STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Dabrafenib for treating unresectable, advanced or metastatic BRAF^{v600} mutation-positive melanoma [ID605

Replacement pages – changes highlighted in green

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1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE from GlaxoSmithKline in support of the use of dabrafenib (Tafinlar) for the treatment of advanced or metastatic $BRAF^{V600}$ mutation-positive melanoma. In Europe, dabrafenib is licensed 'for the treatment of adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation.'

1.2 Critique of the decision problem in the manufacturer's submission

The patient population and intervention addressed in the manufacturer's submission (MS) broadly reflects that in the NICE scope and for whom dabrafenib is licenced. However, the ERG notes that relevant comparative evidence only exists for treatment naïve patients and hence the manufacturer presents clinical and cost effectiveness evidence to support the use of dabrafenib for treatment-naïve patients with $BRAF^{v600}$ mutation-positive melanoma. Vemurafenib and dacarbazine are appropriate comparators to dabrafenib, being the current standard of care and previous standard of care, respectively. Outcomes addressed in the decision problem include overall survival (OS), progression-free survival (PFS), overall response rates (ORRs), adverse events (AEs) and health-related quality of life (HRQoL). These outcomes are standard in this disease area and are appropriate.

1.3 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer presents direct and indirect clinical effectiveness evidence to support use of dabrafenib. Direct evidence comes from BREAK-3, a phase III randomised controlled trial (RCT) which compares dabrafenib to dacarbazine in treatment-naïve patients with $BRAF^{v600E}$ mutation-positive metastatic melanoma. Compared with dacarbazine, a statistically significantly improvement in PFS (6.9 vs 2.7 months) but not OS (18.2 vs 15.6 months) was reported; however, OS data are not yet fully mature and a large proportion of patients (57%) crossed over from the control arm to receive dabrafenib on disease progression. Hence OS data adjusted for the effects of crossover using the Rank Preserving Structural Failure Time method (RPSFTM) were also reported. It was not possible to report the median RPSFTM adjusted OS in months but the manufacturer noted that there was no statistically significant difference between treatment arms (Hazard ratio [HR] 0.55,95% Confidence Interval [CI]: 0.21 to 1.43). This is to be expected as the RPSFTM maintains the p-value of the ITT analysis.

(1) survival data from BREAK-3 are immature (the results are based on an interim analysis with few deaths) (2) it is questionable whether dabrafenib is the same when received on diagnosis as it is on disease progression (the assumption of a 'common treatment effect' is required for the appropriate use of the RPSFTM) and (3) subsequent treatments received on disease progression in the dabrafenib and dacarbazine arms differ. [redacted]

Both trials included in the ITC (BREAK-3 and BRIM-3) appear to be broadly similar in terms of patient eligibility criteria. Patients with V600K were inadvertently enrolled into BRIM-3. However, a potentially clinically meaningful baseline difference between the trials is that at baseline a greater proportion of patients had lactate dehydrogenase (LDH) levels above the upper limit of the normal range in both arms of BRIM-3 than either arm of BREAK-3. This may have had a negative impact on the prognosis of patients in BRIM-3 compared to patients in BREAK-3. Indeed, the ERG notes that the unadjusted median OS for the dacarbazine arm of BRIM-3 is lower than that of BREAK-3.

The ERG questions the validity of the approach used to conduct the ITC as key underlying assumptions are not met. Specifically, constant HRs for both PFS and OS data within both the BREAK-3 and BRIM-3 trials are not evident while comparison of dacarbazine OS data between the two trials indicates that constant proportion hazards are not supported ($p<0.001$). Hence the ERG does not believe there is sufficient evidence to support the results of the comparison between dabrafenib and vemurafenib.

1.5 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer developed a de novo partitioned survival model. It was constructed in Microsoft Excel and structured using three patient health states (Progression-free, Post progression and Death). Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE Single Technology Appraisals. Three treatment options were considered - dabrafenib, vemurafenib and dacarbazine.

Progression-free survival and OS for dabrafenib were modelled using parametric survival functions fitted to BREAK-3 trial data. Hazard ratios, based on BREAK-3 trial data for dacarbazine and generated by the ITC for vemurafenib, were used to project survival up to the end of the 10-year model period. In the case of dacarbazine, the RPFSTM adjusted HR from BREAK-3 was used to project OS. For the remaining 20 years of the model timeframe, UK general population mortality data were used. Trial data have not been used directly in the

ORR was also assessed by independent review, and results from this assessment were provided in the CSR.[30] Again, these results were only available for the December 2011 data-cut. Confirmed ORRs were lower for independent review (50% vs 6%, dabrafenib vs dacarbazine) than those reported by investigator assessment (53% vs 19%, dabrafenib vs dacarbazine).

4.2.6 Results when adjusting for confounding due to treatment switching

Participants of the BREAK-3[2] study were allowed to crossover from the dacarbazine arm to the dabrafenib arm when their disease had progressed; patients in both arms also received other second-line treatment at disease progression. At the time of the analysis, it is reported in the MS[3] that 36 (57%) crossed over from dacarbazine to dabrafenib. In a clinical trial, when patients are allowed to crossover to a different treatment, a simple ITT analysis of OS may underestimate the incremental difference in effect between the intervention and the comparator arms if any effect of this additional treatment is not taken into account. In the MS[3] the manufacturer has highlighted that the optimal method to adjust for the effect of crossover in survival analyses in RCTs remains an area of academic debate, with each approach having different advantages and limitations.

The manufacturer employed a team from the University of Sheffield to consider the potential effect of crossover in the BREAK-3[2] study (results from a range of possible approaches are shown in Table 26 of the MS[3] and reproduced here in **Error! Reference source not found.**). The team concluded that the most appropriate crossover adjustment technique to use on the dacarbazine OS data from the BREAK-3[2] trial was the treatment group Rank Preserving Structural Failure Time method (RPSFTM). However, in a report prepared for the manufacturer by external consults,[35] it is concluded that the results of the RPFSTM analyses:

[redacted]

The ERG agrees with the main conclusions of the authors of this report.[35] The ERG highlights the three key points regarding the use of the RPSFTM model for consideration of the effect of crossover in the BREAK-3[2] study.

First, survival data from the BREAK-3[2] study are immature; the results are based on an interim analysis with few deaths.

2, Using the earlier data-cuts ensures comparability of follow-up times across the two trials (see Table 1 for details).

Table 1: Comparison of data-cuts

	BREAK-3[2] **December 2012**	[redacted]	**BRIM-3[1]** **February 2012**
Proportion of patients who crossed over	57%	[redacted]	34%
Median follow-up (control arm) in months	12.7	[redacted]	9.5
Median follow-up (treatment arm) in months	15.2	[redacted]	12.5

Median OS values and the HRs used in the manufacturer's ITCs are presented in **Error! Reference source not found.**. The BRIM-3 OS HR used in the manufacturer's ITC is the uncensored result taken directly from the vemurafenib NICE Guidance (TA 269). The ERG also notes that the unadjusted median OS for the dacarbazine arms of BREAK-3[2] and BRIM-3[1] appear to differ. This may be indicative of differences in the patient population (see section **Error! Reference source not found.**) and/or differences in subsequent treatment received following disease progression in the two trials. Post-progression treatment is not reported for BRIM-3[1] but in a response to the first ACD for vemurafenib, the manufacturer of vemurafenib noted second-line use of ipilimumab in the dacarbazine arm was 19%.[37] In BREAK-3,[2] the ERG note that 3% of dacarbazine patients received subsequent ipilimumab.

4.5 Critique of the adverse events data

A summary of general AE data from all relevant dabrafenib[2,25-28] and vemurafenib[1] studies (RCTs and non-RCTs) is presented in **Error! Reference source not found.**. Most patients receiving dabrafenib, dacarbazine or vemurafenib experienced at least one AE. The majority of AEs were deemed to be treatment-related, particularly those experienced by patients receiving dabrafenib or vemurafenib. Adverse events leading to treatment discontinuation were relatively rare in all studies, except in the vemurafenib arm of BRIM-3[1] where these were reported to occur in around a quarter of all patients at the original data-cut (December 2010) presented in the MS for vemurafenib.[23] However, the ERG notes that a conference presentation[40] from an later data-cut (March 2011), cited by in the GlaxoSmithKline MS,[3] reports the treatment discontinuation rate for vemurafenib to be much lower (7%). Dose modification was not required for the majority of AE cases for any drug and permanent discontinuations due to AEs were infrequent. The highest incidence of Grade 3+ AEs was reported for patients in the BRIM-3[1] trial who received vemurafenib (50%). The ERG notes that, compared with BREAK-3[2] a lower proportion of Grade 3+ AEs were reported for patients in the BRIM-3[1] trial who were treated with dacarbazine (30% vs 42%, respectively). The incidence of Serious adverse evebts (SAEs) were reported to be highest for vemurafenib (33%) and lowest for dacarbazine (16%), both in BRIM-3.[1] Serious adverse events related to treatment were only reported in the dabrafenib studies,[2,25-28] being higher in the dabrafenib arms (15% to 23%) than the dacarbazine arm (3%). Fatal AEs were rare and only one fatal AE possibly related to study treatment was reported. Within the MS,[3] the manufacturer also cites its systematic review report[32] which includes findings from an ITC of AE data in which dabrafenib was compared with other treatments, including vemurafenib. No significant differences between dabrafenib and vemurafenib were reported for any of the general AEs summarised in **Error! Reference source not found.**.

The most common (≥5%) non-serious AEs from BREAK-3[2] reported in Table 39 of the MS[3] are summarised in **Error! Reference source not found.** alongside those from BRIM-3[1] extracted by the ERG. The ERG cautions that the different types of AEs reported (all common, non-serious vs all-Grade) mean that the incidences of AEs are not directly comparable. Nevertheless, based on these data, the ERG notes that the most common (≥25%) AEs associated with both dabrafenib and vemurafenib were hyperkeratosis, arthralgia, headache, alopecia, nausea and skin papilloma. Pyrexia was experienced by ≥25% of patients with dabrafenib but not ≥25% of patients with vemurafenib whereas the opposite was true for fatigue, photosensitivity, rash, diarrhoea and pruritis. The most common AEs (≥25%) associated with dacarbazine were nausea, vomiting, fatigue, asthenia and constipation. Results from the ITC showed that dabrafenib was associated with

significantly fewer incidences of diarrhoea, nausea, and photosensitivity/phototoxicity in comparison to vemurafenib.[32]

Complex model structure for survival

To provide lifetime estimates of cost effectiveness, the manufacturer of dabrafenib has adopted a complex model structure for representing patient survival involving three phases:

- Phase 1 - from randomisation until 1.8 years (96 weeks) a parametric model of BREAK-3[2] trial dabrafenib survival data based on a log-normal distribution is applied, modified by a HR (1.16 for vemurafenib and 1.82 for dacarbazine) to represent the survival associated with the comparator treatments
- Phase 2 - from 1.8 years to 10 years a parametric model, based on a log-logistic distribution calibrated from 10 year AJCC registry data,[8] is applied to survivors at time 1.8 years and is applied equally to dabrafenib, vemurafenib and dacarbazine treated patients
- Phase 3 - from 10 to 30 years, survival is estimated separately for each treatment arm by applying UK life table mortality rates to those surviving at 10 years.

This complex approach to modelling long-term survival involves a number of assumptions.

Critique of Phase 1 assumptions:

- The use of a log-normal distribution to represent the trial survival data is based on comparison of Akaike and Bayesian information criteria scores (AIC/BIC) and correspondence of AUC estimates (Tables 130 & 131 of MS). However, such a comparison is not definitive as the basis for choosing a parametric function. The significance of small AIC/BIC score differences is difficult to interpret, and also assumes that the 'true' distribution is included in the set of five candidate distributions being compared (exponential, Weibull, log-normal, log-logistic and gamma). For neither AUC nor AIC/BIC is a single functional form clearly superior across all comparisons in the manufacturer's analyses, and the log-normal distribution is known to exhibit a 'long tail' which tends to exaggerate long-term survival. A more fundamental problem is that using the full data set as the basis for projecting the experience of the minority of patients still alive (at risk) at the end of trial fails to recognise the strong influence of survivor bias altering the case-mix and risk profile of long-term survivors compared to the original randomized population. This can only be overcome by concentrating curve-fitting on the data (events) towards the end of the trial.
- The use of the dabrafenib parametric model as the basis for modelling survival in the comparator arms is also vulnerable to challenge as this approach relies heavily on belief in a) the suitability of the parametric function chosen to model dabrafenib and b) the ability of this function to represent survival for the comparator treatments. The approach also assumes that hazards are proportional across all three treatments.

Substituting these ERG estimates for OS in the manufacturer's model results in a large reduction in the incremental life years (-68.3%) and incremental QALYs gained per patient (-35.7%), but a smaller decrease in incremental cost per patient (-11.4%). The net result is that the ICER for dabrafenib vs dacarbazine increases from £49,019 to £99,560 per QALY gained.

6.1.3 Minor issues

Dacarbazine drug acquisition and administration costs

In estimating the acquisition cost of dacarbazine the manufacturer has assumed that BSA conforms to a log-normal distribution with a mean of 1.926 and standard deviation of 0.224.

This is incorrect as BSA within the general population and in cancer chemotherapy populations (Sacco[58] paper) conforms to a normal distribution, unlike body weight which is best represented by the log-normal function. In addition, the manufacturer has failed to recognise that separate analysis by gender is an important factor when calculating the average dose and related cost of medication The ERG has re-estimated the cost of dacarbazine assuming the same gender balance as in the BREAK-3[2] trial (101 females: 149 males) and average UK patients' chemotherapy BSA values for a similar age range (females: mean BSA 1.726, standard deviation 0.182; males: mean BSA 1.929, standard deviation 0.197[58]). In addition, the most recently reported eMIT[59] prices for dacarbazine have been applied in the most efficient manner across the population BSA range to achieve a more accurate overall mean cost per dose of £35.79 in place of the manufacturer's estimate of £58.36 per dose.

The cost of dacarbazine administration has been updated using the most recent NHS Reference Costs 2012/13,[31] resulting in an increase from £203.16 to £214.16 per dose.

The net effect of these parameter value changes is to increase the incremental cost by £86 per patient, and the ICER for dabrafenib vs dacarbazine by £87 per QALY gained.

Cost of additional lines of chemotherapy

The manufacturer's base case analysis features different mean costs of subsequent lines of chemotherapy (PSACT) for patients treated with dabrafenib and dacarbazine, based on the number of such treatments recorded in the BREAK-3[2] trial.The totals in the two trial arms are small (38 among 248 patients), and do not suggest a statistically significant difference. Appendix 10.2 of the MS[3] records:

> *'The validity of the approach outlined above to incorporating PSACT costs into the model was explored with experts during an advisory board meeting. They commented that it would be appropriate not to include any PSACT costs given that in UK practice*

Table 26 Cost-effectiveness results with ERG modifications to manufacturer's base case

Model scenario & revisions	Dabrafenib			Dacarbazine			Incremental			ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY
Manufacturer's base case	**£70,968**	**2.615**	**4.831**	**£22,366**	**1.624**	**2.929**	**+£48,603**	**+0.992**	**+1.902**	**£49,019**
Dacarbazine treatment costs	£70,968	2.615	4.831	£22,280	1.624	2.929	+£48,689	+0.992	+1.902	£49,106
Common PSACT costs	£70,968	2.615	4.831	£19,344	1.624	2.929	+£51,624	+0.992	+1.902	£52,066
ERG PFS model	£74,137	2.621	4.831	£22,461	1.628	2.929	+£51,676	+0.993	+1.902	£52,035
ERG OS model	£65,815	1.672	2.567	£20,138	1.213	1.825	+£45,677	+0.459	+0.742	£99,560
Base case + cost revisions	**£70,968**	**2.615**	**4.831**	**£19,258**	**1.624**	**2.929**	**+£51,710**	**+0.992**	**+1.902**	**£52,153**
Base case + cost and survival revisions	**£69,024**	**1.678**	**2.567**	**£17,119**	**1.217**	**1.825**	**+£51,905**	**+0.460**	**+0.742**	**£112,727**

ICER=incremental cost effectiveness ratio; QALY=quality-adjusted life year