STA Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma

Addendum for 3rd AC meeting

18 September. 2012

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1 SUMMARY OF KEY POINTS

- Following the 2nd Appraisal Committee meeting the manufacturer was asked by the Committee to provide further clarification and analysis.
- Two of the three key assumptions underlying the RPSFT method are not valid. The extent to which RPFST results under- or over-estimate the effect of vemurafenib is unclear.
- Other methods used to compensate for the impact of crossover also have limitations.
- The manufacturer carried out the scenario analysis requested by the Committee but chose not to present the requested cost-effectiveness results, sensitivity analysis and revised model.
- The ERG therefore carried out the scenario analysis requested by the Committee and found that it resulted in an ICER of £120,933 per QALY gained.

2 HISTORICAL CONTEXT

Vemurafenib for the treatment of BRAF V600 mutation positive metastatic melanoma was first considered by the NICE appraisal committee on 14 May 2012. The release of the Appraisal Consultation Document (ACD) on 15 June, 2012 prompted the manufacturer to submit additional data for consideration at the 2nd Appraisal Committee (AC) meeting held on 18 July, 2012. Discussions at the 2nd Appraisal Committee meeting led to the Committee seeking clarification from the manufacturer on a number of points, namely:

- 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. A discussion of the plausibility of using alternative approaches to adjust for switching in the BRIM3 study population, or the use of data from other trials to represent the clinical effectiveness of dacarbazine should also be provided.
- An additional scenario analysis for vemurafenib compared with dacarbazine, estimated by separately applying exponential hazards to each arm of the BRIM3 study (using the February 2012 data cut-off) from 14 months.
- For the above scenario analysis:
    - information that would allow sufficient critique of the model and its parameters should be provided, including details of how censoring was incorporated into the progression-free survival, post-progression survival and overall survival analyses
    - probabilistic sensitivity analyses should be provided
    - incremental costs and QALYs gained should be reported
    - a revised fully executable economic model should be provided that clearly includes the above revisions.

Additionally, the manufacturer was presented with a detailed list of further errors in the economic model that had been identified by the ERG. Six areas of concern were described (five errors and one of an over-elaborate costing method). Three of these lead to increases and three to decreases in the estimated ICER (as detailed in Table 4). The net effect of implementing these amendments is a small reduction in the manufacturer's baseline ICER from £52,327 to £51,764 per QALY gained. The manufacturer has accepted the alterations identified by the ERG.

This report summarises the ERG's response to the report submitted by the manufacturer in answer to the Committee's request for clarification.

3 CLARIFICATION ISSUES

3.1 RPSFT method

Committee request: 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 ERG welcomes the clear explanation provided by the manufacturer which details the rationale behind the RPSFT method, advice on how to interpret the acceleration factor and a description of how the acceleration factor is calculated. The manufacturer has also provided details about the key assumptions underpinning the RPSFT method and their validity in BRIM3.[3] These assumptions, along with ERG comments are presented in Table 1.

Table 1: Summary of RPSFT assumptions and their validity in BRIM3

Assumption	Key points identified by the manufacturer	ERG comment
Assumption 1.1: The acceleration factor is time invariant	a) Evidence from BRIM3 suggests that the effect of vemurafenib on mortality is highest for the first few months of treatment and then declines over time. This implies that RPSFT estimate is biased, but it is unclear by how much and in which direction as there are competing biases involved. b) Underadjustment is likely at later time points. RPSFT estimate is unreliable beyond 8 months, (evidenced by apparent 'kink' in adjusted survival curve) and should not be used for modelling survival.	a) The ERG agrees with the manufacturer that Assumption 1.1 is invalid for BRIM3 data. b) The ERG rejects the manufacturer's argument against use of RPSFT corrected results for projective modelling beyond 8 months, since the claimed 'kink' in the survival curve is also present in the unadjusted curve and is therefore attributable to random effects, not to underadjustment.
Assumption 1.2: The acceleration factor derived for the intervention is valid for both the randomised and comparator arms	The two key determinants of whether this would hold in a study are: a) The treatment is as effective second line as it is first line b) There are no differences between the randomised and crossover groups that would be expected to result in differential levels of treatment effect.	a) There is no Phase III trial evidence in this patient group to support this assumption. A randomised sequential trial would be required to clarify this issue b) Study of BRIM3 data shows that patients who crossed over to receive vemurafenib were, on average, a slightly better prognosis group than those originally randomised to it. Also, there is no evidence to allow us to determine the extent to which the identified prognostic factors predict efficacy in terms of survival.
Assumption 2: The assumptions underlying the hypothesis test utilised in order to derive the acceleration factor are valid	The acceleration factor was originally derived using a Log-Rank model. This approach relies on the assumption of proportional hazards (an assumption that is clearly invalid in the BRIM3 data). However, repeating the derivation of the acceleration factor using a Wilcoxon test produces an acceleration factor that is equivalent to that produced by the Log-Rank test.	The statistical test used in the derivation of the acceleration factor appears to have little effect on the magnitude of the result for BRIM 3[3] trial data.

The manufacturer's summary of the issues concerning RPSFT recognises that there are various problems associated with it, but goes on to conclude that the RPSFT analysis undertaken underestimates the benefit of vemurafenib. The ERG considers this inference to be inappropriate as there is clearly considerable uncertainty as competing potential biases are present which cannot be reliably quantified. There is a clear violation of the assumption of time invariance (and any analysis based on the assumption of proportional hazards), and therefore the ERG considered that the RPSFT results presented should be viewed with caution.

3.2 Plausibility of using other methods to adjust for crossover

Committee request: A discussion of the plausibility of using alternative approaches to adjust for switching in the BRIM3 study population, or the use of data from other trials to represent the clinical effectiveness of dacarbazine should also be provided.

The manufacturer has provided a description of four alternative methods of adjusting for crossover and a discussion of the plausibility of each in conjunction with BRIM3 trial data. An overview of each approach and details of its key limitations as outlined in the manufacturer's response is included in Table 2.

Table 2 Overview of approach and key limitations of four different methods to adjust clinical trial results for the impact of crossover

Method	Overview of approach	Key limitations
Censoring patients at the point of crossover	Patients are censored at the time of crossover	Violates trial randomisation; High potential for selection bias.
Branson and Whitehead method	Approach takes the same form as the RPSFT method and is subject to many of the same assumptions. However, whilst the RPFST method derives the acceleration factor iteratively using a non-parametric function, the Branson and Whitehead method assumes a parametric survival method in carrying out the adjustment of data.	Relies on many of the same assumptions as the RPSFT method as well as the additional assumption that survival times fit a parametric function.
Inverse Probability Censoring Weighting (IPCW)	Patients are censored at the time of crossover and a weighted analysis is applied in which the event times of patients who did not crossover but who had similar characteristics to those patients who did crossover are given a higher weighting.	Highly subjective – all relevant patient characteristics must be pre-specified by the analyst and it must be assumed that these covariates capture all variability in expected event times
Use of external data	Involves use of control arms from other clinical trials which are not subject to crossover. For this method to be unbiased it is important that those patients in the study used as a proxy are similar to those in the study impacted by crossover.	Often reporting of prognostic factors is inconsistent between studies making use of these data problematic.

3.3 Requested scenario analysis

Committee request: An analysis of vemurafenib compared with dacarbazine, estimated by separately applying exponential hazards to each arm of the BRIM3 study (using the February 2012 data cut-off) from 14 months.

The manufacturer carried out the analysis but chose not to present their results. The manufacturer explained that their view is that the extrapolation was inappropriate. Their reasons, as well as ERG comments, are summarised in Table 3.

Table 3 Manufacturer's reasons for not presenting cost-effectiveness results from the scenario detailed by the Appraisal Committee

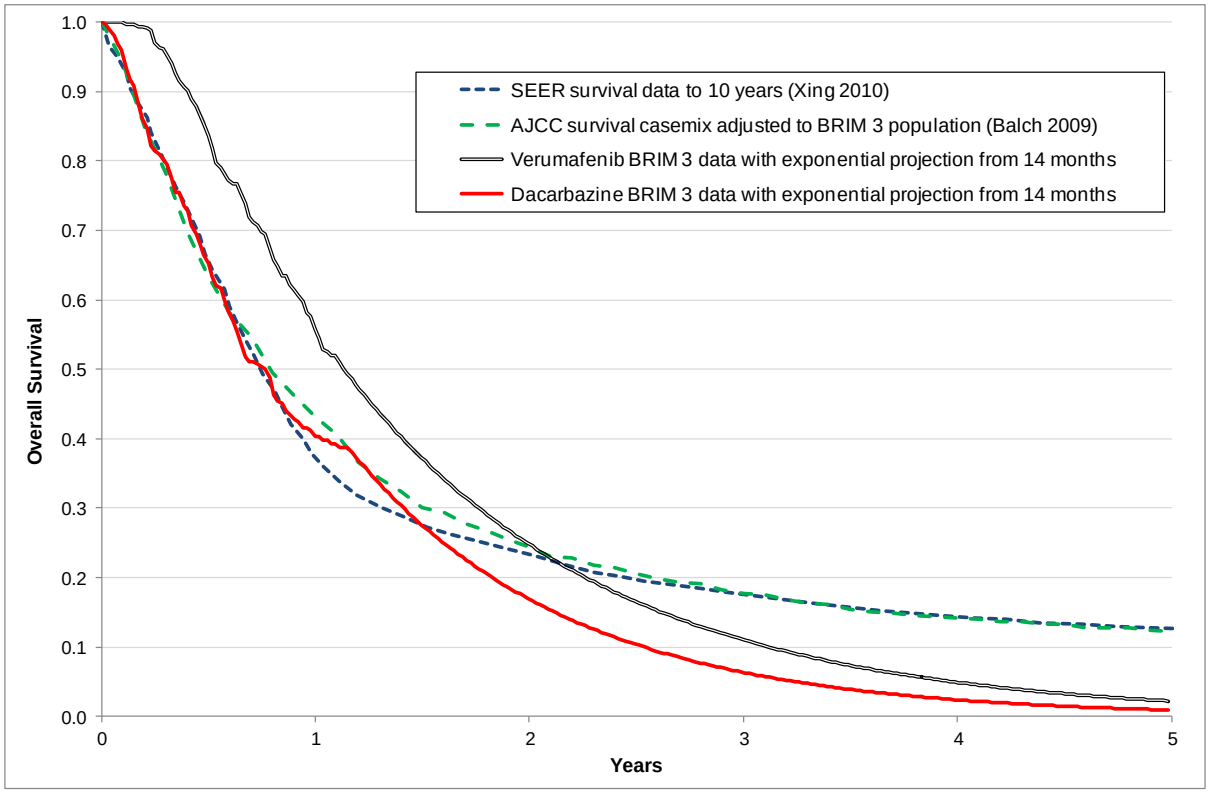
	Manufacturer's reason	ERG's comment
1	The analysis suggests that post-progression survival following treatment with vemurafenib is 2.2 months shorter than post-progression survival following dacarbazine. This appears implausible	The ERG disagrees with the manufacturer's view of implausibility. Vemurafenib may provide only a temporary inhibition to the normal process of disease progression, as indicated by analysis presented in the ERG report. As the two trial arms converge over time this inevitably means that average post-progression survival will be reduced prior to convergence. The apparent loss of post-progression duration of life may be partly a reflection of the influence of improved quality of life and reduced clinical symptoms on the determination of the time of progression. Whereas OS is an unequivocal outcome, both PFS and Post Progression Survival must be considered 'softer' measures both dependent on the manner of determining when progression has occurred.
2	Registry and trial data suggest that the probability of death associated with melanoma reduces over time. An exponential model assumes a constant probability of death over time and as a result an exponential modelling approach has poor external validity.	The ERG agrees with the manufacturer's view. Comparison with AJCC and SEER registry data indicates that survival is markedly greater at 5 years than is shown by the exponential projection in Figure 5 of the manufacturers response to the ACD (1-2% vs 12% in Figure 1 below).
3	Due to a belief that RPSFT under-accelerates the dacarbazine arm when crossover to vemurafenib is at its earliest stage the dacarbazine arm should not be used for modelling after month 8.	This assertion is based on the subjective judgement of a 'kink' in the RPSFT adjusted data at 8 months. As commented above (Table 1), there is no justification for such a restriction as this feature is also evident in the unadjusted data and is therefore not an artefact of the RPSFT process (as illustrated in Figure 2 below)

In addition, the manufacturer did not provide (as requested by the committee):

- information that would allow sufficient critique of the model and its parameter, including details of how censoring was incorporated into the progression-free survival, post-progression survival and overall survival analyses
- probabilistic sensitivity analyses
- incremental costs and QALYs gained
- a revised fully executable economic model that clearly includes the above revisions.

The ERG has carried out an analysis in line with the committee's request, using exponential trends as shown in Figure 5 of the manufacturer's response to the second ACD. This has resulted in estimated mean incremental costs of [redacted] per patient, and incremental QALYs of [redacted] per patient, leading to a revised ICER of £120,933 per QALY gained.

Figure 1 BRIM 3[3] survival data with exponential projection from 14 months compared with SEER[1] and AJCC[2] malignant melanoma survival analyses



Note: Dacabazine data RPSFT adjusted

Table 4 Cost-effectiveness results incorporating corrections and amendments identified by the ERG in the revised manufacturer's model (all figures discounted)

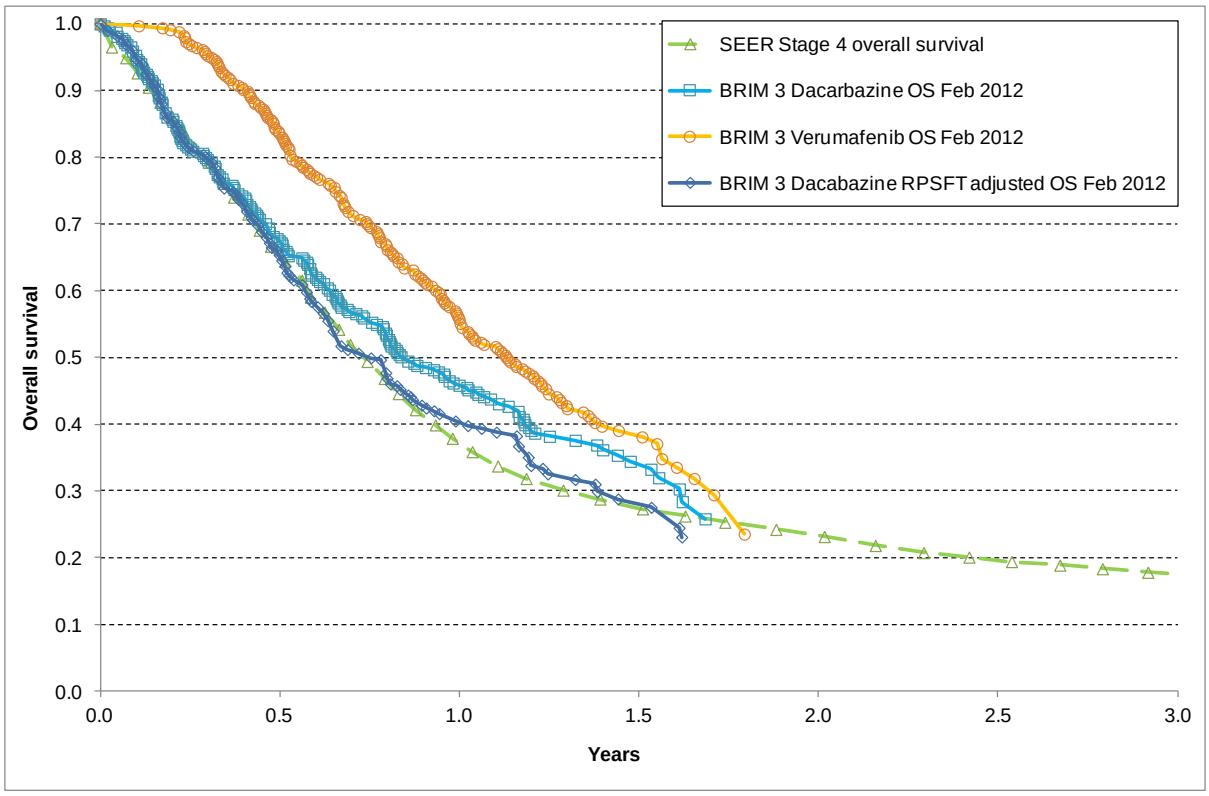
	Dacarbazine			Vemurafenib			Incremental			ICER
	Cost per patient	Life years per patient	QALYs per patient	Cost per patient	Life years per patient	QALYs per patient	Cost per patient	Life years per patient	QALYs per patient	Cost per QALY gained
Manufacturer's revised base case analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£52,327**
Half-cycle formula errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,766
Omitted OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,465
Double-counted BRAF test costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,088
Double discounting of terminal costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,199
ERG estimate of vemurafenib costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,553
Errors estimating progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,328
Revised base case analysis with all ERG corrections and changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£51,764**

4 CONCLUDING REMARKS

There is no doubt in the minds of clinicians and patients alike that treatment with vemurafenib is beneficial in terms of PFS. The important issue is therefore related to the extent of overall survival benefit of vemurafenib treatment.

Figure 2 compares the most recent OS data available from the BRIM 3 clinical trial with the RPSFT adjusted dacarbazine trial arm and the published long-term survival trend for Stage IV malignant melanoma from the SEER registry.[2] This allows consideration of the demonstrated survival benefit prior to the application of any projective modelling. Any method adopted for projecting survival trends beyond 18 months should show close correspondence with these trial data, and be supported by credible justification for differences from the epidemiological evidence.

Figure 2 BRIM 3[3] February 2012 and SEER[1] Stage 4 overall survival trends



5 REFERENCES

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2. Balch C, Gershenwald J, Soong S, Thompson J, Atkins M, Byrd D, *et al.* Final version of 2009 AJCC melanoma staging and classification. Journal of Clinical Oncology. 2009; 27:6199-206.
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