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BY EMAIL

7 July 2012

RE: Vemurafenib for the treatment of BRAF V600 mutation positive metastatic melanoma

Dear [REDACTED]

Thank you for giving us the opportunity to comment on the ACD for the above appraisal. We are disappointed with the Committee's decision and hope that the information provided within this response will allow NICE to make vemurafenib available to a group of patients with a poor prognosis and no alternative effective treatment options.

Due to the confounding effect of crossover in BRIM3 we will never know the extent to which vemurafenib provides a prolonged benefit over dacarbazine beyond the period of BRIM3, and therefore whether the ERG's modeling or Roche's modeling is correct. We firmly believe that the ERG's assumption that patients given vemurafenib die more quickly than patients given dacarbazine following the period of the BRIM3 study is unnecessarily pessimistic. We strongly believe the most reasonable thing to do when extrapolating the BRIM3 data is to assume patients die at an equal rate in each arm beyond the period of the study. Our response to the ACD is focused on two key areas. These are briefly summarized below and provided in further detail under the standard headings later in this document.

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1. New evidence from the February 2012 data-cut of the BRIM3 Study

On the 1st February 2012 a new cut of the BRIM3 data was made available, providing more mature evidence on the efficacy of vemurafenib which has not yet been considered by the Committee. This new data demonstrates that the median progression free survival advantage provided by vemurafenib has now increased to **5.3 months** (from 3.7 months in the December 2010 data-cut), that **5.6%** of vemurafenib patients have now been shown to have a **complete response** to treatment (100% tumour shrinkage – previously 0.9%) and that the response rate associated with vemurafenib has increased to **57%** (from 48.4%). This data presents a clear, compelling and substantially improved case that vemurafenib is extremely effective at suppressing advanced melanoma. As crossover from dacarbazine to a BRAF inhibitor upon disease progression is substantial in this latest data-cut (34% of patients in the comparator arm received a BRAF inhibitor for an average duration of 4 months), interpretation of the results observed is difficult. As a result of this crossover the median overall survival in the dacarbazine arm has now reached 10.3 months compared to the 7.8 months recorded in the December 2010 data-cut.

In order to adjust for crossover in this data-set a rank preserving structural failure time (RPSFT) model has been utilized (as recommended by NICE's Decision Support Unit). This method reduced the median OS for dacarbazine to 8.9 months whilst leaving the vemurafenib arm median unaffected at 13.6 months. When utilised in an economic model featuring the assumption of equal rates of death in both arms from month 14 onwards this data is associated with an estimated cost per QALY of **£52,327**. As this figure does not incorporate the impact of higher use of other BRAF inhibitors (other than vemurafenib) and higher use of ipilimumab in the dacarbazine arm of BRIM3 this is likely to be an over-estimate of the true ICER of vemurafenib.

2. The external validity of the ERG's modelling of survival with dacarbazine

In order to validate the modeling of dacarbazine undertaken by the ERG a systematic review of recent studies featuring dacarbazine monotherapy was undertaken. This review demonstrates that the ERG's modeled dacarbazine arm has strong face validity when compared to the crossover confounded data from the February 2012 data-cut of the BRIM3 study. However this review also demonstrates that the ERGs model has poor external

validity when compared to data which represents current NHS practice (where post-progression use of vemurafenib is not currently funded following dacarbazine). As a consequence we believe the ERG has substantially over-estimated the efficacy of dacarbazine in UK practice and that the benefit of vemurafenib has been underestimated. If these alternative data sources identified in the literature review are utilized in order to model the dacarbazine arm rather than the confounded BRIM3 control arm the ICER falls to comfortably below £50,000/QALY (i.e. use of control arm data from a 2011 study conducted by the Bedikian et al dropped the ICER to £45,003).

In addition to these two key points our response provides further information on the rationale for vemurafenib providing a prolonged benefit to a small proportion of patients and the plausibility of the ERG's assumption that patients given vemurafenib die more quickly than patients given dacarbazine at a point in time where 47% of patients are still receiving vemurafenib.

In light of the above we believe there are three fair ways of estimating the cost-effectiveness of vemurafenib.

1. Utilizing the less confounded March 2011 data (£45,618/QALY gained)
2. Utilizing the RPSFT adjusted February 2012 data (£52,327/QALY gained)
3. Utilizing a control arm from an unconfounded RCT (£45,003/QALY gained)

Each of the above include the fair assumption that patients in both arms die at the same rate beyond the period of the BRIM3 study (i.e. a HR of 1 was applied).

Given the magnitude of these ICERs, the fact that advanced melanoma has had no new effective treatment options for over 40 years and the extremely poor prognosis of patients treated with the current standard of care we firmly believe that vemurafenib should be regarded as a cost-effective use of NHS resources.

Yours Sincerely,

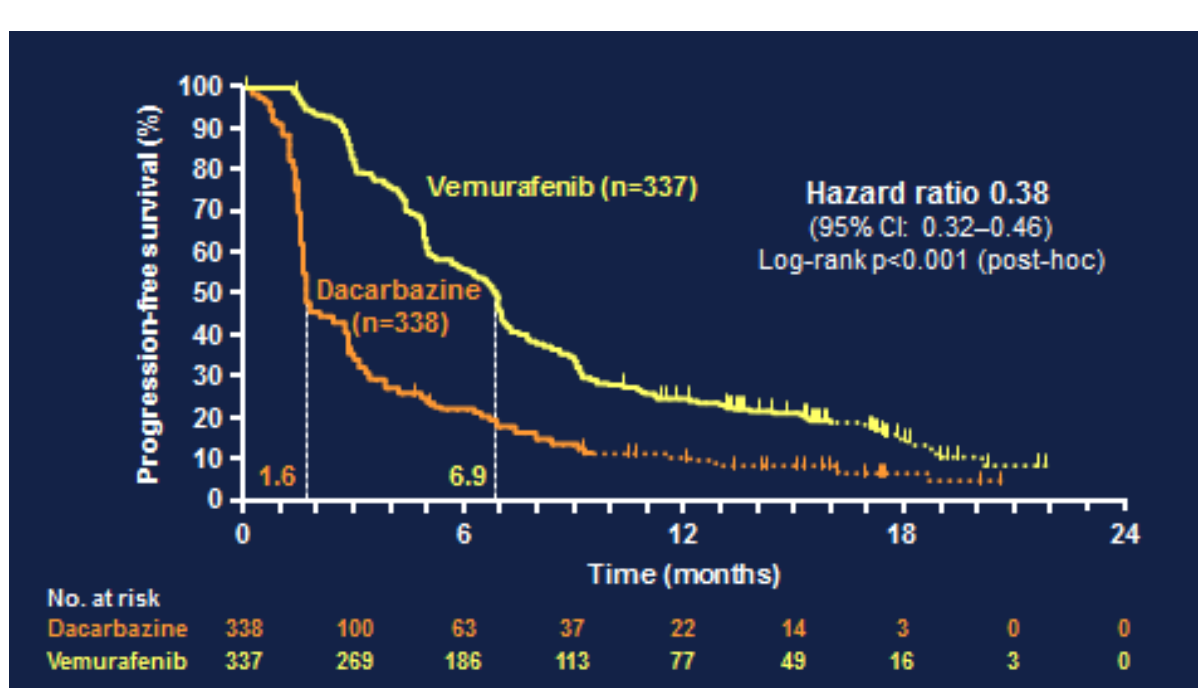


Has all of the relevant evidence been taken into account?

1. New evidence from the February 2012 data-cut of the BRIM3 Study

Below new evidence from a February 2012 data-cut of the BRIM3 study is presented. This data features a median follow-up of 12.5 months in the vemurafenib arm and 9.5 months in the dacarbazine arm.

Figure 1. Progression-free survival in BRIM3 (February 1st 2012 data cut-off; Chapman et al, 2012)



Median PFS for patients randomised to vemurafenib has now increased to 6.9 months (compared to 5.3 months for the December 2010 cut-off). The median PFS for patients randomised to dacarbazine remains unchanged at just 1.6 months (the time of first assessment for disease progression). This equates to a **5.3 month** median PFS advantage for patients receiving vemurafenib.

Whilst the median advantage provided by vemurafenib is noticeably improved, it should also be noted that the PFS curve for vemurafenib appears to be 'levelling out' above the dacarbazine arm in the tail of the curves.

1.1 Response Rates

Table 1. Response rates in BRIM 3 as presented at ASCO 2011 (Dec 2010 data cut-off) and ASCO 2011 (Feb 2011 data cut-off) (Chapman et al, 2012)

	ASCO 2011		ASCO 2012 (post-hoc)	
	DTIC (n=220)	Vemurafenib (n=219)	DTIC ^a (n=338)	Vemurafenib (n=337)
No. of evaluable pts				
Median follow-up, months	2.3	3.8	9.5	12.5
ORR, %	5.5	48.4	8.6	57.0
CR, %	0	0.9	1.2	5.6
PR, %	5.5	47.5	7.4	51.3

The response rate associated with vemurafenib is now **57%**. This level of response (defined as a 30% reduction in tumour size) is unprecedented in the treatment of advanced melanoma and compares extremely favourably the **5-10%** response rates typically seen with dacarbazine.

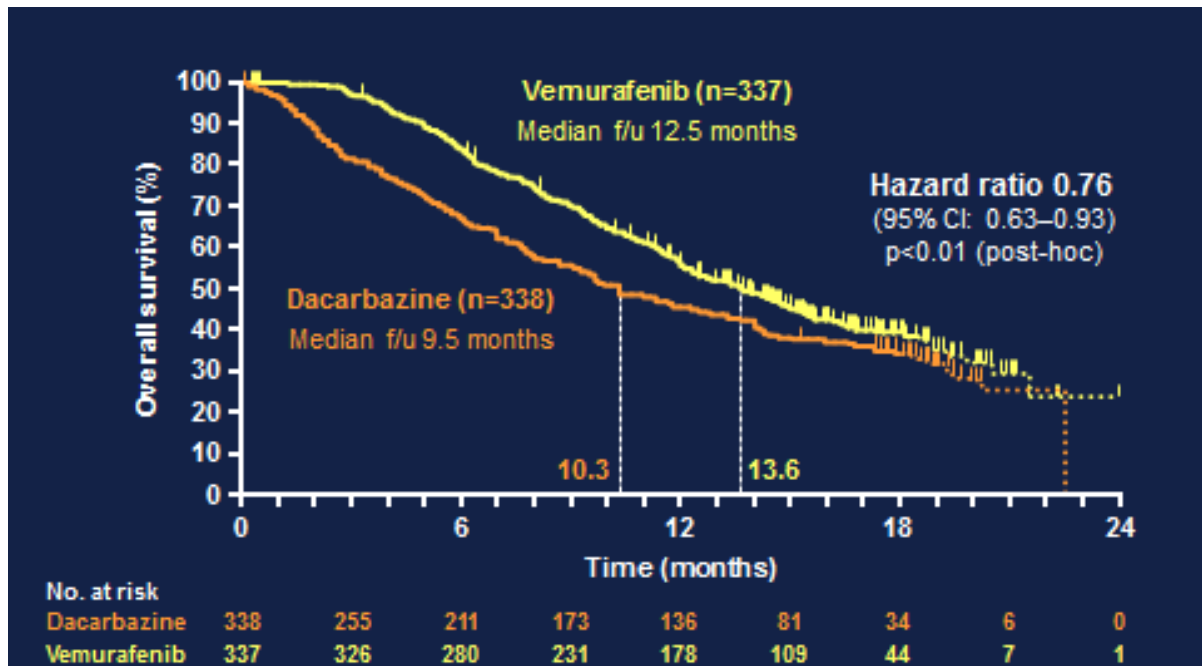
As it is the presence of large tumour bulk that gives rise to symptoms and, ultimately, kills people with advanced melanoma this remarkable level of tumour shrinkage is extremely important.

In addition to the increase in the number of patients responding it is important to note that there has also been an important increase in the proportion experiencing a complete response to treatment with vemurafenib. **More than 1 in 20 patients treated with vemurafenib have now been shown to achieve a complete response to treatment (disappearance of all evidence of disease on scans).**

1.2 Overall Survival

Crossover to a BRAF inhibitor has now reached 34% with average crossover treatment duration of over 4 months. As a result of this crossover the dacarbazine OS curve has moved further to the right (median 10.3 months compared to 7.8 months in December 2010) and the median advantage provided by vemurafenib has reduced to 3.3 months. Despite this crossover the OS HR observed remains significantly in favour of vemurafenib (OS HR = 0.76 {0.63, 0.93}, $p < 0.01$).

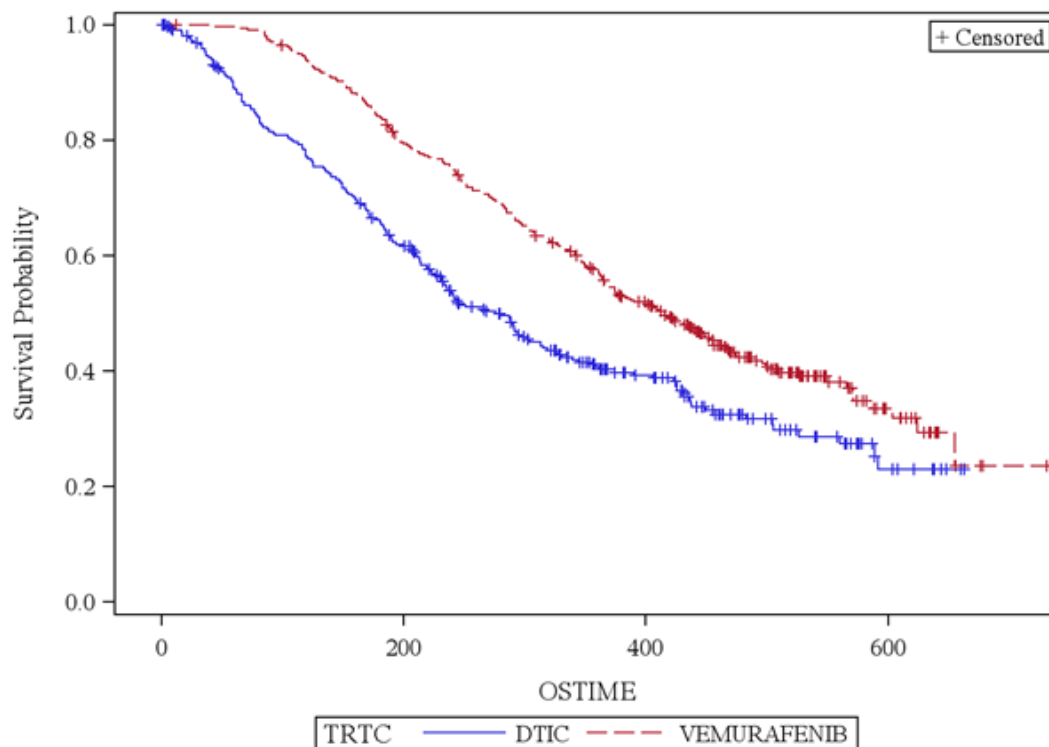
Figure 2. Overall survival in the BRIM 3 study (Feb 1st 2012 data cut off; Chapman et al, 2012)



1.3 “Uncrossing” the February 2012 Data

As this data was confounded by crossover a Rank Preserving Structural Failure Time (RPSFT) model was utilised in order to adjust for this crossover without violating randomisation (Robins and Tsiatis 1991). The results of the RPSFT adjusted February 2012 data-set are presented below:

Figure 3. Rank Preserving Structural Failure Time Adjusted February 2012 Overall Survival Data



This approach is one recommended by NICE's Decision Support Unit (Morden et al 2011) and has been utilised in several recent NICE technology appraisals featuring crossover (trastuzumab in combination with an aromatase inhibitor for the treatment of HER2+/HR+ metastatic breast cancer (TA257), bevacizumab in combination with capecitabine for the treatment of HER2- metastatic breast cancer (ID54), everolimus for the treatment of renal cell carcinoma (TA219), pazopanib for the treatment of renal cell carcinoma (TA215), sunitinib for the treatment of GIST (TA179)).

With RPSFT adjustment the median OS in the dacarbazine arm fell from 10.3 months to 8.9 months (1.4 months to the left) compared to 13.6 months in the vemurafenib arm (unaffected by RPSFT). This equates to an RPSFT adjusted median survival gain of 4.7 months (a **52%** increase in median survival attributable to use of vemurafenib). The overall survival hazard ratio associated with the RPSFT adjusted analysis was 0.64 {0.53, 0.78} ($p < 0.0001$).

It should be noted that this RPSFT analysis does not account for the imbalance in use of post-progression ipilimumab or BRAF inhibitors other than vemurafenib (both of which favour the dacarbazine arm). As a consequence the results of this analysis and any cost-effectiveness estimated derived using it can be regarded as conservative.

1.4 Applying the February 2012 data in an economic model

The February 2012 data was included in the Roche economic model as follows:

- The ERG's suggested amendments to discounting, utilities and costs for 'long term survivors' were implemented
- Response rates were updated to reflect the improved rates observed in the latest data-cut
- The progression free survival curves were updated to reflect the improved PFS results
- The RPSFT adjusted February 2012 OS data were applied

The long-term extrapolation of this survival data was done utilising the assumption that patients die at the same rate following the period of the BRIM3 study. This updated analysis resulted in an estimated ICER of **£52,327/QALY** gained.

With further adjustment for the impact of greater use of ipilimumab and BRAF inhibitors other than vemurafenib after progression in the dacarbazine arm this ICER would likely fall below £50,000/QALY gained. Furthermore as this ICER is based upon an economic model which assumes that a patient receiving 7 tablets of vemurafenib a day will be dispensed 4 packs of vemurafenib at each 'dispensing date' when these patients will be dispensed 4 packs on every other visit (with only 3 packs required at each other visit) it is likely an overestimate of the true

ICER of the use of vemurafenib in English/Welsh practice (as the cost of vemurafenib has been overestimated).

Full results of the analysis and further detail on the extrapolation approach taken are provided in Appendix 1.

2. The external validity of the ERG's modelling of survival with dacarbazine

In the ACD the Committee are *inclined* to prefer Overall Survival data from the October 2011 data-cut of the BRIM3 RCT rather than Overall Survival data from the March 2011 data-cut (ACD Section 4.2). This conclusion was made on the basis that the Committee believed '*more information on the long term effectiveness of vemurafenib outweighed concerns about the robustness of the data*'.

Neither we, nor the clinical experts or academic health economists we sought advice from believe that this conclusion is legitimate.

Use of the later data-cuts of the BRIM3 study without appropriate consideration of crossover will result in the misattribution of the efficacy of vemurafenib to dacarbazine. As a consequence the true effectiveness of dacarbazine will be over-estimated in any modelling undertaken and the benefit provided by the introduction of vemurafenib will be significantly underestimated.

In order to aid the committee in their consideration of the impact of crossover in BRIM3 new evidence is provided below. This evidence demonstrates conclusively that:

- Crossover to a BRAF inhibitor in the BRIM3 October 2011 data cut-off was significantly higher than in the March 2011 data cut-off:
 - In terms of the proportion of patients crossing over (an increase of 50%) *and*
 - The average duration of their crossover therapy (an increase of 133%)
- As a consequence the amount of BRAF inhibitor therapy received by patients in the dacarbazine arm was **3.5 times** higher in the October 2011 than March 2011 data-cut
- This increase in crossover had a clear confounding influence upon the overall survival curve for patients randomised to dacarbazine when comparing the four available data-cuts
- As a consequence the ERGs model has poor face-validity when compared to other RCTs in this disease area (in which crossover to vemurafenib did not occur)
- If the cost of crossover treatment with a BRAF inhibitor or ipilimumab is included in the economic model based upon the October 2011 data-cut the ICER falls to £50,413

Due to this evidence we firmly believe the Committee should reconsider their position on use of the October 2011 BRIM3 data without consideration of the impact of crossover (as has been done by the ERG in their modelling).

2.1 *The proportion of patients in BRIM3 crossing over to receive a BRAF inhibitor*

Within our submission the proportion of patients randomised to dacarbazine “crossing over” to receive vemurafenib after progression in each of the two data-cuts was provided (with 15% crossover in March 2011 and 24% in October 2011).

In early June 2012 data from the BREAK3 RCT were reported at the annual conference of the American Society of Clinical Oncologists (ASCO). This data demonstrated the efficacy of dabrafenib, another BRAF inhibitor, in the treatment of BRAF mutation positive melanoma.

In light of this data we have revised our estimates of crossover to consider *not only* the proportion of patients crossing over to vemurafenib, but those patients crossing over to a BRAF inhibitor (BRAFi) other than vemurafenib. When these alternative BRAF inhibitors are considered *in addition* to vemurafenib the proportion of patients ‘crossing over’ in the October 2011 data-cut was 50% higher than in the March 2011 cut.

Table 2. Proportion of patients crossing over to receive a BRAF inhibitor in BRIM3 study

Data-cut	Proportion of patients crossing over to receive a BRAFi
March 2011	20%
October 2011	30%

2.2 *The average duration of crossover BRAFi at the point of data-cut off*

When assessing the impact of crossover it is important to note that the confounding influence of crossover is not simply a function of the *proportion* of patients who crossover to receive another treatment but also the *length* of time they have been receiving the crossover treatment.

In our submission we presented solely the proportion of patients crossing over to vemurafenib and did not consider the duration of therapy received by these patients. Table 3 (below) provides the average duration of BRAFi therapy received by patients who crossed over in each of the two groups.

Table 3. Average duration of crossover BRAFi therapy for patients who crossed over in the dacarbazine arm

Data-cut	Average duration of BRAFi crossover
March 2011	45 days
October 2011	105 days

As shown above the average duration of BRAFi treatment received by patients crossing over increased substantially between March and October 2011. This increase was largely due to the fact that crossover to vemurafenib was only permitted by the Independent Data and Safety Monitoring Board on 14th January 2011. As a result of the combination of the increased proportion of patients crossing over, and the increase in average duration of crossover therapy, **3.5 times** more BRAFi therapy was received by dacarbazine randomised patients in the October 2011 data cut than in the March 2011 data-cut.

In addition to the imbalance in post-progression use of BRAF inhibitors it should also be noted that in the October 2011 data-cut more patients randomised to dacarbazine received post-progression ipilimumab (19%) than in the vemurafenib arm (13%).

2.3 *The impact of crossover upon the survival observed for patients randomised to dacarbazine*

Given the fact that less than 4% of deaths were recorded in the first 3 months of the vemurafenib arm of BRIM3 (compared to nearly 20% in the dacarbazine arm) it appears logical that the consequence of 30% of patients randomised to dacarbazine receiving nearly four months of treatment with a BRAFi (as observed in the October 2011 data-cut) would have a substantial impact upon the survival times observed for patients randomised to dacarbazine.

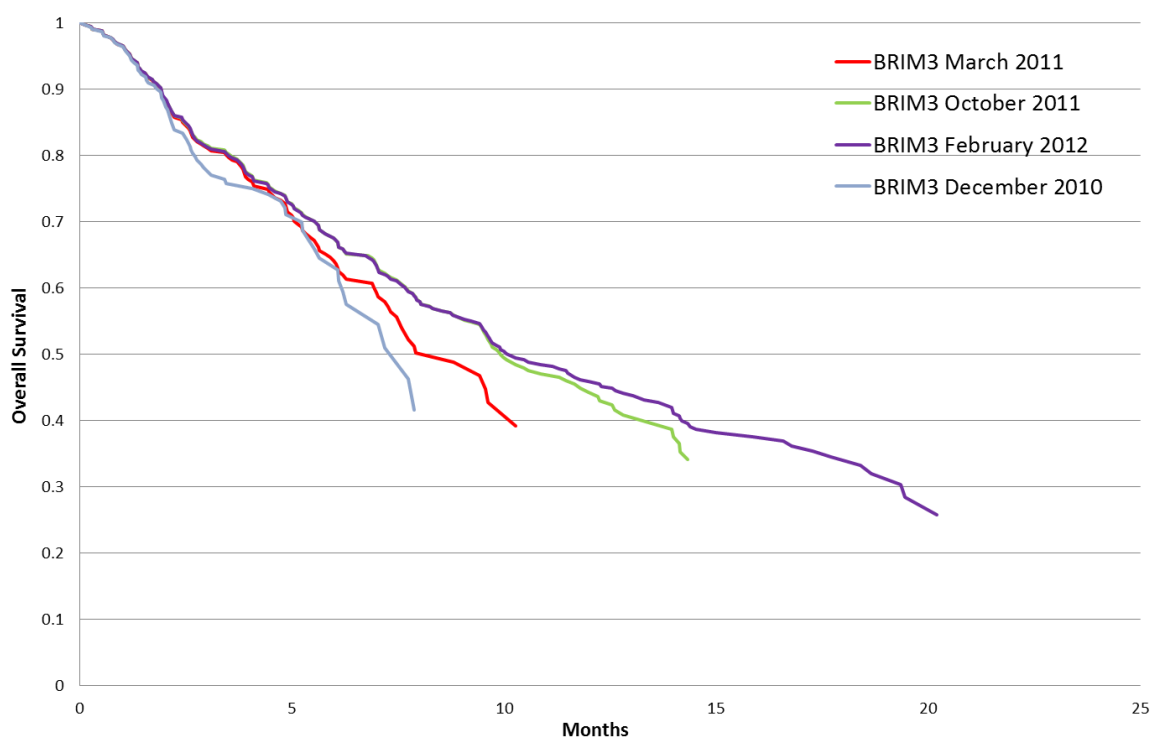
This hypothesis is strongly supported by the observed evidence across multiple data-cuts in BRIM3. If the median survival for patients randomised to dacarbazine over the four data-cuts now available (December 2010, March 2011, October 2011 and February 2012) are compared it is clear that crossover had a significant impact upon the results observed in BRIM3.

Table 4. The impact of crossover upon Overall Survival in BRIM3

Time of Data-cut	Proportion of patients crossing over to receive a BRAFi	Average duration of BRAFi crossover	Dacarbazine OS Median (months)	Vemurafenib OS Median (months)
December 2010	0%	0 days	7.8	Not reached
March 2011	20%	45 days	8.8	Not reached
October 2011	30%	105 days	9.6	13.2
February 2012	34%	125 days	10.3	13.6

Similarly if the actual overall survival Kaplan-Meier curves for dacarbazine randomised patients from these four cuts are compared it is clear that crossover had a substantial influence upon the survival outcomes observed (see Figure 4 below).

Figure 4. Movement of dacarbazine OS curve over time demonstrates impact of increased crossover

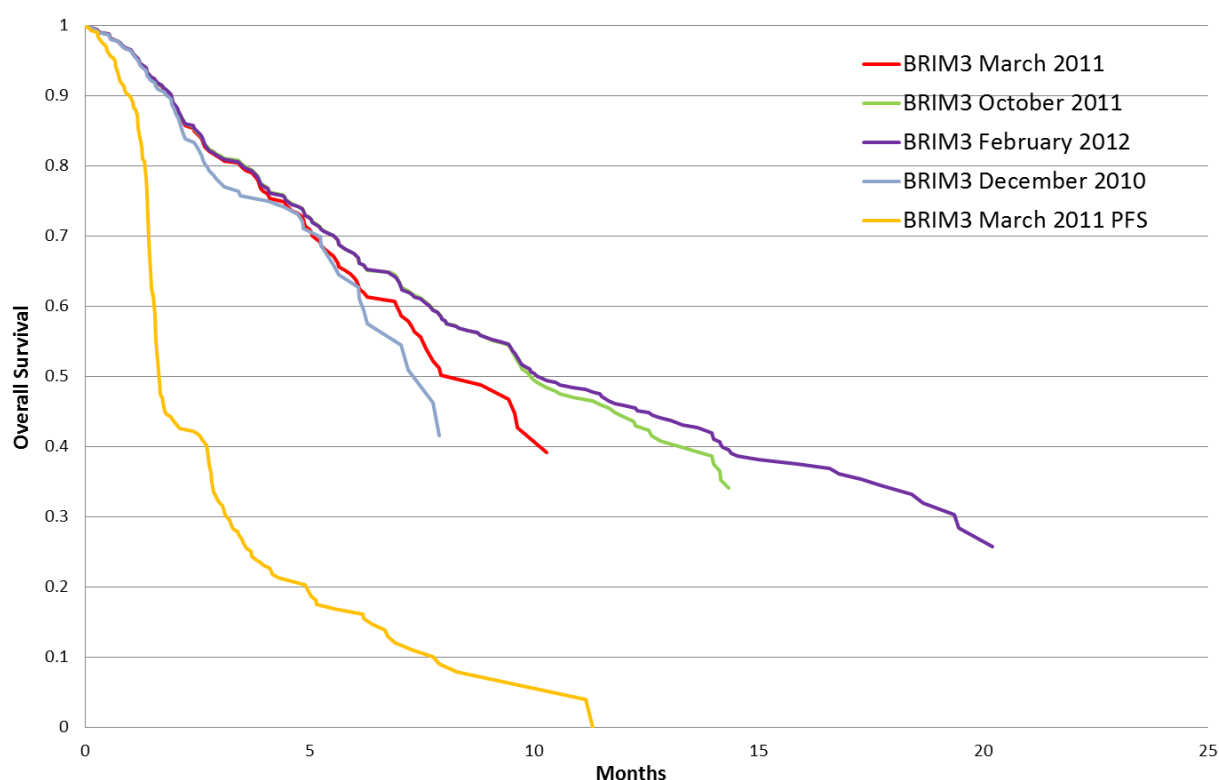


The fact that over the four cuts of data the dacarbazine survival curve remains fairly stable for the initial few months and only begins to shift towards the right further down the curve indicates

strongly that crossover is the cause of this movement (as patients randomised to dacarbazine would still be receiving dacarbazine for these first few months and could not have crossed over yet).

This theory is supported by Figure 5 below in which the dacarbazine PFS curve from the March 2011 data-cut is compared to the OS curves observed across the four available data-cuts.

Figure 5. Major shifts in dacarbazine curve occur when low proportion of patients still receiving dacarbazine



This figure demonstrates that the overall survival curves from the four cuts remain fairly consistent until less than 20% of patients remain on treatment with dacarbazine (at roughly 5 months post-treatment initiation). The fact that the curves begin to separate when such a low proportion of patients are still receiving dacarbazine is highly suggestive of the separation being due to something that occurs after first line treatment (i.e. crossover to a BRAF inhibitor).

2.4 The external validity of a dacarbazine arm based upon modelling of the October 2011 data

In order to further investigate the hypothesis of the dacarbazine arm of BRIM3 being confounded by crossover, a systematic review of recent RCTs in melanoma was undertaken (described in further detail in Appendix 2). This review confirmed that the control arm observed in the later follow-up periods of BRIM3 substantially over-estimates the efficacy of dacarbazine relative to

recent comparable studies in the same disease area. This strongly suggests that crossover was an important factor in the later cuts of BRIM3.

The four figures below demonstrate that the later cuts of BRIM3 over-estimate the survival associated with dacarbazine treatment relative to the four melanoma RCTs featuring dacarbazine monotherapy control arms containing more than 100 patients published since 2005:

- **Bedikian 2006**; Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group
- **Robert 2011**; Ipilimumab plus dacarbazine for previously untreated metastatic melanoma'
- **Bedikian 2011**; Phase 3 study of docosahexaenoic acid-paclitaxel versus dacarbazine in patients with metastatic malignant melanoma
- **Patel 2011**; Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: final results of a randomised phase III study (EORTC 18032)

Figure 6. Dacarbazine arm from Bedikian 2006 et al RCT compares favourably to BRIM3 March data but not more confounded later data

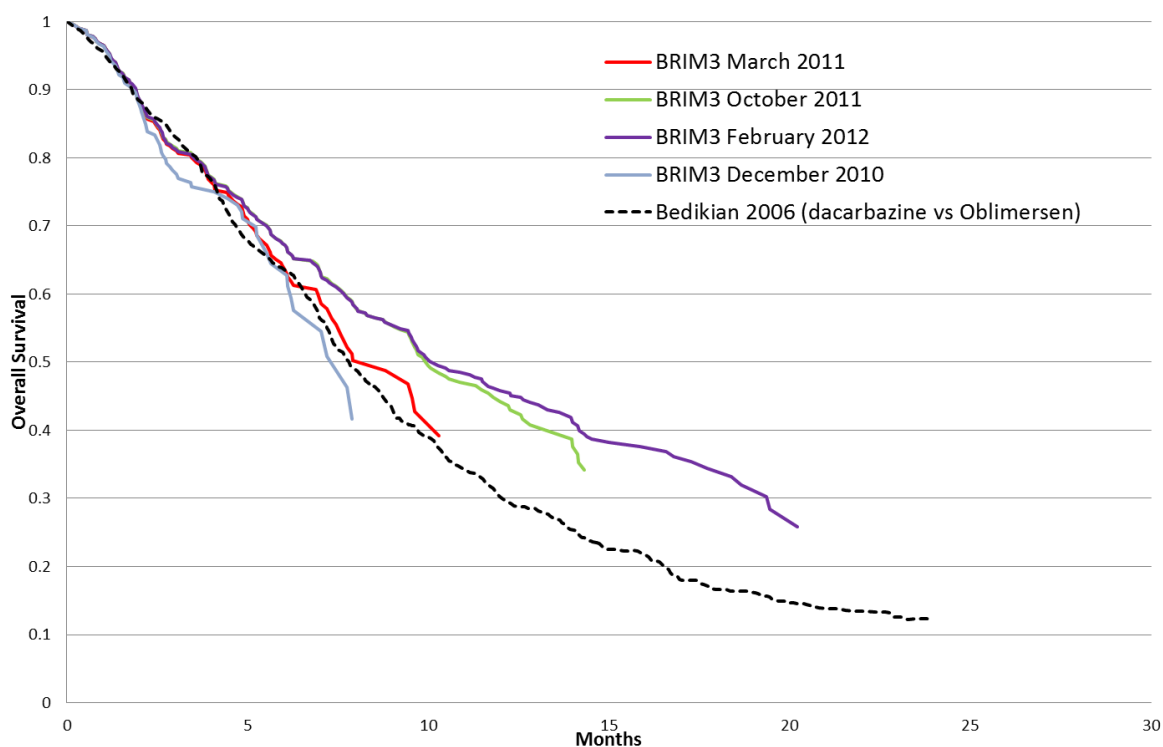


Figure 7. Later cuts of BRIM3 over-estimate efficacy of dacarbazine when compared to Robert 2011

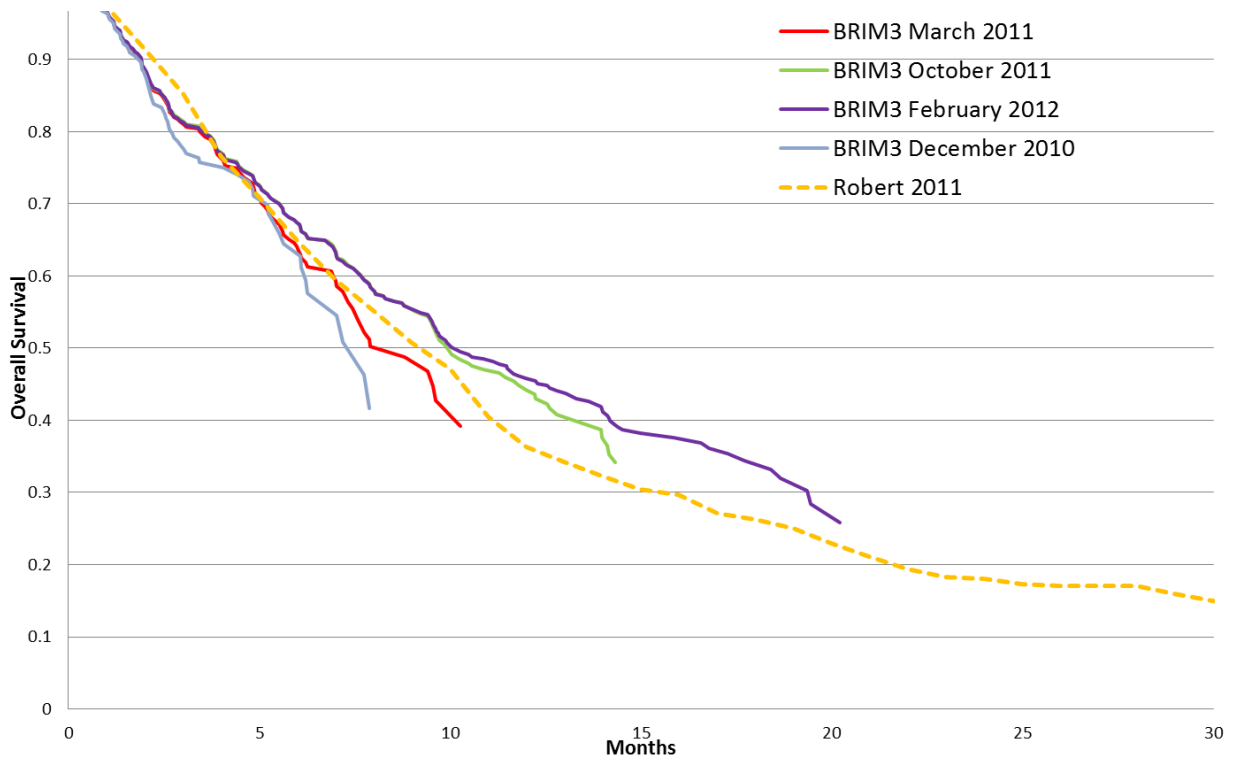


Figure 8. Later cuts of BRIM3 over-estimate efficacy of dacarbazine compared to Bedikian et al 2011 control arm – note the below represents a different RCT to the Bedikian 2006 plot above

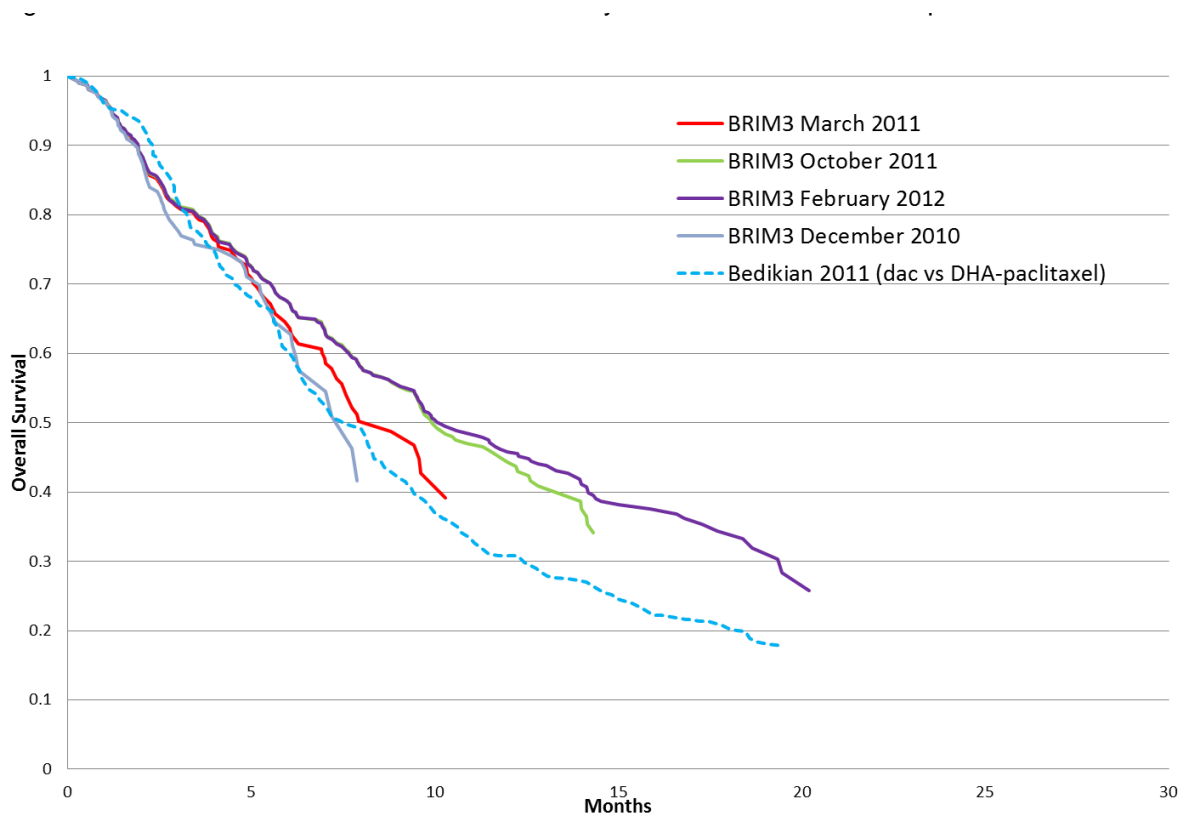


Figure 10. Later cuts of BRIM3 over-estimate efficacy of dacarbazine when compared to Patel 2011

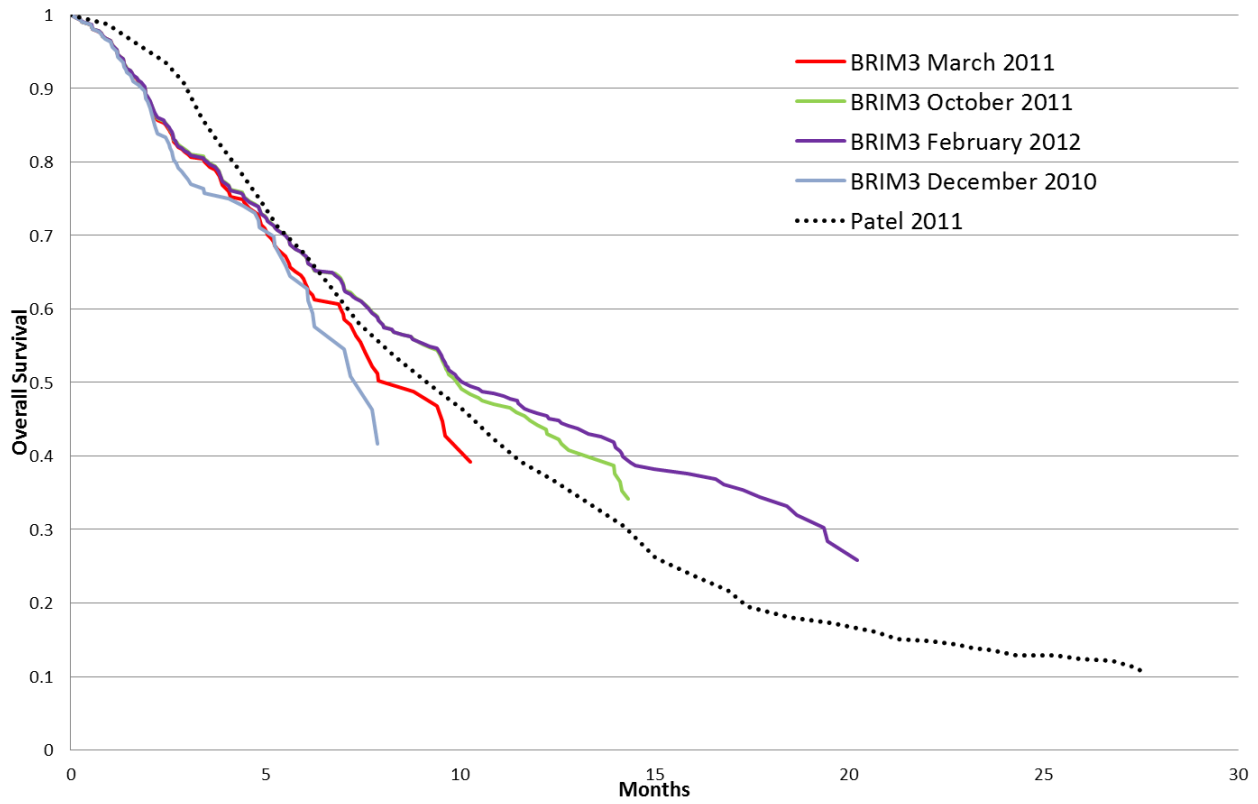
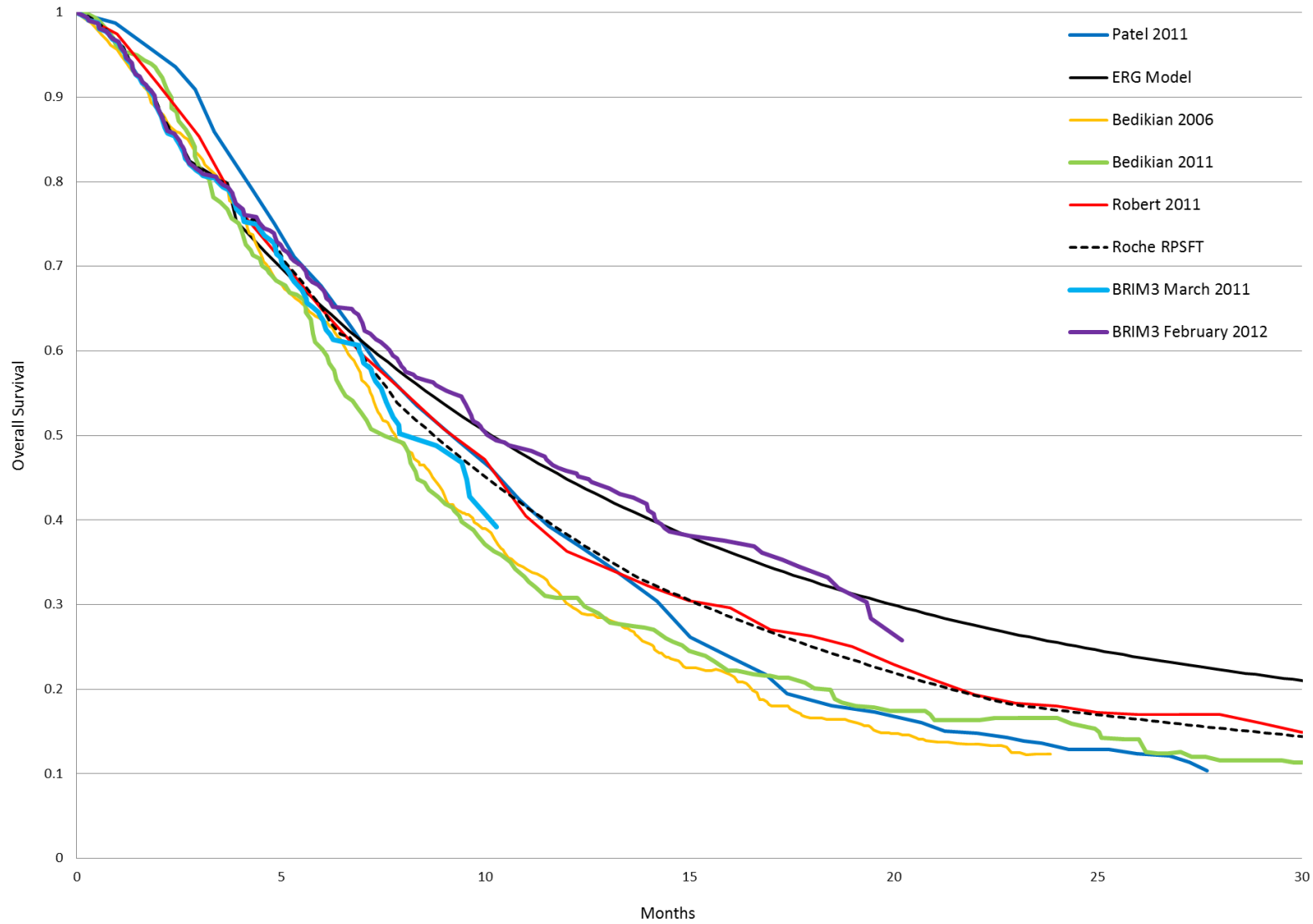


Figure 11. ERG model mirrors confounded February 2012 BRIM3 data well but lacks face validity compared to other data-sources in same disease area - Roche RPSFT adjusted model has stronger face validity compared to external data



When the ERGs modelling of survival with dacarbazine based upon the crossover confounded October 2012 data-set is compared to the external data available and Roche’s RPSFT adjusted model (shown in figure 11 above) it is clear that the ERG have substantially overestimated the efficacy of dacarbazine.

As the Roche RPSFT model appears to slightly overestimate the efficacy of dacarbazine relative to 3 of the 4 unconfounded studies identified (potentially because post-progression use of ipilimumab or BRAF inhibitors other than vemurafenib has not be controlled for by the RPSFT) the use of one of the poorer prognosis dacarbazine arms was tested in the model. Use of the Bedikian 2011 data as a control arm in the model resulted in the base-case ICER falling £45,003/QALY gained (provided as a scenario analysis in the revised model submitted – discussed further in Appendix 4).

2.5 Including the cost of crossover in an economic model using the October 2011 data

In the October 2011 data-set 30% of patients randomised to dacarbazine received post-progression treatment with a BRAF inhibitor for an average of 105 days. Similarly post-progression use of ipilimumab in this data-cut favoured the dacarbazine arm (19% of patients in the dacarbazine arm received ipilimumab compared to 13% in the vemurafenib arm).

Both Roche and the ERG’s models generated using this October data misattribute the benefit of these crossover treatments to dacarbazine without including the cost of these treatments to the NHS (i.e. the efficacy modelled is not consistent with the costs included in the model). If the cost of post-progression treatment with a BRAF inhibitor or ipilimumab is included in the model based upon the October 2011 data, and if the ERG amendments are incorporated, the estimated cost-effectiveness of vemurafenib improves significantly.

Figure 12. Adjustment of Committee preferred October 2011 Roche model taking into account ERG amends and cost of cross-over therapy

Scenario	Cost per QALY gained
Roche submitted ICER for October 2011 scenario analysis	£75,500
+ with ERG amendments to discounting, utilities and long term costs	£64,168
+ with cost of crossover treatments	£50,413

The method of including the cost of these crossover treatments is described further in Appendix 3.

3 Durable benefit, including a longer time from progression to death is plausible for a proportion of patients on vemurafenib

In Section 4.6 of the ACD the Committee notes that “there was considerable uncertainty about whether people who received vemurafenib would maintain significant long-term survival benefit over those who received dacarbazine”.

Given the contents of sections 1 and 2 above on the need to consider crossover in the BRIM3 study the question of the long-term survival benefit provided by vemurafenib becomes pivotal to the decision faced. If the Committee believe there is no long term benefit of vemurafenib and the survival curves come together at 4 years (as assumed by the ERG) vemurafenib is not cost-effective. If the Committee believes a small proportion of patients (around 4% at 5 years as assumed by Roche) experience prolonged benefit from vemurafenib then vemurafenib is cost-effective.

We believe that what is known of the pharmacology of vemurafenib supports its long-term benefits in a proportion of patients and we would ask the Committee to consider two arguments in support of sustained benefit, including prolonged time from progression to death:

- 1. Significance of tumour shrinkage prior to progression upon time from progression to death** – As “progression” in BRIM3 was defined by tumour growth relative to the previous assessment of tumour size and not a baseline measurement “progression” is not a consistent health state between the two arms of the study. If a patient experiences a response to treatment they will have a smaller tumour burden at the point of progression than a patient who has not and so will take longer to die after “progression” than those treated with dacarbazine. As vemurafenib is associated with a higher response rate than dacarbazine patients who progress on vemurafenib would be expected to take longer to die after progression than patients who progress on dacarbazine.
- 2. Late responses to vemurafenib** - A minority of patients have “late” responses to vemurafenib after many months of treatment. Such late responses are incompatible with the ERG’s belief that vemurafenib results in a short period of disease control before resistance sets in resulting in rapid progression to death. These late responses are unlikely to be a direct result of BRAF inhibition which is almost instantaneous on starting the drug and may be due to an immune response triggered by the impact of vemurafenib upon the tumour (Wiltong 2011). This immune response could result in sustained benefit for a proportion of patients.

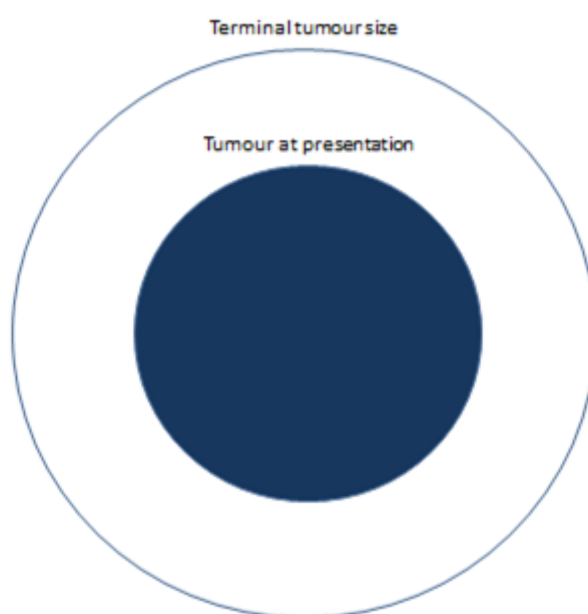
3.1 *The impact of response to treatment to tumour size upon 'progression'*

It is not necessary to suppose that vemurafenib has any effect on tumour cells or the host response after disease progression to anticipate that patients treated with vemurafenib will live longer between progression and death than those receiving dacarbazine first-line.

In simple terms, death from metastatic disease is associated with tumour burden – when the total tumour burden reaches a critical level the patient is overwhelmed by it and dies. Therefore, if both are progressing unchecked it is reasonable to expect a tumour that is currently large to kill a patient more quickly than one that is currently small – it will reach a lethal size first.

In a large randomised study like BRIM 3, it is further reasonable to assume that both dacarbazine and vemurafenib recipients had a similar average tumour burden at baseline and, if untreated, would progress to a terminal tumour bulk and die at the same rate:

Figure 13. Representation of the growth needed before a patient's tumour reaches a lethal burden/size



However, tumour progression after treatment in clinical trials is determined by growth relative to the last assessment of disease status rather than baseline tumour bulk. Using RECIST criteria progressive disease requires a 25% increase in tumour diameter. So, for a patient who has had a good response (high degree of tumour shrinkage) to treatment, progression will require only a small absolute increase in size on a much reduced baseline, so that immediately after progression their tumour is much smaller than it was at the start of therapy.

Figure 14. After a response to treatment tumour burden is lower than at presentation

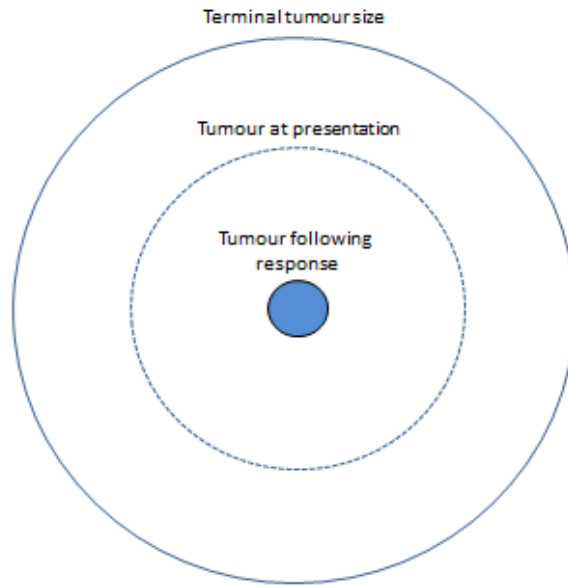
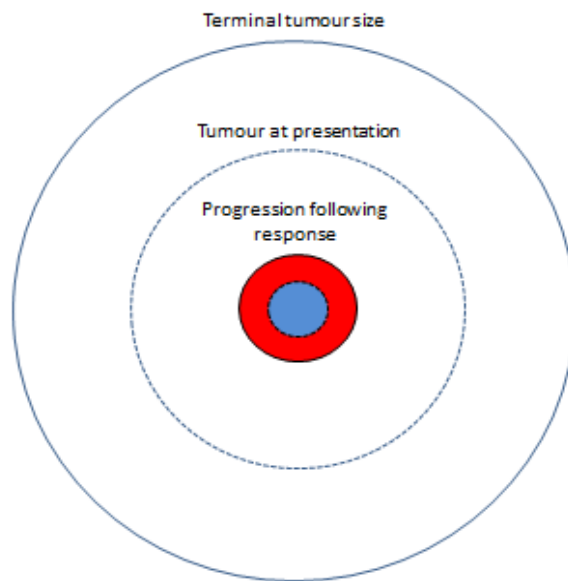


Figure 15. Immediately after progression a patient who had a good response still has a much lower tumour burden that at presentation and is further away from reaching a lethal tumour mass



By contrast a patient experiencing only disease stabilisation will have a tumour 25% bigger than it was at the start of therapy before they are deemed to have disease progression

Figure 16. A patient with disease stabilization remains as close to a lethal tumour bulk as they were at presentation

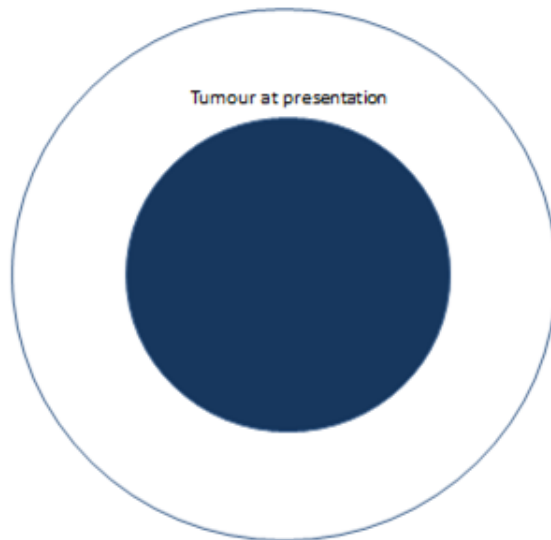
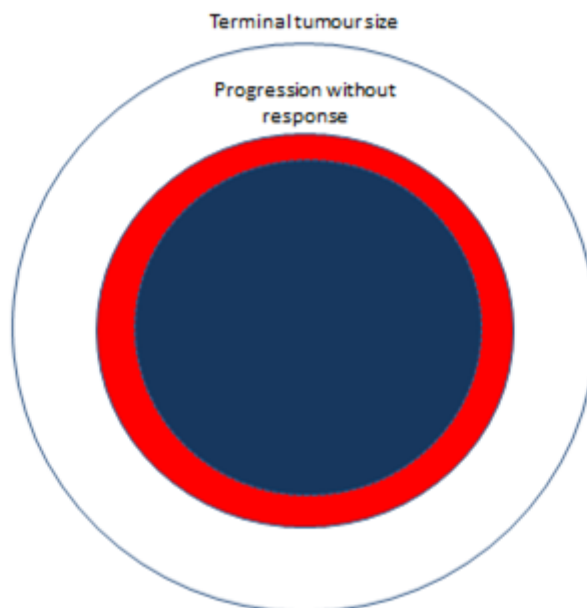


Figure 17. Patient with disease stabilization is closer to achieving a lethal tumour bulk than they were at presentation, as soon as they start to progress



Assuming that, regardless of pre-progression treatment, a patient's tumour will grow to a terminal bulk at the same rate once it reaches its baseline size, it is clear that patients with objective responses will take longer, post-progression, to reach terminal tumour size and succumb to their disease than those whose disease is only stabilised during treatment or progressed through therapy.

In BRIM 3 only 8.6% of dacarbazine recipients achieved tumour shrinkage sufficient to qualify as a partial response, whereas nearly all vemurafenib patients show some degree of tumour shrinkage, 57% achieve a Partial Response by RECIST and 5.6% a Complete Response (disappearance of all signs of tumour by the imaging technique used at baseline).

Therefore one would expect the average vemurafenib patient to have a much smaller tumour bulk at the point of disease progression than the average dacarbazine patient and to live longer from progression to death. For vemurafenib patients not to live longer post-progression one would have to postulate that the drug somehow speeds up tumour growth beyond that which would have occurred had it not been given once administration is terminated. To date, no evidence for such an effect has been presented, nor has any plausible hypothesis supporting it been proposed.

In summary, because vemurafenib recipients have a lower tumour burden at progression it is to be expected that they will have a longer post-progression survival with some conservation of treatment benefit post-progression. This is consistent with our survival modelling, which assumes 4.2% more patients are alive at 5 years after vemurafenib than dacarbazine, and contrasts with the approach of the ERG who assume death rates are higher patients who received vemurafenib over dacarbazine 1st line, thereby allowing no long-term residual benefit associated with the dramatic short-term responses to vemurafenib. We believe that greater magnitude of tumour shrinkage provides the "plausible rationale for expecting vemurafenib therapy to be associated with any better post-progression survival than dacarbazine" which the Appraisal Committee report as lacking in Section 4.9 of the ACD.

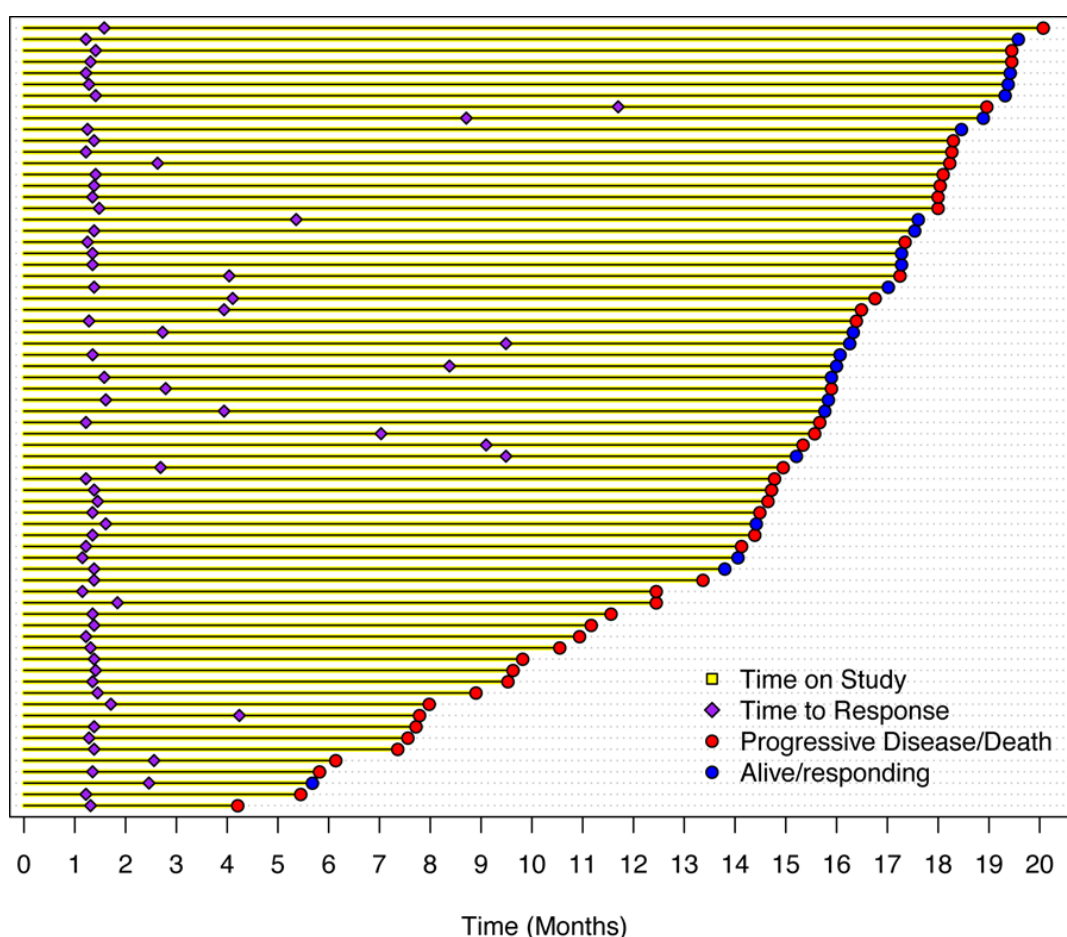
3.2 *Late responses to vemurafenib*

The ERG appears convinced that benefit from vemurafenib is short-lived. Their position is summarized in Section 3.21 of the ACD which states that ACD "vemurafenib is effective at suppressing disease progression leading to death in the early phase (that is, on average 97 days) but, after a short period, this effect ceases and patients revert to the pattern of mortality seen in the dacarbazine arm". This view underpins their decision to allow no long-term survival benefit from vemurafenib therapy which appears to be endorsed by the Appraisal Committee.

In fact, there is evidence that the pattern of response to vemurafenib is more complex than presented by the ERG and also that some responses are extremely durable:

1. The Progression-Free survival curve for BRIM 3 is flattening above the dacarbazine arm with time and more than one-quarter of patient are still progression-free at one year (see Figure 1)
2. The response rate and median progression-free survival for vemurafenib are still increasing at the most recent analysis – more than a year after the last patient was entered on to vemurafenib. This indicates that not only are some responses durable, but also that some are “late”, pointing to a more complex pattern of benefit than that relied upon by the ERG
3. Late responses are a characteristic of vemurafenib and were seen in BRIM 2, where some patients achieved an objective response many months after starting treatment (see Figure 18). Such responses cannot easily be attributed directly to BRAF inhibition – which occurs pretty much instantaneously on starting treatment- and suggests long-term modification of the disease process, again in contradiction to the ERG belief that vemurafenib benefit is a short-term one before inevitable resistance and progression.

Figure 18. Time to response and progression for responding patients receiving vemurafenib in the BRIM 2 Study (Sosman, 2012) showing some responses many months after starting vemurafenib



Having observed that there are “late responders” to vemurafenib it is pertinent to consider what may underpin these responses and what they may signify. The ERG note (as reported in Section 3.21 of the ACD) that there appear to be two distinct groups of patients with malignant melanoma – the majority, who die within the first year after diagnosis and a small group who can survive for 10 years or more.

It is unlikely that these long-term survivors are cured by the direct cytoreductive effect of any systemic therapy given early in their disease. More likely is that they have mounted an immune response to their tumour. Evidence for host immune responses in melanoma has been the basis of a long search for effective immune therapies in this disease (Begley and Ribas, 2008). For example, the drug interleukin 2 is believed to result in a small chance of long-term remission in the tiny group of patients fit enough and willing to tolerate its toxicity, though it is not used in this country, and ipilimumab has recently been introduced on the basis of its ability to reduce the risk of death by stimulating an immune response when administered as a second-line treatment.

An alternative approach to direct immune manipulation is enhancing the ability of the patient to mount their own immune response. This is more likely to occur if:

- Their tumour bulk is reduced increasing their general fitness and reducing the immunosuppressive effect of advanced cancer. During debulking tumour lysis occurs which presents large quantities of tumour antigen to stimulate the immune system
- The drug therapy used to debulk their tumour is not immunosuppressive in itself (in the way that conventional cytotoxic drugs are)
- Patients are kept alive long enough and in good enough health to mount an immune response

The idea that targeted therapies, like vemurafenib, could be used to indirectly improve the host immune response was proposed just before the first clinical data on vemurafenib emerged (Begley and Ribas, 2008). There is growing evidence that vemurafenib, as well as its direct effect on the tumour interacts beneficially with the host immune system.

For example, it has been shown that BRAF inhibitors increase the levels of certain melanoma cell proteins that are crucial for recognition of the tumour by the immune system (Boni et al. 2010); increase the infiltration of human melanomas by T-lymphocytes considered crucial for an effective immunological response (Wilmott et al, 2012) and improve the effectiveness of immunotherapy in a murine model of human melanoma (Koya et al, 2012).

These positive interactions between the immune system and BRAF inhibition may explain why, although most patients who have a response to vemurafenib do so within a few days, consistent

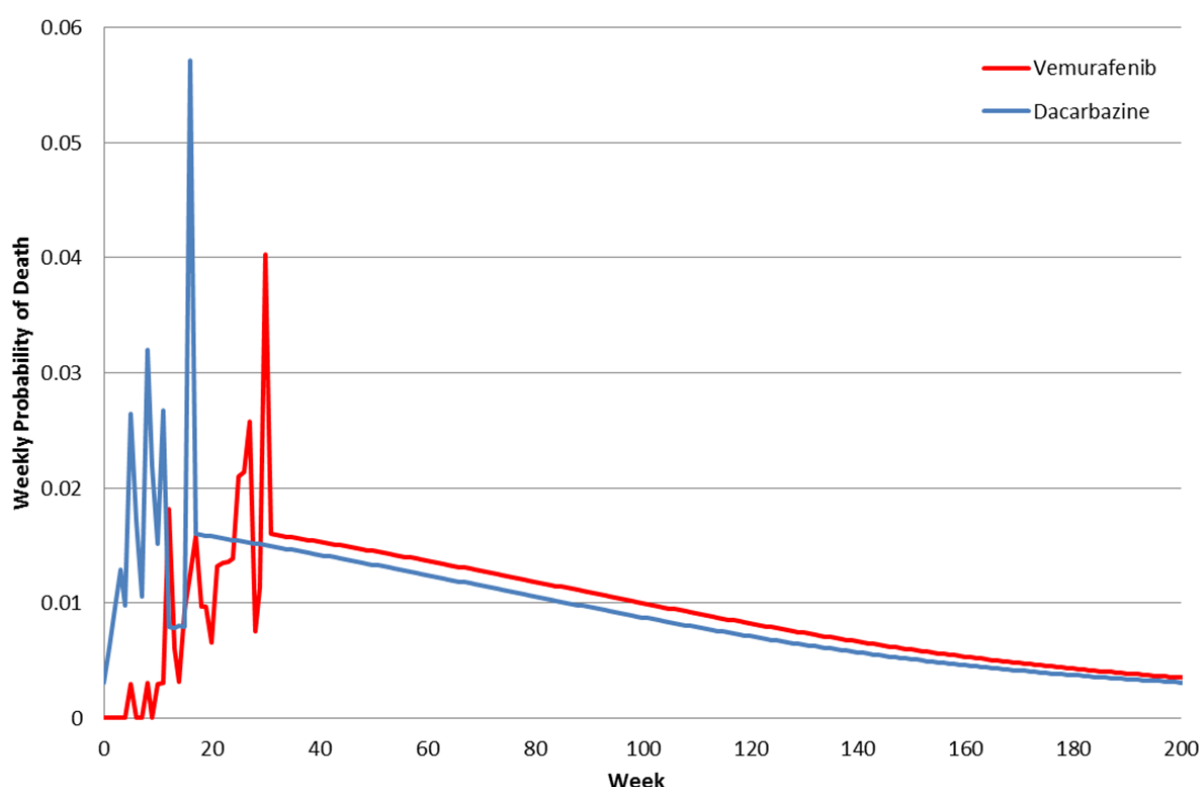
with the almost instantaneous switching off of their mutant BRAF, a significant minority only do so after a prolonged period of disease stabilisation (Figure 18).

If late responses are immune facilitated one might expect them to be particularly durable in a proportion of patients.

4 The ERGs modeling of Overall Survival for patients randomized to vemurafenib

The ERG's modelling of Overall Survival assumes that patients randomised to vemurafenib will die more quickly than patients randomised to dacarbazine from week 30 onwards (See Figure 19 below).

Figure 19. Weekly probabilities of death by arm in ERG model



This is a point in time in which 47% of patients randomised to vemurafenib are still receiving treatment (February 2012 data-cut).

We do not believe the Committee have considered this evidence when determining that the ERG's modelling of Overall Survival is "equally plausible" to the Roche model in which an equal rate of death is assumed beyond the period of the BRIM3 study.

Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

As noted above the current summaries of clinical and cost-effectiveness omit a range of new evidence available. As a result we believe the current summaries are incomplete.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We believe the Committee's current conclusion is based upon the use of confounded data without appropriate consideration of crossover and the extremely pessimistic assumption that patients given vemurafenib die more quickly than patients given dacarbazine whilst 47% of patients are still receiving vemurafenib. We therefore have concerns about the decision reached in the ACD and believe it not to be a sound and suitable basis for guidance to the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not that we are aware of.

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- NICE TA179: Sunitinib for the treatment of gastrointestinal stromal tumours <http://guidance.nice.org.uk/TA179> (last accessed on 06/07/2012)

NICE TA215: Pazopanib for the first line treatment of metastatic renal cell carcinoma

<http://guidance.nice.org.uk/TA215> (last accessed on 06/07/2012)

NICE TA219: Everolimus for the second-line treatment of advanced renal cell carcinoma

<http://guidance.nice.org.uk/TA219> (last accessed on 06/07/2012)

NICE TA257: Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2

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Appendix 1 – Updated cost-effectiveness model

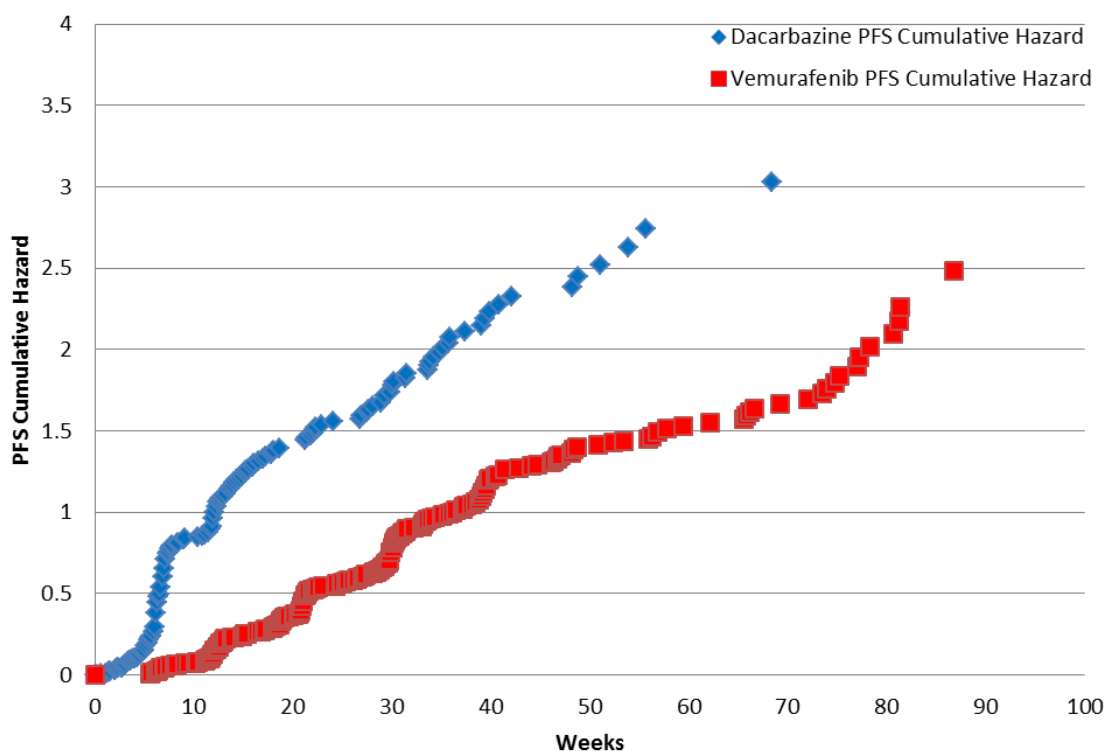
As detailed within section 1.4 of our ACD response, due to the availability of new data from BRIM3 the economic model provided within our submission has been updated. This updated model features the changes to discounting and utilities/costs with ‘long-term’ survivors suggested by the ERG, updated response rates (linked to the utility values) and updated PFS and OS curves based on the new February 2012 data-cut. All other aspects of the model (dosing, adverse events etc) remain as described in our submission.

The extrapolation of PFS and OS are detailed below.

Extrapolation of progression free survival

As the progression free survival data from BRIM3 was not complete it was necessary to extrapolate the data observed beyond the period of the study. In order to determine the most appropriate method of extrapolating the data observed, PFS cumulative hazard plots were produced and assessed.

Figure 20. February 2012 BRIM3 Cumulative Hazard Plot demonstrates treatment effect beyond 97 days (i.e. curves continue to diverge)



Contrary to the opinion expressed by the ERG in the ERG report these cumulative hazard plots demonstrate that the effectiveness of vemurafenib is not limited to the first 97 days of treatment.

There is clearly further separation of the two plots far beyond 97 days (particularly from week 40 onwards).

In order to extrapolate this PFS data it was hypothesised that the constant dacarbazine PFS hazard observed from week 14 onwards would be maintained beyond the period of BRIM3 whilst the constant vemurafenib PFS hazard observed from week 40 onwards to week 75 (with the volatility observed in the tail of this curve due to low patient numbers).

Figure 21. 2012 Defining the PFS hazard for extrapolation beyond the period of BRIM3

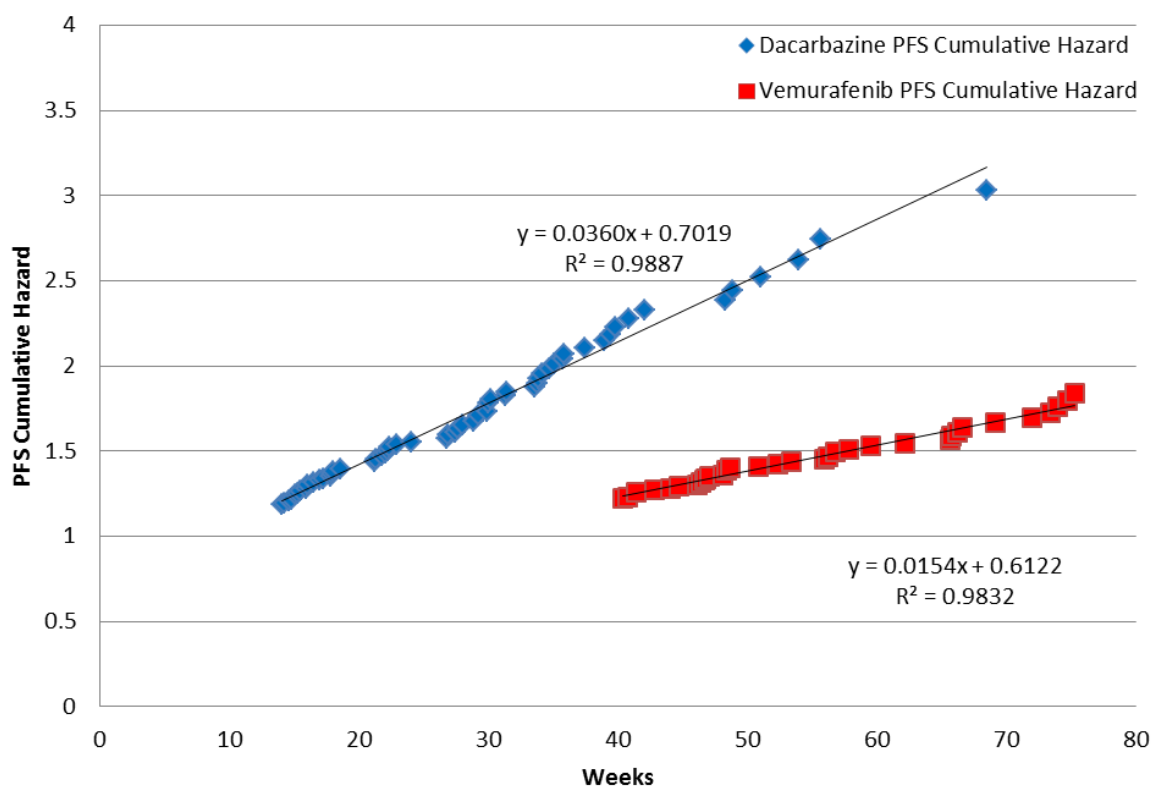
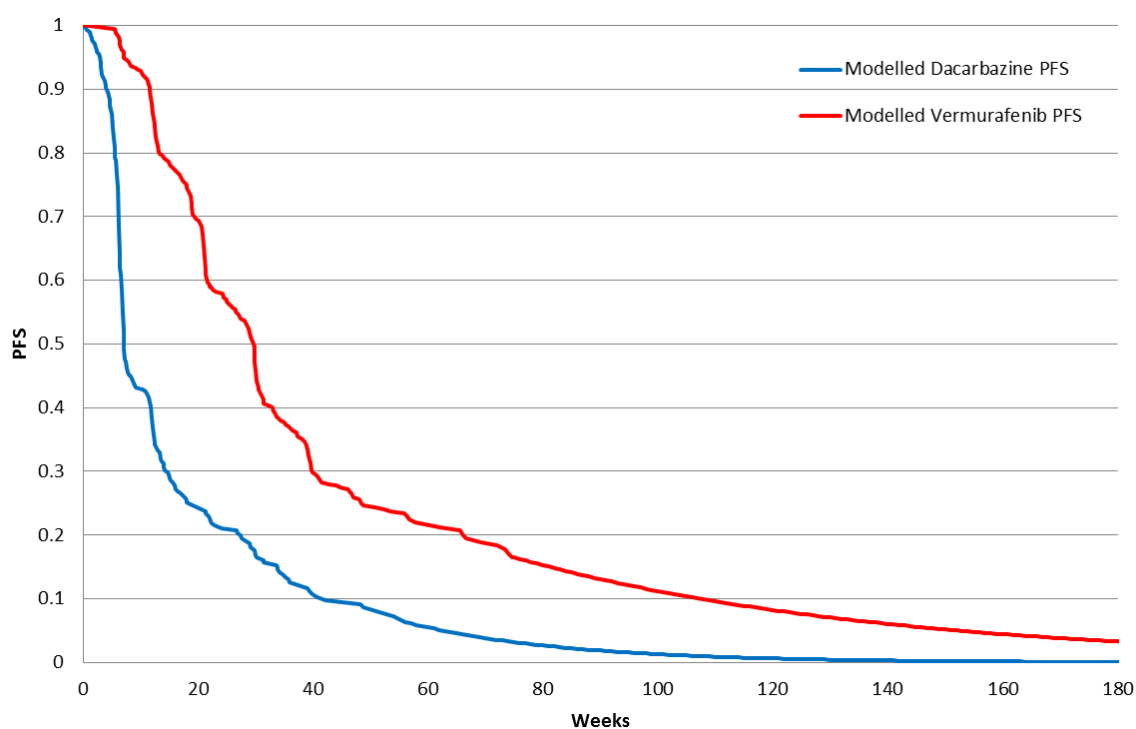


Figure 2 above demonstrates the linear functions fitted to each of these hazard phases - note the R^2 values estimated for each of these functions was extremely high. It should be noted that the ratio of these two slopes (around 0.43) is far below 1 (indicating that vemurafenib produces continued benefit when compared to dacarbazine).

These functions were then utilised to extrapolate the 'tails' of the PFS data observed. In the vemurafenib arm the observed data was used up until week 75 (the point at which the hazard function became erratic) whilst in the dacarbazine arm the observed data was used up until week 56 (when the data is nearly complete).

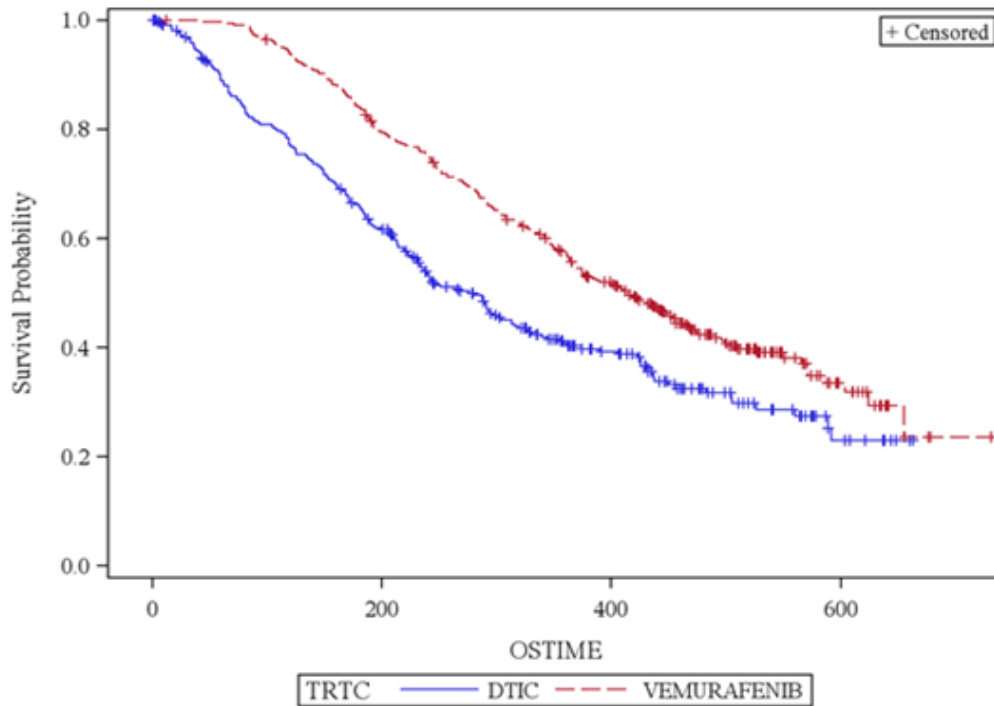
Figure 22. PFS curves modelled utilising approach detailed above



Extrapolation of overall survival

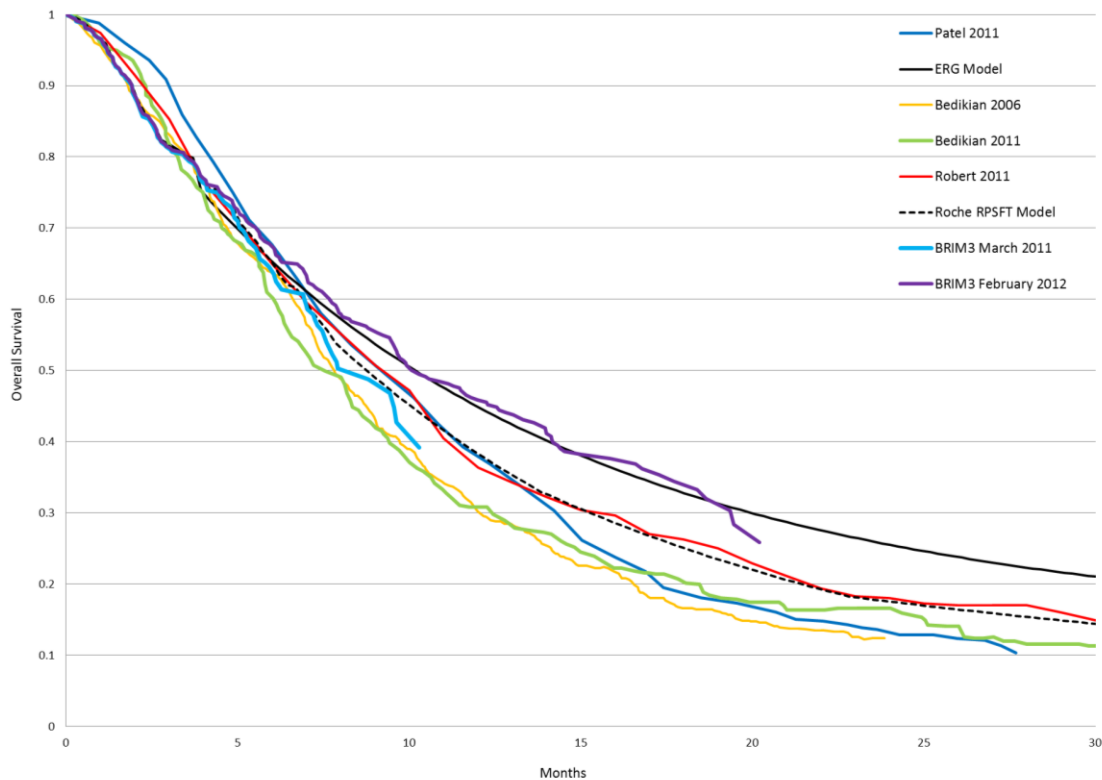
As noted in section 1.3 of our ACD response, the February 2012 data-cut of the BRIM3 study was heavily confounded by crossover. In order to adjust for crossover to vemurafenib a rank preserving structural failure time (RPSFT) model was utilised. The OS curves produced using the RPSFT approach are shown in Figure 4 below.

Figure 23. RPSFT Adjusted BRIM3 data



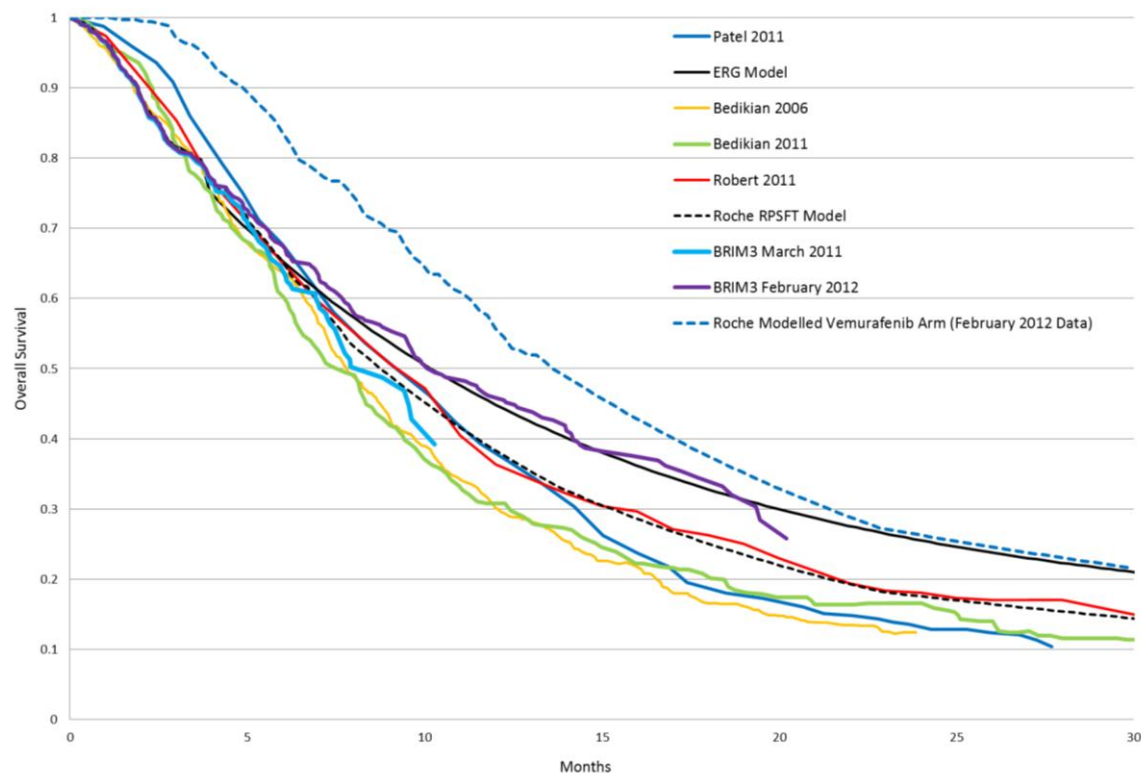
Due to the heavy censoring in the dacarbazine arm from around day 240 onwards (and an associated volatile shift in the survival curve observed) the RPSFT adjusted KM data was utilised only up to this point in time. From month 8 to month 14 the constant hazard observed in these first 8 months was then extrapolated and extrapolated over the full time horizon as used in Roche’s submission (use of the Robert 2011 study and data from the SEER registry).

Figure 24. Strong external validity of Roche modelling of dacarbazine using RPSFT adjusted February 2012 data



As the vemurafenib arm was not subject to the heavy censoring around month 10 seen in the dacarbazine arm data from the February 2012 cut-off was utilized directly in the model up to month 14. Beyond this point in time it was assumed that patients in both arms would die at the same rate.

Figure 25. Roche modelling of Vemurafenib overall survival compared to dacarbazine



Cost effectiveness results

Table 5: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) vs baseline (QALYs)
Dacarbazine	██████	██████	██████				
Vemurafenib	██████	██████	██████	██████	██████	██████	£52,327

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 6: Summary of QALY gain by health state

Health state	QALY (vemurafenib)	QALY (dacarbazine)	Increment	Absolute increment	% absolute increment
PFS	■	■	■	■	■
PD	■	■	■	■	■
Total	■	■	■	■	■

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Appendix 2 – Review of recent evidence on the efficacy of dacarbazine

A literature review was undertaken in order to identify recent evidence on the efficacy of dacarbazine monotherapy in the treatment of advanced melanoma. For the purpose of providing a focused review in the time frame available it was assumed that studies published after 2005 would provide outcomes most relevant to current UK practice.

Proquest Datastar was utilised to search MEDLINE and EMBASE. The search was conducted on 04/07/2011.

The search strategy utilised was as follows:

((Advanced OR Metastatic) AND Melanoma) AND Dacarbazine AND (Randomised OR Randomized OR RCT)

Results were then limited to records published since 01/01/2005 and those marked as 'Randomised Controlled Trials' within the databases concerned.

This search identified 30 potentially relevant records that were then assessed against the predefined inclusion/exclusion criteria.

Figure 26. Inclusion/exclusion criteria

Inclusion criteria	Dacarbazine monotherapy, Advanced/metastatic melanoma, previously untreated patients
Exclusion criteria	No dacarbazine monotherapy arm (i.e. dacarbazine combination therapy, experimental treatments), adjuvant melanoma, previously treated patient, publication of BRIM3

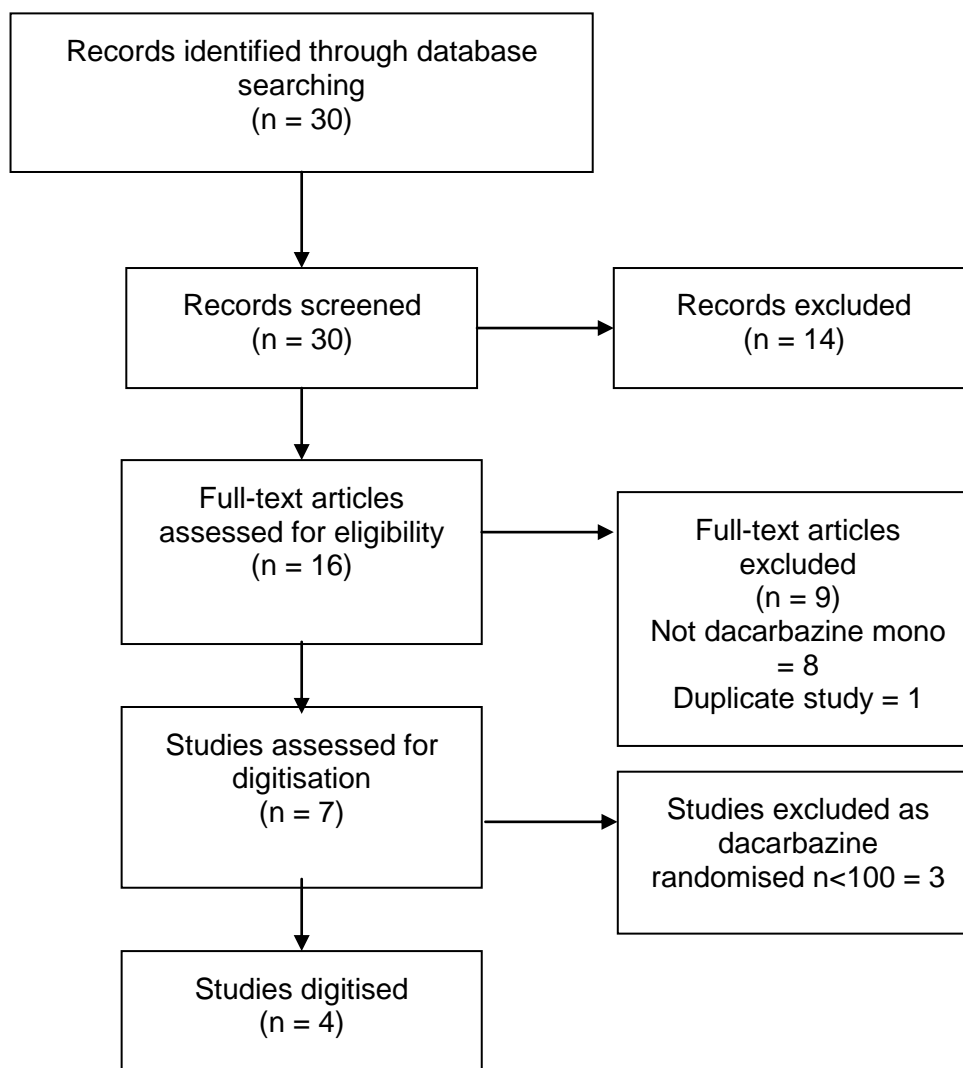
In total 7 RCTs that met the inclusion/exclusion criteria: Robert 2011, Patel 2011, Bedikian 2011, Kefford 2010, McDermott 2008, Bedikian 2006 and Schadendorf 2006.

The dacarbazine overall survival curves of those studies featuring more than 100 patients randomised to dacarbazine (i.e. not Kefford 2010 (n=44), McDermott 2008 (n=50) or Schdendorf 2006 (n=53)) were then digitised using TechDIG.

The curves for these smaller studies were not digitised as it was felt that due to the small size of the studies concerned KM data from these studies would provide unreliable evidence on the expected efficacy of dacarbazine in the period of interest (i.e. particularly after month 5 where the dacarbazine arms of the four BRIM3 data-cuts begin to diverge).

The conduct of the search is detailed in the PRISMA figure below.

Figure 27. PRISMA Flow of search undertaken



The comparator arms of the four digitised studies (Patel 2011 (n=430), Robert 2011 (n=252), Bedikian 2011 (n=199), Bedikian 2006 (n=385)) were then compared to the observed evidence from BRIM3 over the four data-cuts, the ERGs modelling and Roche’s modelling of the RPSFT adjusted February 2012 data in order to assess the external validity of each of the modelling approaches taken (described in section 2.4 of the response).

Appendix 3 – Including the cost of crossover treatments

The cost of crossover treatments was implemented in the model as follows:

- The proportion of patients crossing over to a BRAF inhibitor or ipilimumab was recorded
- The average treatment duration was estimated
- For post-progression BRAF inhibitors the proportion of patients crossing over to receive a BRAF inhibitor was multiplied by the expected cost of vemurafenib for a patient treated for that period of time (as estimated within the model) in order to derive the expected cost of post-progression BRAF inhibitors.
- For post-progression use of ipilimumab the average number of doses observed was rounded up to the nearest dose and multiplied by the cost of ipilimumab at the 3 mg/kg regimen it is currently licensed at.

This resulted in an incremental cost of post-progression treatments of £6,468 for patients randomised to dacarbazine in the October data-cut.

Appendix 4 – Utilising an alternative unconfounded dacarbazine arm

As all data-cuts utilised in modelling are confounded by crossover all cost-effectiveness derived using this data are over-estimates of the true ICER of vemurafenib in this indication. In order to simulate what the true ICER of vemurafenib may be a sensitivity analysis was conducted in which the dacarbazine arm from a recent study known not to be confounded by crossover (Bedikian 2011) was utilised as the dacarbazine arm within the model.

This approach resulted in a cost per QALY of £45,003.

The face validity of this modelling approach is shown in **Figure 9** below.

Figure 28. Sensitivity analysis using Bedikian data simulates true cost-effectiveness of vemurafenib by generating a comparator arm representative of that expected in UK clinical practice

