Quarry House
Quarry Hill
Leeds
LS2 7UE

Emily Marchke
Technology Appraisal Manager
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

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Dear Emily

Single Technology Appraisal (STA) Bortezomib for Multiple Myeloma - Appraisal Consultation Document

Thank you for inviting comments from the Department of Health on your appraisal consultation document on bortezomib for multiple myeloma under the single topic selection process.

Please see below a summary of the detailed comments I have received from the Department of Health's clinical advisors on cancer topics. I have also attached detailed comments for your reference and information.

Issues with Treatment Pathway

There is a need to present a clear treatment pathway for the patient group and where bortezomib is in the treatment schema.

You maybe aware that the British Committee for Standards in Haematology (BCSH) has shown a relatively clear way forward, and it is suggested that the appraisal committee consider adopting/supporting their approach

Impact on clinical trials

Concern was expressed that NICE's recommendation on further research may be seen as a 'negative' endorsement and will encourage trusts/networks to refuse to sanction participation/entry into UK trials which will undermine availability of further trial data.

I hope you will find these comments helpful.

Yours sincerely

SIMON REEVE
Head of Clinical & Cost Effectiveness

Full detailed comments from Department of Health's Clinical Advisors for National Institute for Health and Clinical Excellence's Technology Appraisal Document on Bortezomib for Multiple Myeloma.

Comments from first Clinical Advisor

It is difficult to find flaws with the arguments and this reflects the way that the data is presented. The conclusions however are perverse and would not be popular with the haem-onc community.

The main problem I suspect was the inability of the clinical representatives to present a clear treatment pathway for treatment of this group. The committee quite rightly pointed out that treatment depends on initial response, age and co-morbidities and on this basis a logical treatment pathway can be constructed. The BCSH have shown a relatively clear way forward and it is a shame that such an approach was not adopted and supported as a way ahead to the committee.

The committees understanding of the APEX study was also disappointing. They point out early on the quite remarkable results with a doubling of response to disease progression time (6.2 v 3.5 months) but fail to develop the significance of this. This was a Phase III study of over 600 relapsed
patients. Although a mixture of early and late relapse the results do support a better response in the early phase of the disease, as opposed to later relapse, and the data would support a better cost per QALY in this group. The company perhaps made an error in presenting life years gained (LYG) as opposed to QALYs, as this ignores the potential problems with neuropathy in responders, but I suspect that this would have only made a small difference.

The differences in QALY would particularly be highlighted if, as suggested, treatment is stopped after 3 courses if there is no evidence of response. The London Cancer New Drugs Group certainly came to this conclusion on the evidence. There does therefore appear to be a clear case for supporting its use in first (or early relapse).

We are entering an era of a number of important agents in myeloma that will potentially transform the result in this group. If Bortezomib is not supported then it is unlikely that we will be able to introduce any of the newer agents in the foreseeable future……. What this essentially means is that not only will we not be able to offer this agent but thalidomide (should it obtain a licence) and revlimid (when it does) will equally be unavailable. This will be unacceptable when we look at practice in North America and Europe. While this may save money it is not in patients' interests and the arguments to support the decision are not sustainable when the data on which the decision is made is more clearly analysed.

I make these points as a haematologist who is no longer involved in treating this patient group and has no conflicts of interest.

Comments from second Clinical Advisor

Failure to recommend the use of Bortezomib within its licensed indication except in well designed clinical studies is not a conclusion that is likely to be accepted or acceptable - and is disappointing in the circumstances.

I understand the strict academic correctness of the conclusion but the committee appear not to have not truly understood the realities of where we are in clinical practice and the demands/expectations of a highly informed and motivated patient and patient advocacy community.

Further trial data are, of course, essential - a standard for treatment stated in the UK/Nordic Myeloma Guidelines is that patients should be treated in clinical trials/studies wherever possible; the reality is that it is only a minority of English/UK patients who have the opportunity to be entered in trials.

Currently there are trusts and networks who have not sanctioned entry of patients in to Myeloma 9 because of perceived excess treatment costs with Thalidomide.

The revised NCRN Myeloma 9 protocol represents the only viable Bortezomib trial option in the next 2-3 years for the majority of NHS patients in England (& the UK) - however, it is inevitable that some trust/networks will currently refuse to allow the amendment to assess Bortezomib because of excess treatment costs.

In context, therefore, this report from NICE, as drafted, will be seen as a "negative" endorsement and will simply encourage trusts/networks to refuse to sanction participation/entry into this important and hitherto successful UK trial - it will simply undermine any likelihood of further helpful trial data being available by 2009 and further exacerbate the postcode lottery situation.

New trials for review in 2009 are not a viable UK option. Initiating a major, new clinical trial in an enormously time-consuming and bureaucratic process - from outline to first entry of patients would be 18-24 months at best - assuming the investigators can get funding and a sponsor - any such funding should not exclusively be from Ortho-Biotech and the sponsor would have to be a major academic institution.

Thus pressure on UK clinicians even in academic institutions is such that UK based Bortezomib trials other than amended Myeloma 9 are not going to emerge in the near future because of the above. Thus any data will have to emerge from other international studies and the UK will be seen as being set back from being involved in leading and innovative clinical research.

It would be preferable to be more specific in the recommendation – that Bortezomib is not recommended for fist line myeloma treatment or primary refractory patients except in well - designed clinical studies.

With functioning Cancer Networks in England it should be possible to audit the use and outcomes of Bortezomib usage within its licensed indications, given in accordance with BCSH/Nordic Myeloma guidelines subject to documented approval through MDT's - invoking a mandatory audit process would be both a sanction on inappropriate usage and a means to collect actual clinical data which would perhaps be more representative of practice than data form clinical trials.

Having had reasonable clinical experience with Bortezomib I am more aware of situations wherein I would not consider its usage and - and I would declare an interest as a practising

clinician in myeloma from the experience of seeing a current group of late relapse patients responding well - in one case achieving remission when other therapies were clearly failing.