the VTD regimen is flawed due to the use of the survival data form the Alvares study. We feel that the Alvares study is inappropriate for modeling survival because it reports a highly selected patient group from a single tertiary referral centre whose excellent survival outcomes are unlikely to be representative of the UK patient population with newly diagnosed multiple myeloma who would benefit from a stem cell transplant.
2. The clinical benefit of bortezomib as part of induction therapy in this group of patients is supported by a wealth of clinical trial data, as well as the recent advances in subcutaneous administration and successful prevention and management of treatment–emergent neuropathy. It would be an immense retrograde step for the management of multiple myeloma in the UK if the technology were to be unavailable for these patients, because of uncertainties in health economic modeling that arise from of lack of clinical trial data comparing with CTD, and the current choice of alternative studies.
3. Finally, investing in providing a choice of effective frontline treatments in this incurable disease is crucial because it will impact on the first disease free interval (and hence wellbeing and quality of life). The treatments available differ not only in their mode of action on tumour cells, but also importantly in route of administration, toxicities and likely side effects. Having a choice of active agents around which to base an informed discussion between patient and physician is important for joint decision making, and will ensure that myeloma patients in the UK are able to benefit from the latest therapeutic advances in this disease.

Yours sincerely

Kwee Yong
Jenny Bird

On behalf of UK Myeloma Forum