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NICE

By e-mail
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Dear Professor Longson

Re: Melanoma (BRAF V600E, met) - vemurafenib [ID489] - Appraisal Consultation Document 2 (ACD 2)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 26,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who collaborate to produce joint response to NICE oncological consultations. We are grateful for the opportunity to respond to the above ACD 2 and wish to make the following comments which are also fully supported by the Melanoma Study Group.

Our experts agree with and fully support the Committee's conclusions that:

- vemurafenib represents 'a step change in the management of advanced metastatic melanoma'
- 'few advances had been made in the treatment of advanced melanoma in recent years and vemurafenib is considered to be a significant innovation for a disease with a high unmet clinical need'
- 'vemurafenib has advanced the understanding of this disease and opened the way to new treatments'

We recognise the concerns regarding the uncertainties surrounding cost effectiveness are based on the lack of long-term follow-up information and the confounding of the data because of the cross over that occurred in the BRIM3 trial. However, it is important to impress upon the Committee the reason why cross over occurred which was the overwhelming benefit to patients receiving vemurafenib compared with standard dacarbazine chemotherapy. Cross over had to occur when it did based on the most basic ethical principles that govern the performance of randomised trials. Evidence that this was the correct decision is shown by the fact that by the time that cross over became possible within the UK, the vast majority of patients in the dacarbazine arm had already died of their disease.

Crossover from an ineffective treatment to a highly effective treatment negates long term survival data. We therefore strongly believe that the first BRIM3 trial cut off dataset remains the key comparison and is the most accurate descriptor of the true benefit of vemurafenib. There are no accurate long term data because

there is no validated way of analysing data that is corrupted by cross over to the extent that those in BRIM3 are because of the magnitude of the difference in efficacy between the two arms of the trial.

As clinicians, we are becoming uncomfortable with the direction that the Committee's discussions are taking. There are ever increasingly complex and unvalidated modeling methodologies being presented in an attempt to measure the unmeasurable. The result is that descriptions of the biology of melanoma, the efficacy of dacarbazine and the benefit of vemurafenib are being presented that bear little or no relationship to our experience. Our concern is that this approach undervalues the most active drugs – there is less pressure for cross-over within trials for drugs which have modest benefits. However for ground-breaking drugs such as vemurafenib, there is an ethical duty to the trial participants to allow cross over when large magnitude benefits are seen at interim analyses. By focusing on post cross-over outcomes that will inevitably show diluted effects, the committee is in danger of rejecting those drugs that will provide the greatest benefit to our patients.

We would like to remind the Committee of the February 2012 BRIM3 cut off update, which reported an increased number of confirmed complete responders, which suggests that durable responses can be achieved with vemurafenib. Extrapolating from other cancers, it is assumed that complete response is a prerequisite for long term survival and this most recent data supports the potential that cure is a realistic outcome for albeit a small number of patients receiving vemurafenib. It is possible that exposure to vemurafenib may change the biology of the disease when no longer exposed to the drug. This therefore argues against the vemurafenib and dacarbazine survival curves coming together, as is assumed in the ERG model.

| | | ASCO 2011 | ASCO 2012 |
|----|-----|------------|-------------|
| RR | ORR | 5.5 vs 48% | 8.6 vs 57% |
| CR | | 0 vs 0.9% | 1.2 vs 5.6% |

We remain cautious regarding suppositions that tumour growth accelerates when vemurafenib therapy ceases. Such observations remain anecdotal at best, there are no robust data to support this assertion. It is of course theoretically possible that accelerated tumour growth could occur due to clonal selection, but if this is the case then the same biology would also result in some tumours gaining signalling pathways that result in a slower growth rate. Clinical observations of patients coming off vemurafenib would align with these considerations.

In clinical practice, accumulating real life experience with vemurafenib is demonstrating remarkable, unique clinical benefits for patients whose disease burden and behaviour would have previously consigned them to end of life care only and death within a few months and in some cases weeks. Poor performance status patients as well as patients with brain metastases can be restored to relative normality within weeks of starting treatment and duration of response is not proportional to initial disease burden. Because treatment is selected by gene mutation status, the expectation is for the majority of patients to experience a degree of objective response, whether they have received prior therapies or as first line treatment.

We urge the Committee to reconsider their decision.

Yours sincerely

