Email: [redacted]

3rd April 2014

To the Chair

I am writing on behalf of the UK Myeloma Forum.

Thank you for the opportunity to comment on the recently issued Appraisal Consultation Document "Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part-review of TA171)".

We are surprised and disappointed that this application has not been approved and believe that the provisional recommendations are neither sound nor a suitable basis for guidance to the NHS. We are particularly surprised with this outcome given that the committee recognized the weaknesses of the models and the many uncertainties in the comparative data identified.

We believe that absence of lenalidomide as a treatment option at this disease stage reduces the potential to deliver optimal care to patients with relapsed myeloma. We believe that the available peer review published clinical evidence (grade A level 1a) supports lenalidomide as the most efficacious drug in the setting of 2nd line treatment following the use of a bortezomib based therapy at first line. It should be noted that there is no evidence to suggest cross resistance between bortezomib (a proteosome inhibitor) and lenalidomide (an immunomodulator) as they have differing mechanisms of action and we would suggest that restricting review of data only to patients who have previously received bortezomib prior to lenalidomide reduces the power of evidence presented.

The draft guidance has significant implications for the large number of patients entered into clinical trials that utilize bortezomib as part of front line therapy (Myeloma XI, for patients not achieving a VGPR, or PADIMAC). These patients will be specifically disadvantaged by the guidance, which restricts their treatment options at relapse. Other patients who will be affected are those who have received frontline bortezomib via NHS England baseline funding (as part of VMP).

For those patients who require second line therapy having received bortezomib for first line therapy there are a minimum of 3 potential clinical scenarios that need to be considered with possible different outcomes.

Executive Committee:
Dr Jenny Bird (Chairman), Dr Gordon Cook (Secretary), Dr Neil Rabin (Treasurer), Dr Faith Davis (past Chair),
Prof Gareth Morgan, Dr John Snowden, Dr Kwee Yong, Dr Guy Pratt, Dr Stella Bowcock
Dr Roger Owen, Dr Ashutosh Wechalekar, Prof Graham Jackson, Dr Matthew Streetly, Mr Eric Low
Registered Charity Number 1082702
Website: www.ukmf.org.uk

1. Patient has achieved less than partial response or relapsed early after bortezomib therapy (e.g. <6months)
2. Patient has achieved at least partial response but developed toxicity associated with bortezomib e.g. peripheral neuropathy
3. Patient has achieved at least a partial response without toxicity and with good duration of response

In clinical practice the only scenario above that bortezomib retreatment would be considered a suitable comparator is scenario 3 i.e. those patients who responded well and tolerated the treatment. Otherwise it would not be appropriate to consider bortezomib retreatment. For the patients for whom bortezomib retreatment is not suitable there are very limited options without the option of lenalidomide. The use of conventional chemotherapeutics such as melphalan or cyclophosphamide would not be considered appropriate at this stage as there is no evidence to support their use in the modern era with only small limited historical reports. Similarly there is currently little data to support the use of a drug such as bendamustine at second line as a therapeutic option. However, there is clear phase 3 evidence that support both a progression free and overall survival advantage for lenalidomide when used at 2nd line and beyond (Overall response rate: 66.9% v 56.8%; Very good partial response rate or better: 39.8% v 27.7% p=0.025; Progression free survival: 14.1 v 9.5months p=0.047 and overall survival: 42 v 35.8months p=0.041 – Stadtmauer et al. Eur J Haem 2009).

For the patients who had previously responded to bortezomib without excessive toxicity bortezomib retreatment is a potential option and should be considered the only relevant comparator. It should be noted however that the level and grade of evidence for bortezomib re-treatment is lower than that for lenalidomide therapy. It comprises a number of small retrospective clinical reviews of highly selected patients as well as a single prospective Phase 2 study. A consistent signal in these studies is the reduced efficacy of bortezomib retreatment compared with initial therapy without clear evidence that there is a consistent superior duration of response with overall survival advantage gained by the use of bortezomib retreatment. In contrast there is robust evidence for the use of lenalidomide at 1st relapse with clear progression free and overall survival advantage gained over what was considered a suitable comparator at the time of the clinical trials (dexamethasone).

Finally we would highlight the recently published FAD (18/3/14 – NICE website) for bortezomib frontline therapy which is likely to increase the numbers of patients for whom the current guideline may be applicable. This makes it imperative to ensure that this guideline accurately reflects best practice based on the available evidence and we would strongly urge the Committee to re-consider their decision regarding lenalidomide in this indication.

We would be very happy to engage and comment further on this consultation if this would be deemed helpful.

Yours faithfully

[redacted]
Advocacy Lead for UK Myeloma Forum