STA REPORT Erratum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

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DOES NOT CONTAIN CIC/AIC

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This document contains erratum in respect of the ERG report following the factual accuracy check by Novartis.

Changes made to the original text in the ERG report are underlined.

evidence to support the use of trametinib+dabrafenib following treatment with ipilimumab or other immunotherapies.

The extent to which the submitted evidence reflects clinical practice is limited by the fact that patients included in the COMBI-d and COMBI-v trials all had an Eastern Oncology Cooperative Group (ECOG) performance status (PS) of 0 or 1 and fewer than 20 patients had stable brain metastases. Clinical advice to the ERG is that patients with an ECOG PS>1 and those with brain metastases are treated in UK clinical practice.

The treatment algorithm presented in the CS suggests that first-line treatment for the patient population being considered in this appraisal is either a BRAF inhibitor or ipilimumab; second-line treatment for those having received a BRAF inhibitor first-line being ipilimumab, and vice versa. It is recognised within the final NICE scope that trametinib+dabrafenib may be prescribed following treatment with an immunotherapy.

Clinical advice provided to the ERG suggests that current NHS clinical practice for the treatment of patients with BRAF mutation-positive disease is uncertain for those patients who are relatively well with slowly progressing disease, i.e. for the patients in the COMBI-d and COMBI-v trials. The treatment options currently available in the NHS include immunotherapy and BRAF inhibitors. Clinical advice to the ERG is that, for patients with BRAF mutation-positive disease who are relatively unwell with rapidly progressing disease, treatment is always a BRAF inhibitor.

The findings from the COMBI-d and COMBI-v trials are only relevant to the cohort of patients in clinical practice with BRAF mutation-positive disease who have an ECOG PS 0-1 (text removed). Clinical advice to the ERG is that some of these patients could have been treated with an immunotherapy instead of a BRAF inhibitor. It is not known whether trametinib+dabrafenib is more effective than an immunotherapy in this group of patients as there are no data available to allow this comparison to be undertaken.

The ERG notes that there is uncertainty around whether pembrolizumab and ipilimumab should have been specified as comparators in the final NICE scope. In previous NICE appraisals, immunotherapy has been a comparator alongside BRAF inhibitor monotherapies for the first-line treatment of people with BRAF mutation-positive melanoma. However, the ERG is also aware that expert clinician opinion may agree with the wording in the final NICE scope for this appraisal i.e. that only dabrafenib and vemurafenib are relevant comparators. Our clinical expert has told us that immunotherapy is only considered as a treatment option

- There is no clinical evidence to support the use of trametinib+dabrafenib in patients with a PS ≥2 and the clinical trials included fewer than 20 people with stable brain metastases
- In current clinical practice, ipilimumab and pembrolizumab are treatment options recommended by NICE for patients with unresectable or advanced BRAF V600 mutation-positive melanoma. The ERG considers that the absence of these comparators limits the relevance of this appraisal to the NHS
- The treatment sequence of BRAF inhibitors and immunotherapy in patients with BRAF mutation-positive melanoma is uncertain. Patients recruited to the COMBI-d and COMBI-v trials appear to be fitter patients who, in clinical practice, could have received an immunotherapy (pembrolizumab or ipilimumab) as a first-line treatment
- The COMBI-v trial was an open-label, unblinded RCT that did not include a blinded independent assessment of radiological outcomes; the extent to which this may have caused trial results to be biased is unclear
- The company has not considered published evidence describing the effectiveness of dabrafenib or vemurafenib other than that from the COMBI-d and COMBI-v trials.

Cost effectiveness evidence

- The company failed to provide a number of the analyses requested by the ERG during the clarification process
- The long-term projections of OS developed by the company lack credibility as they are based on data that were collected prior to the availability of immunotherapy or BRAF inhibitor treatments
- The use of PFS data, rather than TDD data underestimates the cost of trametinib+dabrafenib treatment
- The company model has a structural flaw: the less effective trametinib+dabrafenib becomes at delaying treatment progression, the more cost effective the combination therapy is compared to BRAF inhibitor monotherapy
- The company failed to use scenario analysis to explore any of the assumptions they make on their OS projection, on utility values chosen or on PSACT costs
- The company model does not reflect the current treatment pathway post progression for NHS patients
- The approach used to model OS for patients receiving a BRAF inhibitor lacks credibility
- Study treatment costs have been underestimated and the choice of PSACT costs used by the company is not supported by any statistical evidence
- The company model employs utility values that may be subject to bias.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG suggested five amendments that could be made to the company model. Two amendments offered alternative approaches to the modelling of the OS data. Three amendments suggested changes to the costs and utility values used in the company model. The ERG also noted minor errors related to post-progression monitoring costs, AE costs,

and the company decision problem specify that the patient population is adults with unresectable or metastatic BRAF V600 mutation-positive melanoma.

The ERG notes that no particular treatment line is specified in either the licence[32] or in the final NICE scope. However, the patient populations recruited to the two pivotal trials that underpin the clinical effectiveness evidence presented in the CS (COMBI-d[33] and COMBI-v[34] trials) are described as being previously untreated. The only explicit mention of line of treatment for the trametinib+dabrafenib combination is in the Summary of Product Characteristics (SmPC)[35,36] where it is stated that other treatment options could be considered before treatment with the combination in this prior BRAF inhibitor treated population and that sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

The ERG cautions that the inclusion and exclusion criteria for the COMBI-d and COMBI-v trials meant that only patients with an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 or 1 and stable brain metastases (n=20) were recruited. There is, therefore, no clinical evidence to support the use of trametinib+dabrafenib in patients with an ECOG PS of 2 or higher, or for patients with brain metastases. Clinical advice to the ERG is that patients with an ECOG PS of 2 or higher and patients with brain metastases are treated in UK clinical practice. The SmPC[35,36] explicitly states that the clinical effectiveness of trametinib+dabrafenib in people with brain metastases is currently unknown.

The findings from the COMBI-d and COMBI-v trials are only relevant to the cohort of patients in clinical practice with BRAF mutation-positive disease who have an ECOG PS 0-1. It is stated in the final NICE scope that some of these patients could have been treated with an immunotherapy instead of a BRAF inhibitor. It is not known whether trametinib+dabrafenib is more effective than an immunotherapy in this group of patients as there are no data available to allow this comparison to be undertaken.

3.2 Intervention

The intervention discussed in the CS is trametinib+dabrafenib and matches the intervention specified in the NICE scope.

Dabrafenib is an orally bioavailable and selective inhibitor of BRAF V600 kinase activity.[35] Trametinib is an orally bioavailable and selective inhibitor of the mitogen-activated protein kinase (MAPK) kinases MEK1 and MEK2, the additional key components of the MAPK pathway which sit downstream of BRAF.[36] The company states (CS, p37) that combining trametinib+dabrafenib provides concomitant inhibition of the MAPK pathway by

Table 1 Key characteristics of the COMBI-d and COMBI-v trials

	COMBI-d	COMBI-v
Design	Double-blind, Phase III RCT	Open-label, Phase III RCT
Location	14 countries worldwide, 103 centres (10 UK centres, 33 patients)	28 countries across Europe (7 UK centres, 39 patients)
Intervention	Dabrafenib (150mg b.d.) Trametinib (2mg o.d.)	Dabrafenib (150mg b.d.) Trametinib (2mg o.d.)
Comparator	Dabrafenib (150mg b.d.) Placebo trametinib (o.d.)	Vemurafenib (960mg o.d.)
Patient population	N=423 Previously untreated stage IIIc (unresectable) or stage IV (metastatic) BRAF V600E/K mutation-positive melanoma	N=704 Previously untreated stage IIIc (unresectable) or stage IV (metastatic) BRAF V600E/K mutation-positive melanoma
Primary outcome	Investigator-assessed PFS	OS
Secondary outcomes	OS, ORR, duration of response, HRQoL, AEs	Investigator-assessed PFS, ORR, duration of response, HRQoL, AEs
Trial status	Ongoing. Enrolment commenced in May 2012 and closed in January 2013. Cut off for primary analysis for PFS: 26 August 2013. Cut off for final analysis of OS: 12 January 2015. Follow-up is ongoing for additional survival and safety data (until all subjects have died or all subjects have at least 5 years' follow-up, whichever is earlier)	Ongoing. Enrolment commenced in June 2012 and closed in October 2013. Cut off for interim analysis of OS (which became final): 17 April 2014. Cut off for updated analysis of OS: 13 March 2015. Follow-up is ongoing for additional survival and safety data (until all subjects have died or all subjects have at least 5 years' follow-up, whichever is earlier)

AE=adverse event; b.d=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Co-operative Oncology Group; HRQoL=health-related quality of life; MEK=mitogen-activated protein kinase o.d=once daily; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PS=performance status; RCT=randomised controlled trial; RECIST=Response Evaluation Criteria in Solid Tumours
Source: CS, adapted from Table 14

Characteristics of patients in the COMBI-d and COMBI-v trials

The key baseline characteristics of the patients in the COMBI-d and COMBI-v trials are listed in **Error! Reference source not found.**. The ERG agrees with the company that patients in the COMBI-d trial are well-balanced across the treatment groups, with the exception of the proportions of patients with visceral disease (slightly higher in the trametinib+dabrafenib arm).

The ERG considers that the patients in the COMBI-v trial are also well balanced across the treatment groups, although there were (slightly) more patients in the vemurafenib arm who had received prior immunotherapy treatment. The company has emphasised that in both the COMBI-d and COMBI-v trials, all prior systemic therapy was administered in the neoadjuvant or adjuvant setting.

The ERG notes that the patients recruited to the COMBI-d and COMBI-v trials were limited to those with an ECOG PS of 0 or 1; this suggests that the patients in the trials were relatively well at the time of enrolment. The presence of active brain metastases was also an exclusion factor in the trials. Clinical advice to the ERG is that patients with ECOG

the correct method to perform the crossover adjustment and the results demonstrate that, as only 6% of patients crossed over, there was very little impact on the results.

The company presents the K-M curve for the March 2015 OS data cut for the COMBI-v trial (CS, Figure 14). The ERG agrees with the company that there is early separation of the curves and this separation continues into follow-up.

The company reports (CS, p113) that a greater proportion of patients in the dabrafenib+placebo arm compared with the trametinib+dabrafenib arm received anti-cancer treatment when their disease progressed (51% versus 34% respectively). The ERG notes from Table 36 of the CS that the majority of patients were treated with ipilimumab following disease progression.

4.7.2 Progression-free survival

At the April 2013 analysis of the COMBI-v trial (follow-up of 11 months), median PFS (investigator-assessed) was 11.4 months in the trametinib+dabrafenib arm and 7.3 months in the vemurafenib monotherapy arm, a difference of 4.1 months. The risk reduction associated with trametinib+dabrafenib was 44% (HR=0.56, 95% CI: 0.46 to 0.69, p<0.001).

At the March 2015 data cut, median PFS was 12.6 months in the trametinib+dabrafenib arm and 7.3 months in the vemurafenib monotherapy arm, a difference of 5.3 months. The risk reduction associated with trametinib+dabrafenib was 39% (HR=0.61, 95% CI: 0.51 to 0.73, p<0.001). Text removed

The company conducted five sensitivity analyses of PFS, namely: i) symptomatic progressions determined by the investigator; ii) considering start of new anti-cancer therapy as an event; iii) considering radiological progression after extended loss to follow-up or start of new anti-cancer therapy as an event; iv) Cox regression proportional hazards regression model and v) using derived responses from investigator lesion assessments. The ERG agrees with the company's conclusion that the results of the sensitivity analyses for PFS were consistent with the results of the ITT analysis with HRs in the range of 0.53 to 0.57.

The ERG notes that the COMBI-v trial did not include a blinded assessment of PFS by an Independent Review Committee.

The company presents the K-M curves for the March 2015 PFS analyses (CS, Figure 15). The ERG considers that there is early separation of the curves that continues into follow-up.

This result can be explained by looking at the scenario analysis results in detail – specifically at the changes in costs, LYG and QALYs.

As the progression state is independent of mortality, changing the hazard for progression in the trametinib+dabrafenib arm does not alter OS for patients receiving that therapy. It merely changes the proportion of time patients remain in the progression-free state. This is seen in the company scenario analysis results where LYG from treatment with trametinib+dabrafenib therapy compared to monotherapy remain the same (1.653 years) as LYG for the same comparison in the company base case.

In the company's scenario analysis, the difference in time in the progression-free state between treatment with trametinib+dabrafenib and monotherapy decreases from 0.667 years in the company base case to 0.517 years. As progression is linked directly to time on treatment, the mean difference in cost between trametinib+dabrafenib therapy and dabrafenib monotherapy decreases from £[redacted] in the company base case to £[redacted] in the scenario analysis (a cost reduction of [redacted]). Similar decreases are seen in the comparison of trametinib+dabrafenib therapy with vemurafenib monotherapy.

Compared with the company base case, the scenario analysis predicts less time in the progression-free state for patients receiving trametinib+dabrafenib. Time in the progression-free state is associated with a higher utility than the progressed state. Results from the scenario analysis, therefore, predict that there will be a reduction in QALYs for patients treated with trametinib+dabrafenib even though the total LYG remains the same as in the company base case analysis. Specifically, the QALY gain from treatment with trametinib+dabrafenib in the scenario analysis falls by 0.021 or 1.6%.

A [redacted] fall in costs and a 1.6% fall in QALYs explains, mathematically, why the ICER in the scenario analysis is lower than the ICER in the company base case analysis and highlights either that it is the failure to link progression state with differential mortality rates that leads to illogical model results or that the progression-free state as described is not a useful state to include in the economic model.

Effectively, the model structure makes it impossible to directly explore how changes in the assumption of the effectiveness of treatment with trametinib+dabrafenib at delaying or stopping progression impact on the size of the ICERs. The ERG has partially

[redacted]

Figure 1 Company projected OS to 5 years compared with the AJCC registry data survival curve

From 3 months the company applied a mortality hazard rate for BRAF inhibitor monotherapy of 4.4%. Whilst the mortality hazard rate between months 3 and 4 suggested by the AJCC registry data is 7.0%, by month 14 the monthly mortality hazard has fallen to 4.3% and falls to 1.1% by month 60 (year 5 – when the mortality hazard rate for BRAF therapy converges with the AJCC registry mortality hazard in the company model). For 3.6 years the monthly mortality hazard rate for BRAF inhibitor monotherapy is higher in the company model than for patients in the AJCC registry over the same time period.

For patients receiving trametinib+dabrafenib, the monthly constant mortality hazard is 2.3% from 18 months at which point the monthly mortality hazard in the AJCC registry is 3.4%. The monthly mortality hazard rate for the AJCC data at 30 months – the point at which the company has started to converge mortality hazard rates to the AJCC data – is 2.4%. The monthly mortality hazard for trametinib+dabrafenib, therefore, essentially converges with the AJCC registry data at 30 months rather than at 60 months and is always lower until the hazards converge at year 5.

Further evidence on the implausibility of such a large difference between monthly mortality hazard rates over 5 years is found in the post treatment discontinuation survival curves.

stopped treatment between 28 and 30 months despite there being a steady reduction in patients on treatment up to that point.

The ERG considers that the end of the TTD curves are likely to be influenced by censoring or to be the result of some artefact of the trial and that mortality hazard rates over the last few months of the trial may not be reliable. The ERG has, therefore, focussed only on the first 27 months of data and has extrapolated the TTD data by calculating the average mortality hazard rate in each arm from months 12 to 28 and applied this as a constant monthly hazard from month 28 onwards. This approach has resulted in a monthly mortality hazard for treatment discontinuation of 3.2% for patients treated with trametinib+dabrafenib and 5.6% for those treated with dabrafenib.

The TTD K-M curves and the extrapolation for trametinib+dabrafenib and dabrafenib, compared to the company estimated PFS for trametinib+dabrafenib and BRAF inhibitor monotherapy are shown in **Error! Reference source not found.**.

Figure 2 ERG estimated TTD and company modelled PFS

The ERG considers that application of TTD only partially negates the need for the RDI (relative dose intensity) adjustment applied by the company. In Table 51 of the CS dose interruptions were shown for almost 50% of patients across both arms of the COMBI-d and COMBI-v trials and dose reductions due to AEs were noted for between 14% and 36% of patients. As such, some estimate of RDI would be considered reasonable. The ERG did not request patient level data to recalculate the

RDI based on TTD and so has applied the RDI used in the company base case. As the RDI already adjusts in part for time on treatment, this may mean that the cost using TTD is a slight overestimate for all treatments.

The ERG re-ran the company model using TTD data instead of PFS data to estimate treatment costs. The results of the re-analysis show that mean total costs per patient for trametinib+dabrafenib increase from £[redacted] in the company base case to £320,153. Costs for dabrafenib increase from £[redacted] to £170,405 and for vemurafenib from £[redacted] to £176,803.

The ICER per QALY gained for trametinib+dabrafenib compared to dabrafenib increases from £104,069 in the company base case to £115,457 and, compared to vemurafenib, from £96,437 to £106,580.

The ERG considers that, in clinical practice, TTD is likely to be affected by the availability of pembrolizumab, and possibly ipilimumab, as treatment options. Patients may now choose to switch to immunotherapy and away from BRAF inhibitor therapy either because their individual treatment pathway was planned for them to take BRAF inhibitors until they were well enough to commence immunotherapy or because, on disease progression, they choose to commence immunotherapy rather than remain on a BRAF inhibitor, where this is an option. This means that both the company base case results and the ERG's results may overestimate the time on treatment on all arms and so overestimate costs. This is a further example of how the failure to represent the current treatment pathway casts doubt on any model outputs.

Post-study anti-cancer therapy costs

In the company model it is assumed that patients receiving first-line treatment with trametinib+dabrafenib have different PSACTs from those whose first-line therapy was a BRAF inhibitor. The company offered no justification as to why these costs should be different. No statistical tests were performed to support this assumption and the standard errors presented in Table 96 of the CS would suggest that PSACT costs between arms were not statistically significantly different.

Given the lack of clinical or statistical justification to apply different PSACT costs, a single PSACT of a simple average of the three expected mean PSACT cost per patient used in the company base case model (CS, p215) was used i.e. £63,280. The ERG has applied this cost at the end of treatment discontinuation as a one-off cost, rather than at progression as in the company model. The ERG considers that this cost should be spread across the duration of treatment to allow it to be appropriately

different time points. The ERG considers that values from the subgroup of European patients would provide a more representative estimate of utility values for UK patients than the total dataset.

Dabrafenib versus vemurafenib

As was the case with TTD, the ERG considers the use of utility data from the COMBI-v trial to be inappropriate due to the open-label nature of the trial. Patient reported outcomes, such as quality of life, are likely to be biased by an open-label trial, a view supported by the European Medicines Agency in a workshop on HRQoL in oncology.[69]

In this case, for treatment with trametinib+dabrafenib and dabrafenib at least, utility evidence is available from a fully blinded trial (the COMBI-d trial) and so there is no need to introduce potential bias into utility estimates by using the open-label utilities from the COMBI-v trial.

For vemurafenib, the company data used data collected during the open-label COMBI-v trial. Whilst this evidence would appear to support the view that treatment with vemurafenib should be associated with a lower utility value than dabrafenib, it is noted that in previous NICE submissions, notably for dabrafenib first-line treatment, TA321[12] the same utility value was applied for dabrafenib and vemurafenib in the absence of utility evidence on vemurafenib. The ERG is not convinced that the open-label nature of the COMBI-v trial is compelling evidence that the utility of patients receiving vemurafenib is lower than that for patients receiving dabrafenib. Even if it was the case that utility data from the COMBI-v trial were sufficiently robust, the evidence from the European dataset is that at no time point up to 56 weeks were the utility values from the vemurafenib arm of the COMBI-v trial statistically significantly different from those at the same time point from the dabrafenib arm of the COMBI-d trial (**Error! Reference source not found.**).

estimated by the model between arms. As such, given the minimal impact that the cost differential has on the size of the overall ICERs, the ERG considers that the assumption of on-going monitoring costs is acceptable and does not significantly influence the size of the estimates generated by the model.

Adverse event costs

The ERG considers that, from a cost perspective, the company model should have included more AEs than were actually included, notably those that occurred more often in patients treated with trametinib+dabrafenib rather than a BRAF inhibitor, such as diarrhoea.

However, the ERG considers that the cost of treating the common AEs would have been small relative to the costs of drug treatment included in the model. (Text removed) The ERG notes that as AEs that were more commonly associated with trametinib+dabrafenib treatment than with BRAF inhibitor monotherapy were not included in the model, the ICERs presented by the company and the ERG for trametinib+dabrafenib compared to BRAF inhibitor monotherapy may be slight underestimates.

Discounting

The company applied a discount rate at the end of every week after one year rather than annually as requested by NICE. The company model does not allow for the application of annual discounting without substantial reworking of the model. The ERG considers that the impact of using the NICE method on the size of the ICER, rather than that employed by the company, would be minimal.

AJCC case mix adjustment

The ERG notes that the company adjusted the AJCC registry data for the BRAF inhibitor arms using only the case mix from the COMBI-d trial rather than the case mix from both the COMBI-d and COMBI-v trials. As the ERG remodelled OS data using only data from the COMBI-d trial, this error does not affect the ERG results.

For completeness, a case mix adjustment using data from the COMBI-d and COMBI-v trials for the BRAF inhibitor monotherapy arm was calculated by the ERG and applied to the company base case model. This resulted in change of less than 2% to the size of the ICER for trametinib+dabrafenib compared to dabrafenib or vemurafenib.