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5 July 2012

Dear Professor Longson

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

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 and wish to make the following comments.

Our experts believe that the AJCC data greatly overestimates the survival of patients with stage 4 melanoma. Use of the AJCC staging database (Balch 2009) as a comparator is not valid, since this database is derived from 17 major institutions and is neither population-based nor data from prospective clinical trials. The most consistent prognostic factors after stage are site and serum LDH. It can be seen from the appended table that the data in the AJCC report from 2009 (Balch 2009) is not consistent with those from randomised clinical trials. Data derived from patients entering clinical trials clearly shows that the 2-year survival of patients with melanoma is 15-20% (Figure 1). The data from the AJCC staging publication (Balch 2009) shows that the 2-year survival of patients just with non pulmonary visceral metastases is 20%, ie they are clearly an overestimate compared to patients entering clinical studies. The same over estimate of Stage 4 survival is seen if the data is stratified according to serum LDH levels, by a factor of 2 in the case of those with a normal LDH (Figure 2).

The criticism that BRIM3 is not mature does not take into account the reality of the situation faced by the members of the DMSC of the trial. The effect of Vemurafenib on overall survival is the greatest ever seen in a randomised trial in solid tumour oncology. Cross over had to occur. It would have been ethically impossible to continue the trial. Arguably had the trial continued and cross over not allowed, public confidence in the ability of clinicians to perform ethical research would have been called into question. This background should be taken into consideration.

There is no agreed let alone validated statistical methodology for dealing with the effects of cross over and the confounding of overall survival data. There are two situations where this problem is compounded: firstly, in cancers such as breast cancer where there are multiple lines of active therapy and secondly, where a drug has an unusually high degree of efficacy. A drug with a HR of 0.27 for PFS would be such an intervention and the effect of Vemurafenib in BRIM 3 is the exemplar. There is no way of knowing the long term impact of Vemurafenib in melanoma but what is known is that many standard treatments have exhibited this phenomenon. Furthermore, the crossover effect has been well documented where the efficacy in terms of the impact on response rates and PFS are lower that that seen with Vemurafenib in BRIM 3 trial.

NICE have not agreed a definition of the threshold of HR for PFS that would be accepted as a trigger to declare a cross over effect strong enough to confound overall survival results.

The true effect of Vemurafenib is seen before cross over was allowed. Everything after this date is contaminated and it becomes increasing unreliable with time, ie the later the cut-off date for the data the more confounded are the overall survival results. This situation where a very effective drug being compared against one with poor efficacy is the one circumstance where the longer the follow up the more unreliable are the overall survival data because of the cross over.

The contention that Vemurafenib loses its effect with time is not borne out by clinical experience or indeed the data from BRIM 1 and 2. The results of these two trials are unusual in oncology drug development because the effects seen at phase 1 and 2 are very similar to that seen in the experimental arm of BRIM 3 (Figure 3). Both these trials demonstrate that some patients can benefit for considerably longer than 97 days as theorized in the ERG. 15-20% of patients are disease-free for over a year in BRIM 2. Furthermore, the complete remission rate recorded in BRIM 3 has increased with time: 0.9% reported May 2011, 5.6% reported June 2012. This is consistent with our clinical experience that patients can continue to have incremental responses and slowly enter complete remission over time. This phenomenon is seen with other targeted agents with response rates increasing with length of follow up (Motzer 2007, 2009). The ERG statement about resistance to TKIs is incorrect.

The claim that there are ‘two distinct populations of patients with malignant melanoma’ is incorrect and not substantiated by data, published evidence, clinical experience or expert international opinion.

Vemurafenib is regarded by non-melanoma specialist oncologists as one of the most remarkable step changes seen in solid tumour oncology for several decades.

Yours sincerely

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Encl: Figures and references

Figure 1

	Patient population	n	2-year survival
Keilholz JCO 1998	Database of pts in studies incl IL2	631	20%
Middleton JCO 2000	Temozolomide vs Dacarbazine, RCT	305	18%
Keilholz JCO 2005	Biochemotherapy, RCT	363	15%
Patel EJC 2011	Temozolomide, RCT	859	15%

Figure 2

	Normal LDH		Abnormal LDH	
	n	2-year survival	n	2-year survival
Balch JCO 2009	387	40%	377	18%
Bedikan JCO 2006	508	18%	252	10%
Keilholz JCO 2005	115	22%	213	10%
Keilholz* JCO 2000	268	(24-36%)	314	12%

Figure 3

Data from: ***Flaherty N Engl J Med 2010 ; McArthur ESMO 2011; Chapman N Engl J Med 2011;Sosman N Engl J Med 2012***

	BRIM3 (Phase III, post-hoc) 1st line	BRIM2 (Phase II) ≥2nd line	BRIM1 (Phase 1,expansion) ≥2nd line
No. of pts	336	132	32
Response	57%	53%	81%
Median PFS (mo)	6.9 mos	6.8 mos	7 mos
Median OS	13.6 mos	15.9 mos	13.8 mos

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