NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Vemurafenib for the treatment of BRAFV600 mutation positive malignant melanoma

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Roche Products	Thank you for giving us the opportunity to comment on the ACD for the above appraisal. We welcome the Committee's consideration of the impact of crossover within the BRIM3 study and hope the information provided within sections 1.1 and 1.2 of this document will give further clarity on the crossover adjustment conducted.	Comment noted. The Committee discussed the issue of switching in the BRIM3 trial. The Committee agreed that it was appropriate to adjust the overall survival results from the February 2012 data cut-off to control for switching using statistical modelling or other techniques. However, the Committee agreed that any estimate of overall survival obtained using these techniques would be subject to uncertainty. See section 4.5 of the FAD.
	As requested we have conducted the overall survival extrapolation sensitivity analysis specified in the ACD (detailed in section 2 of this document). This analysis resulted in clinically implausible results - a post-progression survival period 2.2 months shorter in the vemurafenib arm than in the dacarbazine arm. We do not believe this is reasonable and have therefore not presented cost-effectiveness estimates using this approach. Further detail on our rationale for this is provided below.	Comment noted. The Committee discussed the ERG's exploration of an alternative approach to modelling. The Committee reiterated its conclusion that there was significant uncertainty about the magnitude of the survival benefit attributable to vemurafenib but concluded that there was no evidence to support disease acceleration after vemurafenib treatment relative to dacarbazine, as occurred in the ERG exploratory analysis. The Committee therefore accepted the manufacturer's approach to modelling overall survival and its assumption that there was no further beneficial effect of vemurafenib on the risk of death. See sections 3.24 and 4.10 of the FAD.

Consultee	Comment	Response
	As stated in our previous ACD response we believe the most appropriate cost-effectiveness estimates for vemurafenib are those based up the RPSFT adjusted February 2012 data with long term extrapolation based upon the fair assumption that patients given vemurafenib die at the same rate as those given dacarbazine. The ICER for this analysis was stated as £52,327 in our previous ACD response – following correction of some minor errors identified by the ERG this figure has fallen to £51,757 (see Appendix 1).	Comment noted. The Committee discussed the manufacturer's approach to adjusting the survival estimate for the dacarbazine arm of the BRIM3 study. The Committee noted that both the manufacturer and the ERG agreed that the effect of vemurafenib treatment on mortality changes over time and that applying a single acceleration factor may therefore be an oversimplification, and that the results should be viewed with caution. The Committee accepted that there was evidence that vemurafenib increased overall survival compared with dacarbazine and concluded that of the various methods to adjust the BRIM3 trial data for crossover, the RPSFT method was the most plausible because it gave results in-line with those obtained using an alternative indirect method (Bedikian et al. [2011]) for removing the effect of crossover. See sections 3.24, 3.25 and 4.6 of the FAD.
	We hope this information allows the Committee to make vemurafenib available to a group of patients with extremely poor prognosis and no alternative treatment options. Whilst the magnitude of long-term benefits provided by vemurafenib are clearly relevant to this appraisal it should be noted that this is not the key reason that clinicians wish to use vemurafenib – it is the clear, demonstrated and unprecedented benefits provided by vemurafenib in the BRIM3 study which are of key importance to clinicians and people with advanced melanoma.	Comment noted. The recommendation in the guidance has changed. The Committee recognised that vemurafenib could be considered a significant innovation and is a life-extending treatment that meets the criteria for an end-of-life treatment. See section 1 and 4.19 of the FAD.

Consultee	Comment	Response
Roche Products	*A full explanation of the assumptions made and parameter values used for the rank preserving structural failure time (RPSFT) method to adjust survival estimates for patients who switched from dacarbazine to vemurafenib on disease progression* The 'Rank Preserving Structural Failure Time' (RPSFT) (Robins and Tsiatis, 1991) approach to adjusting for crossover is a method that has been utilised in at least six NICE Technology Appraisals to date (NICE TA179, NICE TA215, NICE TA219, NICE TA257, NICE TA263 and NICE ID498 - this Appraisal) The growing use of RPSFT by manufacturers is largely a result of the NICE appraisals of sunitinib for GIST (NICE TA179) and pazopanib for renal cell carcinoma (NICE TA215). In both these Appraisals the RPSFT method was used in order to adjust for crossover, in both Appraisals the RPSFT approach was accepted by the Appraisal Committee and resulted in positive guidance for both technologies under assessment. Whilst other methods have been utilised in NICE Appraisals (for example the Inverse Probability Censoring Weight (IPCW) approach), in the cases where RPSFT has been presented alongside these alternative methods the Appraisal Committee have opted to use the RPSFT results as a basis for decision making (everolimus for renal cell carcinoma (TA219) and pazopanib for renal cell carcinoma (TA215)). As a result, the combination of these Appraisals has sent a clear signal to manufacturers that the RPSFT approach is acceptable for use in adjusting for crossover. The use of RPSFT was further supported by a publication by members of NICE's Decision Support Unit (DSU) (Morden et al 2010). This publication reports the results of a simulation study which indicates that the RPSFT method and a parametric variant of the RPSFT method (the "Branson and Whitehead" approach) are the least biased of the methods assessed. In this report it was noted that the RPSFT methods gave treatment effect estimates *'close to the true treatment effect'.*	Comment noted. The Committee considered all the plausible methods to adjust the survival estimate for the dacarbazine arm of the BRIM3 to account for people who switched to vemurafenib on disease progression, including the RPSFT method. See section 3.21 of the FAD. The Committee noted that both the manufacturer and the ERG agreed that the treatment effect of vemurafenib on mortality changes over time (see section 3.25) and that applying a single acceleration factor may therefore be an oversimplification, and that results should be viewed with caution. Therefore, the Committee was minded to compare the results of the RPSFT analysis with a scenario in which external data from trials in which dacarbazine was used without switching to another drug (that is, Bedikian et al. [2011]). See section 4.6 of the FAD.

Consultee	Comment	Response
Roche Products	In light of the findings reported in this publication and the precedent set in the previous NICE Appraisals featuring RPSFT, the RPSFT method was utilised in order to adjust for crossover in the February 2012 data-cut of the BRIM3 study. A brief introduction to RPSFT, the assumptions underlying it and their applicability in the case of BRIM3 is provided below. ***Supplementary analysis as requested by the appraisal committee in section 1 of the ACD [Details not reproduced here]***	See sections 3.21 -3.25 of the FAD
Royal College of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO	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'	Comment noted. Comment noted. The Committee accepted that vemurafenib represents a valuable new therapy in an area of unmet need and that its mechanism of action is novel. It acknowledged that vemurafenib had a very high disease response rate compared with dacarbazine, and that symptomatic improvement is often rapid. The Committee accepted that vemurafenib is a step change in the management of advanced malignant melanoma. See sections 4.1 and 4.19 of the FAD.

Consultee	Comment	Response
	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.	Comment noted. The Committee discussed the issue of switching in the BRIM3 trial. It was aware that people from the dacarbazine arm could receive treatment with vemurafenib on disease progression, and recognised that this change to a more effective treatment could have confounded the calculation of overall survival benefit from vemurafenib. The Committee agreed that it was appropriate to adjust the overall survival results from the February 2012 data cut-off to control for switching using statistical modelling or other techniques. However, the Committee agreed that any estimate of overall survival obtained using these techniques would be subject to uncertainty. See section 4.5 of the FAD.

Consultee	Comment	Response
Royal College of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO	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.	Comment noted. The Committee discussed the four different data-cut points from the BRIM3 trial. It noted that with each subsequent data cut-off point, more participants switched from dacarbazine to vemurafenib on disease progression. The Committee recognised that the data on overall survival from later data-cut off points were confounded not only by switching from dacarbazine to vemurafenib, but also by the fact that patients whose disease did not show an objective response were able to receive a range of other therapies including ipilimumab and other investigational BRAF inhibitors. However, the Committee were minded to accept that more information on the long-term clinical effectiveness of vemurafenib at the February 2012 data cut-off outweighed concerns about the robustness of the data compared with the earlier data cut-offs. See section 4.4 of the FAD.

Consultee	Comment	Response
Royal College of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO	As clinicians, we are becoming uncomfortable with the direction that the Committee's discussions are taking. There are ever increasingly complex and unvalidated modelling methodologies being presented in an attempt to measure the unmeasureable. 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.	Comment noted. The Committee discussed the issue of switching in the BRIM3 trial. It was aware that people from the dacarbazine arm could receive treatment with vemurafenib on disease progression, and recognised that this change to a more effective treatment could have confounded the calculation of overall survival benefit from vemurafenib. The Committee agreed that it was appropriate to adjust the overall survival results from the February 2012 data cut-off to control for switching using statistical modelling or other techniques. However, the Committee agreed that any estimate of overall survival obtained using these techniques would be subject to uncertainty. See section 4.5 of the FAD.

Consultee	Comment	Response
Royal College of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO	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. We urge the Committee to reconsider their decision.	Comment noted. The Committee discussed whether the benefit from vemurafenib over dacarbazine was likely to continue once treatment was stopped, or conversely whether there will be accelerated disease progression. It acknowledged that the existence or magnitude of continued benefit from vemurafenib after treatment is stopped is uncertain, but recognised that there is no evidence currently available to suggest that people who stopped vemurafenib treatment will experience accelerated disease progression compared with those who have been treated with dacarbazine. See section 4.7 of FAD. Comment noted. See above response to RCP's ACD comments.

Consultee	Comment	Response
	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.	Comment noted. The recommendation in the guidance has changed. The Committee recognised that there few advances had been made in the treatment of advanced melanoma in recent years and vemurafenib could be considered a significant innovation for a disease with a high unmet clinical need. It considered vemurafenib to be a life-extending treatment that meets the criteria for an end-of-life treatment. The Committee concluded that the combined value of these factors meant that vemurafenib could be considered a cost-effective use of NHS resources. See section 1 and 4.19 of the FAD.

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisals Service (CSAS)	On behalf of the Commissioning Support Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive melanoma. We are in agreement with the recommendations in the ACD not to recommend vemurafenib for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered cost effective in real life clinical practice. • **There is uncertainty about the longer term clinical effectiveness of vemurafenib because the BRIM3 trial was ended early.** An open-label RCT investigated the effectiveness of vemurafenib compared to standard treatment with dacarbazine in patients with previously untreated advanced BRAF V600 mutation-positive metastatic melanoma (BRIM3 trial). The study ended early after the planned interim analysis, and cross-over onto vemurafenib was permitted. At this point, vemurafenib led to statistically significant reductions in death and tumour progression and a statistically significant increase in overall survival at six months. The manufacturer later submitted follow-up evidence from February 2012. At this point 34% of patients had crossed over from dacarbazine to vemurafenib. Despite potential confounding due to cross-over onto vemurafenib or treatment with other investigational treatments, vemurafenib led to statistically significant increases in progression free survival, reduction in tumour progression and median overall survival. The difference in median survival was increased when the manufacturer adjusted for switching using the rank preserving structural failure time (RPSFT) method. NICE has asked for details of the assumptions made and the parameter values used in the RPSFT model.	Comment noted. Comment noted. The Committee discussed the issue of switching in the BRIM3 trial. It was aware that people from the dacarbazine arm could receive treatment with vemurafenib on disease progression, and recognised that this change to a more effective treatment could have confounded the calculation of overall survival benefit from vemurafenib. The Committee agreed that it was appropriate to adjust the overall survival results from the February 2012 data cut-off to control for switching using statistical modelling or other techniques. However, the Committee agreed that any estimate of overall survival obtained using these techniques would be subject to uncertainty. See section 4.5 of the FAD.

Commentator	Comment	Response
Commissioning Support Appraisals Service (CSAS)	• **There is uncertainty about the overall survival benefit of vemurafenib.** The manufacturer's submission is based on the results of one open-label RCT(BRIM3), which was halted after the pre-planned interim analysis (December 2010). The manufacturer has also submitted some follow-up data from this trial (March 2011, October 2011 and February 2012). Due to the premature termination of the BRIM3 trial and the permitted crossover onto vemurafenib, there is uncertainty over the estimation of the overall survival benefit with vemurafenib.	Comment noted. See above response to CSAS ACD response.
	• **Vemurafenib is an effective long-term therapy for some patients.** The number of people with a complete response increased from 0.9% in December 2010 to 5.6% in February 2012 in the vemurafenib group, demonstrating that vemurafenib can provide long term benefit for some patients (in February 2012 there was a complete response in 1.2% of the dacarbazine group).	Comment noted.
	• **Vemurafenib represents a step change in the management of advanced malignant melanoma.** Treatment options for advanced metastatic melanoma are limited. The Appraisal Committee agreed that vemurafenib represents a valuable new therapy and that its mechanism of action is novel. The Appraisal Committee was also satisfied that the drug met all of the criteria for being a life-extending, end-of-life treatment. The trial evidence presented for this was robust.	Comment noted. The Committee recognised that there few advances had been made in the treatment of advanced melanoma in recent years and vemurafenib could be considered a significant innovation for disease with a high unmet clinical need. It considered vemurafenib to be a life-extending treatment that meets the criteria for an end-of-life treatment. The Committee concluded that the combined value of these factors meant that vemurafenib could be considered a cost-effective use of NHS resources. See sections 1 and 4.19 of the FAD.

Commentator	Comment	Response
	• **Vemurafenib may cost about £49,000 per patient at full dose.** Assuming an average length of treatment of 28 weeks (7 months) and using list prices. An estimated 1 to 2 people per 100,000 would be eligible for treatment**.** • **The manufacturer has agreed a confidential patient access scheme** • **There is uncertainty over the cost-effectiveness of vemurafenib but the ICER is likely to be higher than £50,000.** The ICER for vemurafenib was highly uncertain and likely to be considerably higher than £50,000 per QALY gained, despite a discounted price offered via a patient access scheme. The uncertainty over long term survival benefit of vemurafenib was a major source of uncertainty during ICER calculation. The Appraisal Committee has requested a cost-effectiveness estimate from the manufacturer in which exponential hazards are applied to each arm of the BRIM3 study from 14 months (the manufacturer had assumed that survival following disease progression at 14 months is equal in both groups).	Comment noted. Comment noted. Comment noted. Comment noted. The Committee concluded that the most plausible ICER was in the range of £44,000 to £51,800 per QALY gained. See section 4.13 of the FAD.

Commentator	Comment	Response
Commissioning Support Appraisals Service (CSAS)	• **Treatment with vemurafenib will require mutation testing.** This testing is being offered free of charge by the manufacturer. In the manufacturer's economic model, they estimate the BRAF testing cost (per test) at £95. However, the Appraisal Committee concluded that BRAF V600 mutation testing is likely to become part of routine management for people with advanced melanoma. • **Despite toxicity few patients stop the drug.** In the BRIM3 trial 38% of patients receiving vemurafenib required dose modification because of toxic effects which included photosensitivity, arthralgia rash, fatigue and development of keratoacanthoma or well differentiated squamous cell carcinoma of the skin. Few patients stopped the drug due to toxicity. All secondary skin cancers were resected and there have been no cases of metastatic secondary cancer. • **Funding for vemurafenib may be available through the Cancer Drugs Fund.** If NICE were not to recommend vemurafenib for this indication, funding for vemurafenib may be available through the Cancer Drugs Fund. The fund may be used to pay for drugs recommended by oncologists that have either been appraised by NICE and not recommended on the basis of cost effectiveness, only recommended in a smaller group of patients than specified in the marketing authorisation, or drugs that have yet to be appraised. The fund is for the purchase of medicines, although it may also be used for molecular diagnostic testing. £200 million is being made available in 2012-2013.	Comment noted. The Committee discussed the costs associated with supporting BRAF V600 mutation testing. It noted the time-limiting factor is accessing and preparing the tumour blocks, and transporting them, rather than performing the test. The Committee considered that BRAF V600 mutation testing would not impose a significant resource impact on the NHS in the future. See section 4.11 of the FAD. Comment noted. The Committee discussed the adverse events associated with vemurafenib. It noted cutaneous events were commonly reported in the BRIM3 trial The Committee concluded that treatment with vemurafenib had an acceptable adverse event profile when taking into account the potential benefits. See section 4.8 of the FAD. Comment noted. The recommendation in the guidance has changed. The Committee recognised that vemurafenib could be considered a significant innovation and is a life-extending treatment that meets the criteria for an end-of-life treatment. The Committee concluded that the combined value of these factors meant that vemurafenib could be considered a cost-effective use of NHS resources See sections 1 and 4.19 of the FAD.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	Appraisal Recommendations	NHS Hampshire is in agreement with the recommendations in the NICE Appraisal Consultation Document (ACD) and Commissioning Support Appraisals Service (CSAS) response, not to recommend Vemurafenib for this indication on the basis that there does not appear to be any published evidence that has considered whether this treatment at its current high cost (approx. £2,100 per week) is cost-effective. Vemurafenib is an expensive drug and its long term benefits and safety profile are difficult to quantify.	Comment noted. The recommendation in the guidance has changed The Committee recognised that vemurafenib could be considered a significant innovation and is a life-extending treatment that meets the criteria for an end-of-life treatment. The Committee concluded that the combined value of these factors meant that vemurafenib could be considered a cost-effective use of NHS resources. See sections 1 and 4.19 of the FAD.
NHS Professional	Technology	Response to Vemurafenib is rapid but the median duration of response is only 5-6 months as most patients develop resistance to Vemurafenib, manifested by progressive disease, and rapid relapse.	Comment noted. The Committee accepted that there was evidence that vemurafenib increased overall survival compared with dacarbazine. But it concluded that, given the uncertainty of the validity of the underpinning principle of the time invariance for the RPSFT method, the exact magnitude of the overall survival gain remained uncertain. See sections 4.4-4.7 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		There are concerns around the safety of Vemurafenib, as experience on the adverse event profile is still accumulating. •In the BRIM3 study 18% patients develop dermatologic complications including squamous cell carcinomas needing treatment.	The Committee concluded that treatment with vemurafenib had an acceptable adverse event profile when taking into account the potential benefits. See section 4.8 of the FAD.
		The impact of extra activity and costs generated from regular dermatological referral, monitoring, evaluation and management, need to be considered	Comment noted. The Committee discussed the costs associated with supporting BRAF V600 mutation testing. The Committee considered that BRAF V600 mutation testing would not impose a significant resource impact on the NHS in the future. See section 4.11 of the FAD.
NHS Professional	Manufacturer's submission	Patients must have BRAF V600E mutation-positive tumour status confirmed by a validated test. The efficacy and safety of Vemurafenib in patients with tumours expressing BRAF V600 non-E mutations have not been convincingly established, although response in BRAF-V600K mutant melanoma has been reported. Vemurafenib should not be used in patients with wild type BRAF malignant melanoma.	Comment noted.
		In the phase II and phase III clinical trials, eligible patients were identified using a real-time polymerase chain reaction assay (the cobas 4800 BRAF V600 Mutation Test). Although the manufacturer of Vemurafenib is currently making BRAF V600 mutation testing free of charge by funding 3 BRAF reference testing centres in the UK, this may change and the potential cost and activity generated from the Roche cobas 4800 BRAF V600 mutation testing on the NHS would need to be considered.	Comment noted. The Committee discussed the costs associated with supporting BRAF V600 mutation testing. It noted the time-limiting factor is accessing and preparing the tumour blocks, and transporting them, rather than performing the test. The Committee considered that BRAF V600 mutation testing would not impose a significant resource impact on the NHS in the future. See section 4.11 of the FAD.

Role*	Section	Comment	Response
NHS Professional	Consideration of the evidence	It is not clear where Vemurafenib sits in the clinical pathway of care for people with locally advanced or metastatic BRAF V600E mutation-positive malignant melanoma, given that there are a range of new therapies (Iplimumab, Dabrafenib) currently being investigated. The following elements have not been considered: Role of Vemurafenib in the adjuvant setting Impact of combination therapy with Iplimumab and dosage. Their optimal sequencing. Further research is still needed to establish appropriate therapeutic options in clinical practice.	Comment noted. Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, and NICE will only issue guidance in accordance with the marketing authorisation. See NICE Guide to Method of Technology Appraisals 2008.
NHS Professional	Implementation	There is a rapid rise in malignant melanoma. Hampshire has a malignant melanoma incidence rate which is higher than the national average. The rates were 19.8 per 100,000 population (2006-2008) 19.6 per 100,000 population (2005-2007) and 18.3 per 100,000 population (2004-2006), significantly worse than the England average (13.6 per 100,000 population, (2006-2008)]. Most (approximately 90%) melanomas are diagnosed early as primary tumours and cured by surgery. Around 10% of patients have metastatic disease at diagnosis or relapse with metastatic spread after treatment for apparently localised disease. It is suggested by the manufacturer that of these, approximately 50% of melanoma patients have tumours which harbour BRAF V600 mutations and 85% would eligible for treatment. Although local intelligence on the prevalence of metastatic disease in Hampshire is not available, given the higher incidence, one would expect proportionately higher numbers of patients eligible for treatment with Vemurafenib if recommended. This would also include extra activity and costs generated from regular dermatological referral to address cutaneous adverse events.	Comment noted.