SS/JA

18 October 2006

Ms Emily Marscheke
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear Ms Marschke

I write on behalf of the UKMF after taking extensive soundings from the UK clinicians with a special interest in myeloma. I would make the point that myeloma is a heterogeneous disease that presents with 1º refractoriness to chemotherapy in 10% to 15% patients and this rises to 30% to 35% at relapse. Bortezomib works through novel mechanisms and is frequently effective in patients who fail to respond in chemotherapy and the available data supports the assertion that it is effective in the treatment of myeloma in early relapse.

There is no enthusiasm internationally for looking at any further clinical trials with Bortezomib as a single agent and not to allow patients in the UK access to this agent on the grounds of lack of data from clinical studies, will put other novel agents such as Thalidomide and Revlimid at risk. This will again put the UK out of step with Europe and North America.

I make these points on behalf of health professional in the UK responsible for managing this difficult and lethal disease.

Yours sincerely

Dr S A Schey
Chairman of the UK Myeloma Forum

We, the members of the United Kingdom Myeloma Forum (UKMF), write as representatives of the health care professionals who treat myeloma in the UK, and as formal consultees of the appraisal process.

We wish to express our disappointment with the preliminary recommendations for the use of Bortezomib in multiple myeloma in England and Wales as summarised in the recent appraisal consultation document.

Fundamental to the understanding of the approach to the treatment of myeloma is the fact that myeloma is currently an incurable disease, extremely variable in its biological pathogenesis and clinical expression. The management approach to myeloma is different to other haematological and non-haematological malignancies, where cure is the goal, and can be achieved with currently available therapy. The aim of all treatments for myeloma at the present time is to improve the quality and duration of life and that this must be taken into account when considering the role of Bortezomib.

Section 1) Whether you consider that all the relevant evidence has been taken into account.

We acknowledge that until the publication of the APEX trial there was no robust large prospective randomised controlled trial to inform the decisions clinicians made at the point of relapse.

There are however defined treatment pathways for myeloma. The choice of treatment for each patient at any one time may differ because of the heterogeneous nature of the disease, and its clinical course, and most patients will receive several treatment regimens during the course of their disease. Choice of therapy at relapse is influenced by initial treatment and the patients' response to it, the inherent characteristics of the disease, patients' performance status and their preferences.

With the publication of the APEX trial physicians do now have evidence on which to base the treatment decision at relapse. The position of Bortezomib in the treatment pathway for myeloma is clear. The APEX trial has established Bortezomib as the only evidence-based standard of care for relapsed myeloma. It is the largest published randomised trial ever undertaken in relapsed myeloma and constitutes level 1 evidence.

We believe that it should, in the group of patients we will define below, be the agent of choice for the treatment of first relapse.

Failure to recommend Bortezomib will deprive patients of the only treatment proven to increase their chance of response, time to disease progression, and overall survival relative to a proven, efficacious treatment in the relapse setting.

All alternative treatments are unproven and unlicensed in this setting, and thus expose the clinician, patient, and the NHS to unknown medical risk.

We note the Appraisal committee's recommendation that the position of Bortezomib is uncertain and that it should be established more clearly by the results of on- going research.

We assert however that further trials are unnecessary because the APEX trial data has unequivocally demonstrated the efficacy of Bortezomib.

We are sure funding bodies would not support such trials. Clinicians would have no enthusiasm for them as they see that the role of Bortezomib as mono-therapy has already been established and are now interested in the question of how Bortezomib performs in combination with other drugs.

It is necessary to clarify the role of one of the currently established national clinical trials. The MRC Myeloma IX is a key clinical trial and Bortezomib was added into the study because it was deemed to be the standard of care at 1st relapse. However the study is not intended to assess either the efficacy or position of Bortezomib as these questions have already been answered in the APEX trial. Myeloma IX simply answers questions about whether patients treated previously or not with thalidomide, or specific subgroups, (based on cytogenetics), have different outcomes.

In addition it is important to be aware that less than 10% of patients nationally are eligible for entry into clinical trials either because of strict entry criteria, geographical location of the trial sites, or resource and funding restrictions. It is clear that patients should not be denied evidence-based standard of care because of their lack of access to a clinical trial.

We believe that the appraisal committee was misguided in questioning the role of High Dose Dexamethasone (HDD) in the APEX trial and we endorse its choice as a suitable comparator.

Often used in combination with other cytotoxic agents (e.g.VAD, CVAD, ZDEX etc) both for initial treatment and at relapse, studies have shown that HDD alone is almost as effective as the combinations (80-85 % of efficacy) and is certainly the most powerful component of the combinations. This knowledge has lead to its widespread use as a single agent worldwide.

It is estimated that 70% of patients with myeloma in the UK now receive a Thalidomide containing regime as initial treatment. This markedly limits the use of thalidomide as an alternative comparator to Bortezomib at relapse and endorses the choice of HDD.

That Bortezomib is more effective than High Dose Dexamethasone is therefore highly significant. We believe this shows that Bortezomib represents a major advance for patients who have commonly had as initial treatment both cytotoxic chemotherapy and, increasingly, Thalidomide. It is important that these chemo- resistant patients have the opportunity of being offered an agent which acts by an entirely different mechanism, as is the case with Bortezomib.

Finally we believe that acknowledging the use of HDD as a valid comparator in this setting is important not only for this trial but also has major implications for future trials of new agents.

Section 2) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.

We suggest that the Appraisal committee has not fully taken into account a number of factors which materially affect their conclusion that Bortezomib had not been shown to be cost effective compared with current practice in England and Wales.

We believe that physicians can, and will, stop therapy appropriately if patients are not responding to treatment. The majority of patients with myeloma have a tumour marker (either an entire monoclonal immunoglobulin or light chain) the measurement of which enables physicians to assess response to disease in a simple and timely fashion. Thus it would be clear after 3 courses of treatment if a patient had responded to Bortezomib, and that treatment could be stopped at that point if there had been no effect. This is already common practice amongst physicians using Bortezomib and could be enshrined in guidelines as will be discussed below. Clearly if treatment were limited in this way, overall cost per QALY would be reduced.

Similarly it is already common practice to use Bortezomib in combination with intermediate doses of steroids which studies have shown to increase response rates at minimal additional cost. This again reduces overall cost per QALY in practice.

We also feel that by not using Bortezomib in the relapse setting physicians will be forced to choose potentially more expensive therapies, which have not been subject to randomised, controlled trials. The options will include, for a significant number, a second high dose therapy and stem cell transplant which may be associated with considerable cost and morbidity and yet is of unproven benefit.

Even for the small proportion of patients who have not already received thalidomide either as initial treatment or maintenance, a thalidomide containing regime would be costly, unlicensed, unproven, and associated with significant side effects and thus cannot be seen as a beneficial alternative to Bortezomib.

W e believe it is possible to define the patient group for whom Bortezomib is most cost effective and that mechanisms are already in place both nationally through the UKMF/ BSCH guidelines group to disseminate such advise. We believe that there are also systems in place locally through Cancer Networks to ensure implementation of such advice. We are indeed aware that regional

groups already have such mechanisms in place where usage, outcomes, and side effects are being audited.

We submit that all of these factors should be taken into account 'on the other side of the equation' when assessing the overall cost per QALY.

Section 3 Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

We do not agree with the provisional recommendations of the appraisal committee but take the view that

- The APEX trial does define the role of Bortezomib in the treatment of myeloma

- It is not necessary, nor feasible, to mount further clinical trials to establish the position of Bortezomib as a single agent in relapsed/refractory myeloma.

- That Bortezomib is an advance in the treatment of relapsed myeloma and can be used cost effectively for patients selected as defined below

- That the mechanisms for enforcing its use in this defined way are in place.

Definition of role and position of Bortezomib

- Patient characteristics
  - Those at 1st relapse
  - With Performance status >60
  - With Peripheral neuropathy < grade 2
  - With Life expectancy > 12 months with treatment
  -
- 'Stopping rules' should be
  - After 3 cycles if a non-responder
  - Maximum of 8 treatment cycles for responders
  -
- Bortezomib should be used
  - In combination with dexamethasone

In the light of the above we urge the appraisal committee to revise its' preliminary recommendations and to recommend the use of Bortezomib for use in relapsed and refractory myeloma in the way defined in this document.

Signed, electronically, by

Dr Steve Schey, Consultant Haematologist, Chairman, UKMF
Dr Judith Behrens, Consultant Haematologist, Secretary, UKMF
Dr Cathy Williams, Consultant Haematologist Treasurer, UKMF
Dr Curly Morris, Consultant Haematologist Vice -chair Clinical trials Committee, UKMF
Dr Gordon Cook, Consultant Haematologist, Member of Executive Board, UKMF
Dr Graham Jackson, Consultant Haematologist Immediate- past Treasurer UKMF
Dr Jenny Bird, Consultant Haematologist, Chair, Guidelines Committee, UKMF
Dr Jamie Cavenagh, Consultant Haematologist, Immediate- past chair, Clinical Trials Committee UKMF
Dr Kwee Yong, Consultant Haematologist,UKMF
Professor Gareth Morgan Professor of Haematology and Member of Executive Board, UKMF