ID923 ERG REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Encorafenib in combination with binimetinib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID923]

Confidential until published

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CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 29 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are presented here.

Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Where an amendment was made to information marked as CiC, the ERG's amendments are indicated between two stars * *

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 has been submitted to NICE by Pierre Fabre Ltd in support of the use of encorafenib (Braftovi®) combined with binimetinib (Mektovi®) for treating advanced (unresectable or metastatic) B-Raf proto-oncogene, serine/threonine-protein kinase (BRAF) V600 mutation-positive melanoma.

Encorafenib combined with binimetinib (Enco+Bini 450) is licensed in Europe for treating adult patients with unresectable or metastatic BRAF V600 mutation-positive melanoma.

1.2 Critique of the decision problem in the company submission

The patient population specified in the final scope issued by NICE and the patient population considered in the company submission (CS) are the same i.e., adults with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The patient population described in the European Medicines Agency (EMA) marketing authorisation for Enco+Bini 450 is adults with unresectable or metastatic melanoma with a BRAF V600 mutation.

No treatment line is specified in either the final scope issued by NICE, the CS, or the EMA marketing authorisation. However, only 6% of patients recruited to the COLUMBUS trial had received prior treatment with an immunotherapy in the metastatic setting, which means that the clinical effectiveness of Enco+Bini 450, as demonstrated in the COLUMBUS trial, is, effectively, for its use as a first-line treatment.

The generalisability of the available clinical effectiveness evidence to patients with brain metastases in the NHS is limited by the fact that only 3.5% of patients recruited to the COLUMBUS trial had brain metastases and all had received prior treatment for their brain metastases. Clinical advice to the ERG is that, in the NHS, patients with brain metastases represent an important patient subgroup. Further, the ERG highlights that as, at baseline, patients in the COLUMBUS trial had an Eastern Co-operative Oncology Group (ECOG) performance status (PS) 0 or 1, there is no clinical effectiveness evidence for the use of Enco+Bini 450 in patients with a poor PS (i.e., PS 2 or 3).

The ERG is aware that there is a move towards treating patients with melanoma in the earlier, adjuvant, setting and two appraisals of treatment with an immunotherapy (pembrolizumab, nivolumab) in this setting are ongoing. The combination treatment of Dab+Tram was

duration of response [DOR]), AEs and HRQoL. The company has also reported the outcomes of an analysis of time to objective response and time to treatment response. Only descriptive, interim OS results are available due to the statistical approach (hierarchical testing) used to analyse the COLUMBUS trial data.

Outcomes for the comparison of the clinical effectiveness of Enco+Bini 450 versus Dab+Tram are available from the company's NMAs; the outcomes presented are PFS, OS, AEs and HRQoL.

Subgroups

In the final scope issued by NICE it is stipulated that, if the evidence allows, two subgroups should be considered, namely people with previously untreated disease and people with previously treated disease that has progressed on or after first-line immunotherapy. The company was unable to conduct any subgroup analyses based on prior treatment due to the limited number of patients (6%) from the COLUMBUS trial who had received prior treatment.

Other considerations

- A confidential patient access scheme (PAS) is in place for Enco+Bini 450. This means that Enco+Bini 450 is available to the NHS at a (confidential) discounted price.
- All of the treatments included in the company's economic model are available to the NHS at (confidential) discounted prices.
- The company did not identify any equality issues.
- The company has not presented a case for Enco+Bini 450 to be assessed against the NICE End of Life criteria.

1.3 Summary of the clinical evidence submitted by the company

Direct evidence

The company conducted a broad literature search. This did not lead to the identification of any relevant RCTs other than the COLUMBUS trial. The COLUMBUS trial is an international, randomised, open-label, phase III trial designed to assess the clinical effectiveness of Enco+Bini 450 compared with vemurafenib and compared with Enco 300 in 577 patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

The primary objective of the COLUMBUS trial was to compare PFS between Enco+Bini 450 and vemurafenib based on blinded independent central review (BIRC). At the data cut-off date of 19th May 2016, median PFS was 14.9 months (95% Confidence Interval [CI]: 11.0 to 18.5 months) and 7.3 months (95% CI: 5.6 to 8.2 months) in the Enco+Bini 450 and vemurafenib arms respectively. The difference was statistically significantly in favour of treatment with Enco+Bini 450, hazard ratio (HR) 0.54 (95% CI: 0.41 to 0.71); stratified one-sided log-rank

test p<0.0001. Results of sensitivity analyses and supportive analyses of PFS were consistent with the results of the primary analysis.

A key secondary efficacy objective was to compare the PFS of Enco+Bini 450 with Enco 300 based on BIRC. At the data cut-off date of 19th May 2016, the HR for Enco+Bini 450 relative to Enco 300 was 0.75 (95% CI: 0.56 to 1.00) but the difference was not statistically significant (one-sided p=0.0256) by the one-sided stratified log-rank test according to the threshold for significance as per the hierarchical testing approach as pre-defined in the protocol (p<0.025).

The PFS of Enco+Bini 450 versus Enco 300 was not statistically significant according to the hierarchical approach of statistical testing; all of the alpha of the trial had been spent and OS could not be formally tested. Nominal p-values for OS from the interim OS analysis (7th November 2017) are, therefore, only descriptive. Median OS was 33.6 months (95% CI: 24.4 to 39.2) in the Enco+Bini 450 arm, 16.9 months (95% CI: 14.0 to 24.5) in the vemurafenib arm and 23.5 months (95% CI: 19.6 to 33.6) in the Enco 300 arm. The HR for the comparison of Enco+Bini 450 with vemurafenib is 0.61 (95% CI: 0.47 to 0.79; nominal one-sided p<0.0001).

Results of updated, supportive and sensitivity analyses of primary (PFS) and key secondary efficacy outcomes (PFS and OS) were consistent with the results of the primary analysis.

The HRQoL results from the COLUMBUS trial demonstrated that treatment with Enco+Bini 450 significantly delayed deterioration compared with vemurafenib, as measured by median time to 10% deterioration on the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) subscale, the EORTC-QLQ-C30 global health status and the EQ-5D-5L questionnaire.

The frequency of AEs was similar across the three arms of the COLUMBUS trial. Patients treated with Enco+Bini 450 had a longer time on treatment compared with patients treated with vemurafenib and patients treated with Enco 300. The most frequently reported Grade 3 and Grade 4 serious AEs in ≥2% of patients treated with Enco+Bini 450 were pyrexia ([redacted]) and anaemia ([redacted]), and in the in the vemurafenib arm they were general physical health deterioration ([redacted]) and back pain ([redacted]). The most common all grade serious AEs (≥2.0% of patients) in the Enco+Bini 450 arm were pyrexia ([redacted]), abdominal pain ([redacted]), acute kidney injury ([redacted]) and anaemia ([redacted]), and in the vemurafenib arm the only common all grade serious AE was general physical health deterioration ([redacted]).

Indirect evidence

In the absence of direct evidence comparing treatment with Enco+Bini 450 versus Dab+Tram, the company conducted Bayesian NMAs to indirectly estimate the relative effects of treatment

PS of 0 or 1 were recruited to the included trials and so are likely to be fitter than patients with highly symptomatic or rapidly deteriorating disease treated in the NHS.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with Enco+Bini 450 versus Dab+Tram when used to treat advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The model comprises three mutually exclusive health states: progression-free (PF), post-progression (PP) and death. The PF health state and PP health state include sub-states which are designed to account for primary treatment status (i.e., on or off primary treatment). All patients start in the PF health state on primary treatment. The model time horizon is set at 30 years with a 1-month cycle length. The model perspective is that of the UK NHS. Outcomes are measured in quality adjusted life years (QALYs), and both costs and QALYs are discounted at an annual rate of 3.5%, as recommended by NICE.

The OS and PFS of patients treated with Enco+Bini 450 are modelled using Kaplan-Meier (K-M) data from the COLUMBUS trial, followed by an extrapolation (fitted using standard methods). For OS, the extrapolation involved using American Joint Committee on Cancer (AJCC) data to year 20 and lifetables for years 20 to 30. A gamma curve was used to represent PFS beyond the trial period. In the absence of direct survival evidence for patients treated with Dab+Tram, the survival curves representing the experience of patients treated with Enco+Bini 450 were calculated using HRs generated by the company's NMAs.

Time on primary treatment data were available from the COLUMBUS trial for patients treated with Enco+Bini 450 and the company assumed that time on treatment for patients receiving Dab+Tram was the same as that for patients receiving Enco+Bini 450. Different relative dose intensity (RDI) multipliers (based on data from the COLUMBUS trial and the COMBI-v and COMBI-d trials) were used for the two treatments. AEs of Grade 3/4 occurring in ≥5% of patients treated with Enco+Bini 450 and Dab+Tram were modelled based on incidence rates from relevant clinical trials (COLUMBUS, COMBI-v and COMBI-d) and results from the company's NMA were used to estimate utility values in the PF and PP health states. In the PF on treatment sub-state, utility values differed by primary treatment but in all other states (including other sub-states) the same utility value was used irrespective of treatment. Resource use and costs were estimated based on information from the COLUMBUS trial, published sources and clinical experts.

A confidential patient access scheme (PAS) is in place for Enco+Bini 450. This means that Enco+Bini 450 is available to the NHS at (confidential) discounted prices. Other drugs used in

the company model, including Dab+Tram are also available to the NHS at discounted prices. However, as these discounts are confidential, the company is unaware of the prices and has, therefore, used full list prices within the model to represent the costs of these drugs. Using the PAS prices for Enco+Bini 450 and list prices for all other drugs, the company base case analysis for the comparison of treatment with Enco+Bini 450 versus Dab+Tram shows that treatment with Enco+Bini 450 dominates, generating 0.453 additional QALYs at a reduced cost.

The results from the company's probabilistic sensitivity analysis are consistent with the company's base case (deterministic) analysis. The company carried out a wide range of deterministic sensitivity analyses. The most influential parameter was found to be the HR for time to treatment discontinuation. Other influential parameters were related to the dose of Dab+Tram (dose per administration and RDI). The two scenario analyses carried out by the company that generated results in which treatment with Enco+Bini 450 did not dominate treatment with Dab+Tram were a scenario in which the PAS price for Enco+Bini 450 was reduced by [redacted] and one in which treatment with Enco+Bini 450 and Dab+Tram were assumed to be equally effective in terms of OS, PFS, PF utility and AE rates.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The company developed a de novo economic model to evaluate the cost effectiveness of Enco+Bini 450 versus Dab+Tram for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The ERG considers that the design of the company model was appropriate, and that COLUMBUS trial data were correctly incorporated into the model.

The Enco+Bini 450 arm of the company model was populated with OS, PFS, time on treatment, utility values and AE rates derived from the COLUMBUS trial, whilst data to populate the Dab+Tram arm of the company model were derived from the company's NMAs. NMA results for the comparison of Enco+Bini 450 versus Dab+Tram for OS, PFS, utility values and Grade ≥3 AEs are not statistically significant. The ERG, therefore, considers that it is inappropriate to model any differences, between treatments, for these outcomes. However, the company has not used the results from the Grade ≥3 AE NMA in the submitted model. Instead, the company has included the incidence rates of Grade 3 and 4 AEs (at least 5% in either the Enco+Bini 450 arm of the COLUMBUS trial or in the Dab+Tram arms of the COMBI-v and COMBI-d trials) in their model. The ERG highlights that such an approach is not robust as it fails to account for any differences in patient baseline characteristics between the three trials.

Based on the available evidence, the ERG considers that the only parameters that could affect model results are treatment-related costs. In the company model these are a function of time on treatment, administration costs, RDI and drug costs. The ERG is convinced by the company's argument that time on treatment estimates for patients receiving Enco+Bini 450 and Dab+Tram are likely to be the same (CS, p117) and is satisfied that the administration costs of the two treatment combinations – given that they have the same mode of delivery – are also likely to be the same. The company, however, has applied different RDI multipliers when estimating the costs of treatment with Enco+Bini 450 and Dab+Tram. The company's rationale for this approach is to be reflective of the conditions within trial that generated the estimates of effectiveness and safety utilised in the model. However, the ERG considers that, as there is no robust evidence to support the use of different Grade 3 and 4 AE rates, there is no robust evidence to support the use of different RDI multipliers. The ERG argues that, with time on treatment, administration costs and RDI being equal for both model treatment arms, the only difference in costs arises from the price of Enco+Bini 450 compared with the price of Dab+Tram. The ERG, therefore, considers that, to establish cost effectiveness, a simple cost comparison analysis, rather than a cost utility analysis, is all that is required.

1.7 Summary of company's case for End of Life criteria being met

The company has not presented a case for Enco+Bini 450 to be assessed against the NICE End of Life criteria.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The company provided a detailed submission that met the requirements of NICE's scope for the clinical effectiveness analysis. The ERG's requests for additional information were addressed to a good standard.
- The COLUMBUS trial was well-designed and well-conducted.
- The patient population in the COLUMBUS trial is similar to the patient populations in the COMBI-v and COMBI-d RCTs and the sources used by the company for clinical effectiveness evidence for treatment with Dab+Tram.
- The PFS outcome results from the vemurafenib arms of the COLUMBUS trial and the COMBI-v trial are comparable.
- The company made good use of the limited available data to construct the NMAs.

Cost effectiveness evidence

- The economic model is largely well described within the CS.

- The ERG considers that the design of the company model was appropriate, and that COLUMBUS trial data were correctly incorporated into the model.
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- There is no direct evidence for the clinical effectiveness of Enco+Bini 450 versus Dab+Tram.
- The ERG considers that NMA results (which indicate no statistically significant difference between treatment with Enco+Bini 450 and Dab+Tram for OS, PFS, AEs and HRQoL) should be interpreted with caution due to methodological weaknesses but highlights that clinical advice to the ERG is that the clinical effectiveness outcomes for patients who are treated with Enco+Bini 450 and Dab+Tram are likely to be similar.
- Clinical advice to the ERG is that, in the NHS, first-line treatment for patients with advanced (unresectable or metastatic) BRAF V600 melanoma is generally an immunotherapy and that patients with a BRAF V600 mutation-positive melanoma will receive a BRAF targeted treatment on disease progression. As only 6% of patients recruited to the COLUMBUS trial had received prior immunotherapy treatment, the evidence presented is only relevant to patients receiving first-line treatment.
- The ERG is aware that there is a move towards treating patients with melanoma in the earlier, adjuvant, setting. The impact of the use of adjuvant treatment with an immunotherapy on the treatment pathway in the metastatic setting is currently unknown.
- The company is only able to provide descriptive OS data from the COLUMBUS trial due to the limitations imposed by the hierarchical approach to statistical testing used to analyse the COLUMBUS trial data.

Cost effectiveness evidence

- The results from the company's NMAs indicate that there are no statistically significant differences in OS, PFS or utility values for the comparison of treatment with Enco+Bini 450 versus Dab+Tram. However, within the company model, differences are modelled.
- Company NMA results also show that there is no statistically significant difference in the incidence of Grade ≥3 AEs when treatment with Enco+Bini 450 is compared with Dab+Tram; however, instead of using the NMA results in the model, the company uses AE data taken directly from the COLUMBUS, COMBI-v and COMBI-d trials. This approach does not account for differences between trials in baseline patient characteristics.
- To be reflective of the conditions within trial that generated the estimates of effectiveness and safety utilised in the model, the company has assumed that different RDI multipliers should be applied to the two model treatment arms. The ERG considers that all available evidence suggests there is no difference in Grade ≥3 AEs and, therefore, there is no evidence to support using different RDI multipliers.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has undertaken a simple cost comparison. Setting all values for Enco+Bini 450 and Dab+Tram, except drug list prices, to be equal in the company model results in total costs and

total QALYs being the same in both arms. Using the PAS prices for Enco+Bini 450 and list prices for Dab+Tram results in Enco+Bini 450 costing *[redacted] per person compared to £373,318 per person for Dab+Tram. Treatment with Enco+Bini 450, therefore, costs *[redacted] per person than treatment with Dab+Tram.

The ERG considers that the evidence for using different RDI multipliers for the two treatments (Enco+Bini 450 and Dab+Tram) is not robust. Nevertheless, the ERG has undertaken a scenario analysis in which the different RDI multipliers employed in the company base case are implemented but no differences in efficacy (PFS or OS), utility values or AEs between the two treatments are modelled. Results from the ERG scenario show that, using list prices, treatment with Enco+Bini 450 is £14,562 per person less expensive than treatment with Dab+Tram. When this scenario is run using PAS prices for Enco+Bini 450 and list prices for Dab+Tram, treatment with Enco+Bini 450 is [redacted] than treatment with Dab+Tram.

1.10 Cost effectiveness conclusions

The ERG considers that the available clinical evidence suggests that when treatment with Enco+Bini 450 is compared with treatment with Dab+Tram there are no differences in OS or PFS outcomes, that utility values are equal and that the AE profiles of the two drug combinations are comparable. The ERG is, therefore, satisfied that there is no robust evidence of any statistically significant clinical differences when treatment with Enco+Bini 450 is compared with Dab+Tram and, as such, a cost-minimisation analysis is an appropriate approach for comparing the cost effectiveness of these two treatments.

Using list prices for Enco+Bini 450 and Dab+Tram, there is no difference in total costs between the drug combinations.

Using the ERG's preferred scenario (equivalent OS, PFS, utility values, AEs and RDI multipliers) and PAS prices for Enco+Bini 450 results in treatment with Enco+Bini 450 costing *[redacted]less than treatment with Dab+Tram. As estimated total QALYs are also assumed to be equal, this means that treatment with Enco+Bini 450 would be considered a cost effective alternative to treatment with Dab+Tram.

Clinical advice to the ERG is that, in the NHS, many patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma are treated first-line with a PD-1 inhibitor immunotherapy (pembrolizumab, nivolumab or nivolumab with ipilimumab) followed by Dab+Tram on disease progression. A subgroup of patients with BRAF V600 mutation-positive melanoma who have highly symptomatic or rapidly progressing disease are offered Dab+Tram as a first-line treatment. Vemurafenib or dabrafenib monotherapy may be used to treat patients with contra-indications to Dab+Tram. Patients whose disease responds to first-line treatment with Dab+Tram are offered immunotherapy as a second-line option; however, disease progression may be rapid after treatment with Dab+Tram, and patients may be unable to tolerate follow-on treatment with immunotherapies.

The ERG notes that the optimal sequencing of targeted treatment and immunotherapies for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma is not yet established.[9,21] There are, at present, no mature overall survival (OS) data from randomised controlled trials (RCTs) available to underpin treatment decisions.[9]

2.3 Place of Enco+Bini 450 in the treatment pathway

The company considers that the place of Enco+Bini 450 in the treatment pathway is as an alternative treatment to Dab+Tram and would be used in the same patient population as Dab+Tram (CS, p12). The company states that the tolerability and toxicity profile of treatment with encorafenib is different to the tolerability and toxicity profile of treatment with Dab+Tram (CS, p12).

2.4 Innovation

The company has not put forward a case for Enco+Bini 450 as an innovative treatment (CS, p84).

2.5 Number of patients eligible for treatment with encorafenib in combination with binimetinib

The company expects that if Enco+Bini 450 is recommended for use in the NHS, 86 patients would be eligible for treatment during the first year after a positive recommendation, rising to 486 patients by the 5th year (CS, Document A, p23). The ERG is unable to comment on the company's estimate as the methods used to calculate the estimate were only included in the budget impact template, to which the ERG did not have access. However, the ERG notes that in TA396,[13] the company marketing Dab+Tram for the treatment of patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma, estimated that a maximum of 992 patients per annum would be eligible for treatment in England.

Table 1 Comparison between NICE scope and company decision problem

Final scope issued by NICE **Parameter and specification**	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS**
Population Adults with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma	Adults with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma
Intervention Encorafenib with binimetinib	Enco+Bini 450 Evidence for the clinical effectiveness of Enco+Bini 450 is available from the COLUMBUS RCT. However, neither of the comparators included in the COLUMBUS trial (encorafenib 300mg monotherapy and vemurafenib monotherapy) are relevant comparators in the appraisal under discussion
Comparator Dabrafenib with trametinib	Dab+Tram In the absence of direct evidence for the clinical and cost effectiveness of Enco+Bini 450 compared with Dab+Tram, the company presents evidence derived from network NMAs
Outcomes PFS OS RR AEs HRQoL	PFS, OS, RR, AEs and HRQoL data are from the COLUMBUS trial. Only descriptive, interim OS results are available due to the statistical approach (hierarchical testing) used to analyse COLUMBUS trial data Presented PFS, OS, HRQoL and AE data for the comparison of Enco+Bini 450 with Dab+Tram are derived from the company's NMAs
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any PAS for the intervention or comparator technologies will be taken into account	The company's economic analysis has been designed to estimate the cost effectiveness of Enco+Bini 450 versus Dab+Tram from the perspective of the NHS The model time horizon is 30 years, approximating a patient's lifetime Results using the PAS agreed with the Department of Health are presented in the company's base case. The ERG has re-run the company's base case analysis using the discounted prices for all drugs included in the company model, and the results are provided in a confidential appendix
Other considerations Where the evidence allows, the following subgroups will be considered: i) people with previously untreated disease ii) people with previously treated disease that progressed on or after first-line immunotherapy Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation	The company explains (CS, Table 1) that only 6% of patients in the COLUMBUS trial had received prior treatment with immunotherapy in the metastatic setting. The company, therefore, did not provide economic results for subgroups based on prior treatment experience

AE=adverse event; CS=company submission; HRQoL=health-related quality of life; NMA=network meta-analysis; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; PSS=personal social services; RCT=randomised controlled trial; RR=response rate. Source: CS, adapted from Table 1

COMBI-v and COMBI-d trials, trials in which Dab+Tram was compared with vemurafenib and dabrafenib, respectively.

The company discussed the anti-cancer treatments that patients in the COLUMBUS trial had received prior to being randomised into the trial (CS, Table 7, p26). The ERG notes from the company's clarification response that approximately 25% of patients had received treatment in the adjuvant setting (most were treated with interferons or interleukins, five patients received ipilimumab), and that 6% of patients had received treatment in the metastatic setting. In the metastatic setting, [redacted] patients had previously been treated with ipilimumab and [redacted] patients with PD1 or PD-L1 inhibitors.

The ERG is satisfied that, overall, patients recruited to the COLUMBUS trial are representative of patients treated with advanced (unresectable or metastatic) BRAF V600 melanoma who are treated in the NHS. The ERG notes that most patients (72%) in the COLUMBUS trial were of ECOG PS 0 and the remainder (28%) were of ECOG PS 1. Clinical advice to the ERG is that patients with PS 2 or PS 3 are treated in the NHS. The ERG notes that, under the exclusion criteria of the COLUMBUS trial, patients with untreated brain metastases were excluded, and very few patients (3.6%) with treated brain metastases were recruited. Clinical advice to the ERG is that patients with brain metastases represent an important subgroup of patients who are treated in the NHS. The ERG notes that life expectancy for patients who develop brain metastases is limited to between 3 and 5 months.[53]

4.4 Risk of bias assessment for the COLUMBUS trial

The company assessed the risk of bias in the COLUMBUS trial using the minimum criteria set out in the NICE Guide to the Methods of Technology Appraisal[28] (**Error! Reference source not found.**).

The ERG considers that the COLUMBUS trial was generally well designed and well conducted and that the trial has a low risk of bias. The ERG notes that the open-label design of the COLUMBUS trial provides the opportunity for subjective results and investigator-assessed outcomes to be biased; however, the primary outcome of PFS and outcomes related to disease response were assessed by a blinded independent review committee (BIRC). The outcome of OS is an objective outcome that should not be prone to bias.

Table 2 PFS by BIRC and local investigator review for Enco+Bini 450 versus vemurafenib

	Enco+Bini 450 N=192	Vemurafenib N=191
BIRC, FAS, Part 1, data-cut off 19 May 2016		
Patients with events (% of total)	98 (51.0)	106 (55.5)
Median follow-up time in months (95% CI)[a]	16.7 (16.3 to 18.4)	14.4 (10.1 to 16.6)
Median PFS (95% CI)[b]	14.9 (11.0 to 18.5)	7.3 (5.6 to 8.2)
HR (95% CI), stratified one-sided log-rank p-value	0.54 (0.41 to 0.71); p<0.0001	
Investigator review, FAS, Part 1, data-cut off 19 May 2016		
Patients with events (% of total)	102 (53.1)	121 (63.4)
Median PFS (95% CI)[b]	14.8 (10.4 to 18.4)	7.3 (5.7 to 8.5)
HR (95% CI), stratified one-sided log-rank p-value[c]	0.49 (0.37 to 0.64); one-sided nominal p<0.0001	
BIRC, FAS, Part 1, data-cut off 7 November 2017		
Patients with events (% of total)	[redacted]	[redacted]
Median follow-up time in months (95% CI)[a,d]	32.3 (31.7 to 34.9)	22.2 (11.1 to 32.3)
Median PFS (95% CI)[b]	14.9 (11.0 to 20.2)	7.3 (5.6 to 7.9)
HR (95% CI), stratified one-sided log-rank p-value	0.51 (0.39 to 0.67); p<0.0001	
Investigator review, FAS, Part 1, data-cut off 7 November 2017		
Patients with events (% of total)	[redacted]	[redacted]
Median PFS (95% CI)[b]	[redacted]	[redacted]
HR (95% CI), stratified one-sided log-rank p-value[c]	[redacted]	

[a] Median duration of follow-up estimates by reverse Kaplan-Meier analysis. Median values reflect the potential follow-up in the absence of a PFS event
[b] Values were calculated using the Brookmeyer and Crowley method
[c] P-values are nominal and for descriptive purposes only
[d] In the company response to ERG clarification letter, medians and interquartile ranges are reported. However, the ERG believes that the results provided are based on reverse Kaplan-Meier analysis and therefore are medians and 95% CIs (rather than IQRs)
BIRC=blinded independent review committee; CI=confidence interval; FAS=full analysis set; HR=hazard ratio; IQR=interquartile range; PFS=progression-free survival
Source: CS, adapted from Table 10, Table 11. CS, Appendix L.3.2, adapted from Table 33, Table 34; COLUMBUS trial publications[30,59]

Concordance of PFS events per BIRC and investigator assessment was presented in the CS, according to the event type for analysis (progressive disease [PD], death or censored) and by timing of PD events (i.e., where the event type in analysis is concordant, whether BIRC and investigator review judged the event to have occurred at the same time, or one review judged the event to have occurred earlier than the other).

At the data cut-off date 19th May 2016, an "event type" discordance occurred for [redacted] in the Enco+ Bini 450 arm and [redacted] in the vemurafenib arm (see Table 12 of the CS). The ERG asked the company for clarification regarding discordance between BIRC and investigator for [redacted] 'death' events in the Enco+Bini 450 and vemurafenib arms. For [redacted] in the Enco+Bini 450 arm, progression, as assessed by the investigators, was not confirmed by the BIRC and all [redacted] subsequently died without having progression confirmed by BIRC. For [redacted] in the vemurafenib arm, progression had not been assessed by the investigator, whereas PD was concluded by the BIRC and these [redacted] patients

died within 8 weeks of the BIRC assessment. For [redacted] in the Enco+Bini 450 arm, the investigator considered that there were no adequate post-baseline tumour assessments for legibility reasons and censored data from that patient. The BIRC was able to perform the tumour assessment (no PD judged) and the patient died within 8 weeks of this BIRC assessment.

A "timing discordance" was observed for [redacted] in the Enco+Bini 450 arm and for [redacted] in the vemurafenib arm (see Section B.2.6.2.2 of the CS). The company notes that a [redacted] between the Enco+Bini 450 and vemurafenib arms were observed.

At the data cut-off date 7th November 2017, the ERG notes that [redacted] of event type discordance occurred compared to the first data cut-off date: [redacted] in the Enco+Bini 450 arm and [redacted] in the vemurafenib arm (see Appendix L.3.2, Table 35 of the CS) and that a [redacted] between the Enco+Bini 450 and vemurafenib arms were also observed (see Appendix L.3.2, Table 36 of the CS). The ERG notes a difference of [redacted] in the median PFS times in the Enco+Bini 450 arms by BIRC and by investigator review which may be due to the timing discordance. The ERG notes that for the two data-cut off dates and both treatment arms, more events were recorded by investigator review than by BIRC (

Table 2) and that the proportion of discordance of events, particularly the timing of events is relatively high for both treatment arms. However, the ERG notes that the HRs and p-values of PFS for Enco+Bini 450 versus vemurafenib are very similar across the two data-cut off dates and according to BIRC or investigator review (

Table 2). Therefore, the discordance present between BIRC and investigator review does not seem to have impacted on the overall PFS results.

Subgroup analyses were performed at both dates of data cut-off, see Section **Error! Reference source not found.** of this ERG report for further details of subgroups considered. At both time points, all subgroups demonstrated point estimates of HRs for PFS in favour of Enco+Bini 450 versus vemurafenib, except for the subgroup with brain metastases present at baseline. However, the number of patients included within this brain metastases subgroup, and in other subgroups, is small; CIs around HRs of small subgroups are wide and, therefore, results should be interpreted with caution. Further details of results from subgroup analyses can be found in Section 2.7, Appendix E.1 of the CS and in the company's response to the ERG clarification letter.

At the data-cut off date of 19th May 2016, multivariate Cox regression was performed (see Section 4.5.1 of this ERG report for further details). The ERG highlights that efficacy results are interpreted in the CS in terms of relative risk rather than hazard and that the correct interpretation is that [redacted]). The only other statistically significant pre-specified covariate was [redacted] which was associated with an increase in PFS ([redacted]). The comparison of [redacted] was also associated with an increase in PFS ([redacted]), but the effect of region was not statistically significant when analysed collectively ([redacted]).

4.6.3 Key secondary efficacy outcomes

PFS for Enco+Bini 450 versus Enco 300

A key secondary efficacy objective was to compare PFS of Enco+Bini 450 with Enco 300 based on BIRC. Results of this key secondary efficacy outcome analysis are summarised in Table 3.

Table 3 Summary of PFS results (BIRC) for Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 19th May 2016

	Enco+Bini 450	Enco 300
Patients with events/patients included in analysis n/N (%)	98/192 (51.0)	96/194 (49.5)
Median follow-up time in months (95% CI)[a]	16.7 (16.3 to 18.4)	16.6 (14.8 to 18.1)
50th (median) percentile of PFS (95% CI)[b]	14.9 (11.0 to 18.5)	9.6 (7.5 to 14.8)
HR (95% CI), stratified one-sided log-rank p-value	0.75 (0.56 to 1.00); p=0.0256	

[a] Median duration of follow-up estimates by reverse Kaplan-Meier analysis. Median values reflect the potential follow-up in the absence of a PFS event
[b] Values were calculated using the Brookmeyer and Crowley method
BIRC=blinded independent review committee; CI=confidence interval; FAS=full analysis set; HR=hazard ratio; PFS=progression-free survival
Source: CS, adapted from Table 15; the COLUMBUS trial publication[30]

There were 98 PFS events (51% of patients) in the Enco+Bini 450 arm and 96 events (49.5% of patients) in the Enco 300 arm. The remaining patients were censored and the most common

[redacted] (see Table 44 and Table 45 of Appendix L.4 of the CS for detailed reasons for censoring).

Additional OS results are summarised in Appendix 2, Section 0 of this ERG report.

Other efficacy outcomes

The results of other secondary efficacy response outcomes for treatment with Enco+Bini 450 versus Enco 300 and versus vemurafenib, which did not inform the company's economic analyses, are summarised in Appendix 1, Section **Error! Reference source not found.** of this ERG report

4.7 Adverse events

Adverse events reported in the COLUMBUS trial

Safety data from the COLUMBUS trial are reported in the CS, Section B.2.10. The company states (CS, p75) that the safety data are derived from all patients in the COLUMBUS trial who received at least one dose of study drug, including 192 patients treated with Enco+Bini 450, 186 patients treated with Enco 300 and 186 patients treated with vemurafenib. The results discussed in this section are taken from the data cut-off date of 9th November 2016.

Summary of adverse events

A summary of time on treatment, AEs and deaths from the COLUMBUS trial are presented in the CS and reproduced in **Error! Reference source not found.**. The company highlights (CS, p81) that patients treated with Enco+Bini 450 remained on treatment for longer (median=[redacted]) than patients treated with either Enco 300 (median=[redacted]) or vemurafenib (median=[redacted]) arms.

The ERG notes that most patients experienced at least one AE across the three treatment arms (range=[redacted]). The incidence of Grade 3 to Grade 4 AEs (range=[redacted]), the incidence of serious AEs (SAEs) of any grade (range=[redacted]) and Grade 3 to 4 SAEs (range=[redacted]) was similar across the three treatment arms.

The percentage of patients experiencing AEs leading to treatment discontinuation was similar among the three arms (range=[redacted]). Slightly more of the patients in the Enco+Bini 450 arm ([redacted]), compared with the vemurafenib *([redacted])* and Enco 300 ([redacted]) arms experienced Grade 3 to Grade 4 AEs leading to treatment discontinuation.

The ERG notes that fewer patients in the Enco+Bini 450 arm experienced an AE requiring dose interruption and/or adjustment compared with the Enco 300 and vemurafenib arms ([redacted] respectively) and AEs requiring additional treatment ([redacted] respectively). Similarly, patients in the Enco+Bini 450 arm experienced

a lower arthralgia ([redacted]), nausea ([redacted]), hyperkeratosis ([redacted]), dry skin ([redacted]), myalgia ([redacted]) and vomiting ([redacted]).

Grade 3 to Grade 4 adverse events

The most common Grade 3 to Grade 4 AEs that occurred in ≥5% of patients receiving Enco+Bini 450 were increased gamma-glutamyl transferase ([redacted]), increased creatine phosphokinase ([redacted]), hypertension ([redacted]), and increased ALT ([redacted]). In the vemurafenib arm, the most common AEs were arthralgia ([redacted]), increased gamma-glutamyl ([redacted] and hypertension ([redacted]). In the Enco 300 arm, the most common Grade 3 to 4 AEs were palmar-plantar erythrodysaesthesia syndrome ([redacted]), myalgia ([redacted]), and arthralgia ([redacted]).

The most frequently reported Grade 3 to Grade 4 SAEs in ≥2% of patients in the Enco+Bini arm were pyrexia ([redacted]) and anaemia ([redacted]). In the in the vemurafenib arm, the most frequently reported Grade 3 to Grade 4 AEs were general physical health deterioration ([redacted]) and back pain ([redacted]). In the Enco 300 arm the most frequently reported Grade 3 to Grade 4 AEs were vomiting ([redacted]), nausea ([redacted]) and pain ([redacted]).

Serious adverse events

Full details of the drug-related SAEs are presented in Table 31 in the CS. The most common all grade SAEs (≥2.0% of patients) in each arm were pyrexia ([redacted]), abdominal pain ([redacted]), acute kidney injury ([redacted]) and anaemia ([redacted]) in the Enco+Bini 450 arm; general physical health deterioration ([redacted]) in the vemurafenib arm and vomiting and nausea (each [redacted]), pain ([redacted]) and back pain ([redacted]) in the Enco 300 arm.

Summary of adverse events from the COLUMBUS trial

The company considers (CS, p84) that the results of COLUMBUS trial generally demonstrate a favourable safety and tolerability profile for patients treated with the combination of Enco+Bini 450, compared with either vemurafenib or Enco 300. The company reports that the 'common' AEs associated with treatment with BRAF and MEK inhibitors that occurred during the COLUMBUS trial were 'generally manageable' and that no SAEs of special interest were identified. The company highlights that the patients treated with Enco+Bini 450 had longer time on treatment compared with patients treated with Enco 300 and that the frequency of AEs was similar in both groups of patients. The company considers that the addition of binimetinib to encorafenib allows patients to tolerate treatment with encorafenib at the higher dose of 450mg.

The ERG agrees with the company that treatment with Enco+Bini 450 appears to be as well-tolerated by patients as treatment with Enco 300 or vemurafenib. The ERG notes, however, that the results of the COLUMBUS trial do not provide evidence for the safety and tolerability

The definitions of PFS and OS from the trial publications are presented in Appendix D.1.3.1, Table 9 of the CS. The ERG notes that the outcome definitions for PFS and OS are generally consistent across trials. However, the ERG also considers, as also acknowledged by the company, that the variability of the trial duration (ranging from 2 years to 6 years) and maturity of data (median follow-up for OS ranged from 11 months to 33.6 months) across the trials is a source of heterogeneity and adds uncertainty to the generalisability of results. Furthermore, six of the seven trials permitted treatment crossover during the OS follow-up period. The company, therefore, investigated the potential impact of crossover in an additional crossover adjusted NMA for OS, with the rank preserving structural failure time (RPSFT)[68] model used to adjust OS data in the COLUMBUS trial as a post-hoc analysis.

The ERG notes that although the definitions of PFS were consistent across the included trials, the methods of assessing PFS were not consistent. All included trials reported results for PFS assessed by local investigator review, but only the COLUMBUS, coBRIM, COMBI-d and BRF113220 Part C trials reported results by BIRC. Therefore, a network of evidence to enable an indirect comparison of Enco+Bini 450 versus Dab+Tram for PFS by BIRC could not be constructed (see Figure 16 of the CS) and only an NMA of PFS by local investigator review was feasible. As acknowledged by the company, local investigator assessment of PFS in open-label trials may be subject to bias and, as five of the included trials were of an open-label design (see Section **Error! Reference source not found.** of this ERG report), the risk of bias in the PFS NMA by local investigator review should be taken into account when interpreting results. During clarification, the ERG requested an additional sensitivity analysis of PFS, restricting the network to the five open-label designed trials only, to investigate whether such bias impacted on NMA results (see **Error! Reference source not found.** and **Error! Reference source not found.** of this ERG report).

The company assessed the PH assumption for investigator assessed PFS and for OS by digitising published K-M curves from all included trials and presented log cumulative hazard plots in Appendix D.1.3.1, Figure 3 to Figure 16 of the CS. For both PFS and OS, the company interpreted that the PH assumption broadly holds across some of the included trials but is violated in others, and performed sensitivity analyses of the NMAs for both PFS and OS removing trials that violated the PH assumption.

The company also performed two further adjusted NMA sensitivity analyses for PFS using post-hoc data from the COLUMBUS trial. Firstly, using a Cox PH regression model to adjust for AJCC cancer stage, ECOG PS, BRAF status, baseline LDH and geographical region, and secondly using a stratified log-rank adjustment for BRAF status and baseline LDH covariates.

central randomisation or minimisation systems for two trials (BRF113220 Part C and BRIM-3). The ERG judges these methods to be adequate and, therefore, the risk of bias for allocation concealment of all trials is low.

The company notes that the five trials of open-label design (COLUMBUS, COMBI-v, BRIM-3, BREAK-3 and BRF113220 Part C) are at higher risk of bias than the two trials of double-blind design (COMBI-d and coBRIM). The ERG judges that the inclusion of open-label and double-blind designs within the NMAs is the only risk of bias present across the trials (see Section **Error! Reference source not found.** of this ERG report for further discussion).

4.9.5 Results from the NMAs

Efficacy and safety results of each of the included trials are summarised in Appendix D.1.3.1, Table 7 and HRQoL results of each of the included trials are summarised in Appendix D.1.3.1, Table 8.

NMA results are presented as the effect size (HR for PFS and OS, OR for incidence of any Grade ≥3 AEs and delta [i.e., difference in utility score] for HRQoL outcomes) with 95% CrIs. Results are presented for Enco+Bini 450 versus Dab+Tram (for consistency with the direction of effect presented from the COLUMBUS trial) and also for Dab+Tram versus Enco+Bini 450 for direct utilisation within the economic model (see Section **Error! Reference source not found.**of this ERG report). For comparisons of Enco+Bini 450 versus Dab+Tram, a HR or OR<1 indicates a result in favour of Enco+Bini 450 for clinical and safety outcomes and a delta>0 indicates a result in favour of Enco+Bini 450 for HRQoL outcomes.

NMA results for investigator assessed PFS

The evidence network for the base case analysis of investigator assessed PFS is provided in Figure 10 of the CS (and the general structure of this network is provided in **Error! Reference source not found.**). As described in Section **Error! Reference source not found.** of this ERG report and demonstrated in Figure 16 of the CS, an evidence network with an indirect comparison of Enco+Bini 450 versus Dab+Tram could not be constructed for BIRC. Four sensitivity analyses of PFS were also performed (see Section **Error! Reference source not found.** of this ERG report). Results for the base case analysis and sensitivity analyses of PFS are presented in **Error! Reference source not found.**.

so it is unclear which trials and which data contributed to this NMA. Results for safety outcomes are presented in Table 4.

Table 4 NMA results for safety outcomes (fixed-effects model)

Analysis	Enco+Bini 450 vs Dab+Tram	Dab+Tram vs Enco+Bini 450
Any Grade ≥3 AEs	OR 1.18, 95% CrI (0.70 to 1.98)	OR 0.85, 95% CrI (0.51 to 1.43)
Any serious AEs	OR 0.86, 95% CrI (0.52 to 1.43)	OR 1.16, 95% CrI (0.70 to 1.92)[a]

[a] Result not presented in the CS, calculated by inverting result for Enco+Bini 450 vs Dab+Tram
AE=adverse events; Bini=binimetinib; CrI=credible interval; Dab=dabrafenib; Enco=encorafenib; OR=odds ratio Tram=trametinib
Source: CS, adapted from Table 24

For the incidence of any Grade ≥3 AEs, the result favours Dab+Tram (OR>1), while for serious AEs the result favours Enco+Bini 450 (OR<1). However, for both analyses, the CrI crosses 1. The ERG notes, however, that these NMA results for AEs are not used in the economic model because, "…if the OR from the NMA is used, a numerical benefit would be assumed for Dab+Tram vs Enco+Bini 450 for all AEs included and this is not reflective of what is observed within the individual trials (CS, p115)." Instead, the company uses data relating to specific Grade 3 or 4 AEs with an incidence of at least 5% in either the Enco+Bini 450 arm of the COLUMBUS trial, or the Dab+Tram arms of the COMBI-v and COMBI-d trials (see Table 42 of the CS).

NMA results for HRQoL outcomes

The evidence networks for the three EQ-5D utility score outcomes (pre-progression, at week 32 and at disease progression) are presented in Figure 11 to Figure 13 of the CS (and the general structure of these network is provided in **Error! Reference source not found.** of this ERG report). Results for HRQoL outcomes are presented in Table 5.

Table 5 NMA results for HRQoL outcomes (fixed-effects model)

	Enco+Bini 450 vs Dab+Tram	Dab+Tram vs Enco+Bini 450
EQ-5D utility score, pre-progression	Dt -0.02, 95% CrI (-0.05 to 0.01)	Dt 0.02, 95% CrI (-0.01 to 0.05)
EQ-5D utility score, DCFB at Week 32	Dt -0.04, 95% CrI (-0.10 to 0.02)	Dt 0.04, 95% CrI (-0.02 to 0.10)
EQ-5D utility score, DCFB at disease progression	Dt -0.04, 95% CrI (-0.12 to 0.04)	Dt 0.04, 95% CrI (-0.04 to 0.12)

Bini=binimetinib; CrI=credible interval; Dab=dabrafenib; DCFB=difference in change from baseline; Dt=delta; Enco=encorafenib; EQ-5D= EuroQol-5 dimensions; OR=odds ratio Tram=trametinib
Source: CS, adapted from Table 23

For all HRQoL outcomes, the NMA results favour Dab+Tram (Delta<0); however, the CrIs cross 0 for all analyses. The company also notes that the numerical improvements in favour of Dab+Tram were also inferior to the minimal difference in EQ-5D-5L score considered to be clinically important (0.08 points).[76]

for the exclusion of the identified studies are presented in the CS (Section B.3.1 and Appendix G).

5.1.3 Findings from the cost effectiveness review

None of the studies identified by the company's literature search included Enco+Bini 450 as a comparator.

5.1.4 ERG critique of the company's review of cost effectiveness evidence

A summary of the ERG's appraisal of the company's search and selection processes is provided in Table 6.

Table 6 ERG appraisal of systematic review methods (cost effectiveness)

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection independently applied by two or more reviewers?	Yes
Was data extracted, independently, by two or more reviewers?	Yes
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted, independently by two or more reviewers?	Yes
Were any relevant studies identified?	No

Source: LRiG checklist 2017

5.2 ERG summary of the company's submitted economic evaluation

5.2.1 Model structure

The company developed a cohort-based partitioned survival model in Microsoft Excel. The model was designed to assess the incremental cost effectiveness of treatment with Enco+Bini 450 versus treatment with Dab+Tram for advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

The model structure comprises three mutually exclusive health states: progression-free (PF), post-progression (PP) and death. The PF health state and PP health state include sub-states which are designed to account for primary treatment status (see Figure 1).The death state is an absorbing health state that captures all-cause mortality. The modelled population enters the model in the PF health state and on primary treatment (PF on primary treatment). At the end of every 1-month cycle, there is a risk of discontinuing primary treatment (transition to PF off primary treatment) and a risk of disease progression (transition to PP on primary

treatment). Patients who are in the PF off primary treatment health state can also experience disease progression (transition to PP off primary treatment). There is a risk of all-cause mortality in the PF and PP health states, whether on or off primary treatment. The company explains that the sub-states in the PF and PP health states are designed to account for the differential cost associated with being on or off primary treatment. Differential HRQoL values are not applied to the sub-states.

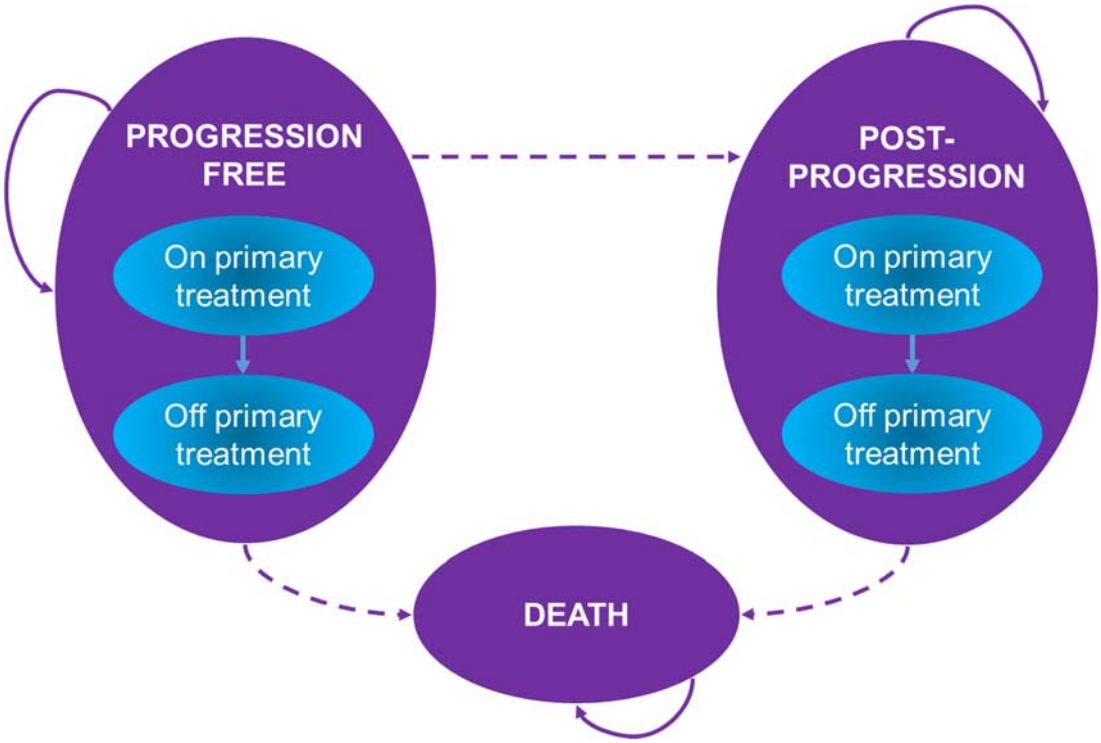

Figure 1 Health state structure of the company model
Source: CS, Figure 17

5.2.2 Population

In line with the final scope issued by NICE, the modelled population is patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The mean baseline age of the cohort (55.3 years) and the percentage of males (57.9%) reflect the characteristics of the population recruited to the COLUMBUS trial.

5.2.3 Interventions and comparators

Intervention

Enco+Bini 450 is implemented in the model as per the EMA marketing authorisation.[23] Encorafenib 450mg is administered as six 75mg oral capsules once daily and binimetinib 45mg is administered as three 15mg oral tablets twice daily.

Comparators

Dab+Tram is also administered orally. Dabrafenib 150mg (two 75mg oral capsules) is administered twice daily and trametinib 2mg (one 2mg oral tablet) is administered once daily (see CS, Sections B.1.2 and B.3.2.3).

Discontinuation

The model permits treatment discontinuation before disease progression and treatment continuation beyond disease progression in both the intervention and comparator arms. For the Enco+Bini 450 model arm, estimates of time to treatment discontinuation (TTD) are derived from TTD data from the Enco+Bini 450 arm of the COLUMBUS trial. The TTD data for the Dab+Tram model arm was assumed to be equivalent to that for the Enco+Bini 450 model arm.

5.2.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS). In line with the NICE's Guide to the Methods of Technology Appraisal,[28] the analysis excludes out-of-pocket expenses, carer costs and productivity costs. The cycle length is 1-month and the base case time horizon is set at 30 years, assuming an 85-year mean life expectancy. The NICE guide to the methods of technology appraisal[28] recommends a lifetime time horizon. Both costs and outcomes are discounted at 3.5% per annum in line with the NICE guide,[28] and a half-cycle correction is applied.

5.2.5 Treatment effectiveness and extrapolation in the base case

The company model has been constructed using K-M data from COLUMBUS trial and results from the company's NMAs. The follow-up period in the COLUMBUS trial was shorter than the model time horizon and, therefore, the company extrapolated OS, PFS and TTD trial data. The extrapolation method employed by the company involved fitting parametric models.

Overall survival

The company estimated the OS for the Enco+Bini 450 and Dab+Tram model arms using a three-part approach.

The OS K-M data from the Enco+Bini 450 arm of the COLUMBUS trial were used directly in the model up to month 44. From month 44 to year 10, digitised OS K-M curves from the AJCC[2] melanoma registry data were used. Then, a constant hazard extrapolation of the digitised OS K-M curves from the AJCC[2] melanoma registry data were used from year 10 to year 20. Thereafter, the model OS curve is constructed using age- and gender-matched general

population mortality rates,[85] scaled up proportionally to account for the increased relative risk of mortality in this population. The company highlights that the notion of 'scale-up' means that the cohort in the model cannot be cured throughout the entire time horizon of the analysis. The scale-up multiplier used by the company was calculated as the HR between the mortality hazard rate from the AJCC[2] case-mixed adjusted survival at 20 years and the corresponding rate from the general population (matched for age and gender distribution). In the model, general population mortality rates were derived from National Life-Tables for England and Wales.[85] At 20 years, the model cohort is 75 years of age and 57.9% of the model population are male. The resulting HR (scale-up multiplier) was 2.2. For the Dab+Tram arm, the point estimate HR derived from the company NMA is applied to the OS curve for the Enco+Bini 450 model arm. Figure 2 shows the OS K-M curve for both model arms.

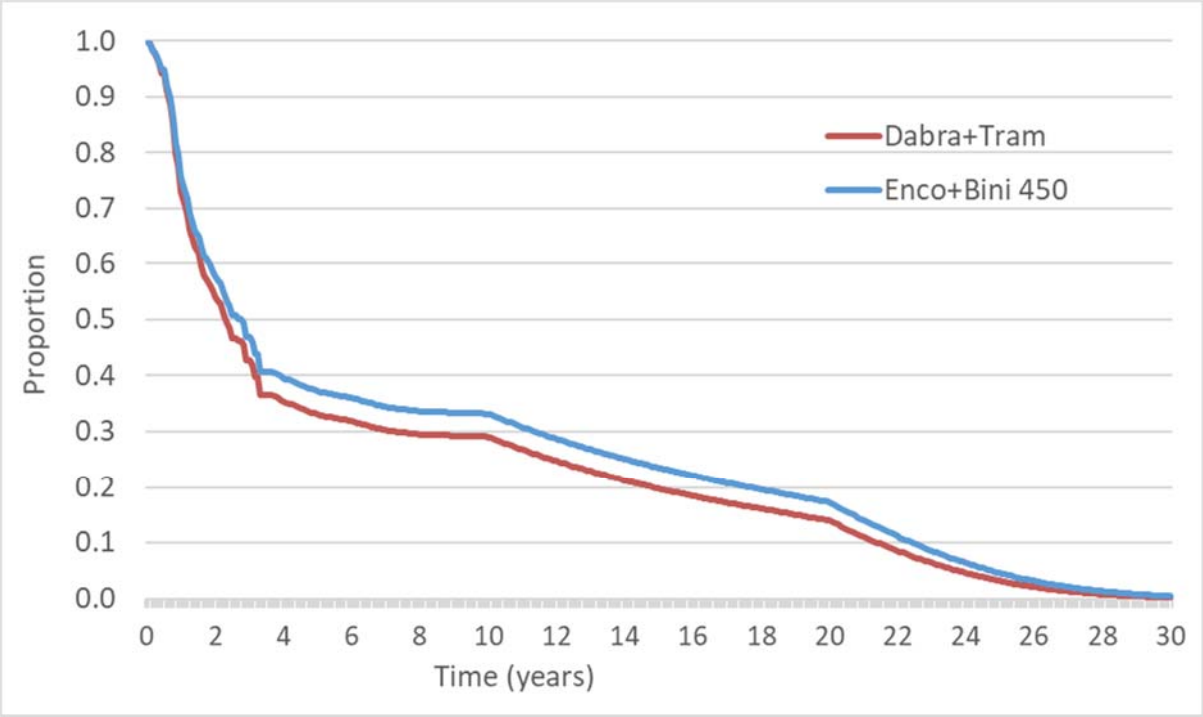

Figure 2 Reconstructed OS K-M curve for the Enco+Bini 450 and Dab+Tram arms used in the company model

Source: CS, Figure 19

Progression-free survival

Disease progression was assessed in the COLUMBUS trial by BIRC and, locally, by study investigators (local review). The company used data from the local review of progression in their model.

The PFS data for the Enco+Bini 450 arm of the COLUMBUS trial (November 7th, 2017 data cut) are available for up to 43 months. To identify the best PFS curve for the Enco+Bini 450

model arm, the company compared 13 possibilities. The first six curves were parametric models (exponential, gamma, Gompertz, log-logistic, log-normal and Weibull) that the company fitted to the PFS data for the Enco+Bini 450 arm from the COLUMBUS trial. The next six curves were piecewise PFS curves. The piecewise curves are a combination of the PFS trial data for the Enco+Bini 450 arm up month 43 and each one of the previously fitted parametric models (i.e., PFS trial data+parametric extrapolation). The 13th PFS curve was also a piecewise curve. To construct this last curve, the company first plotted the cumulative hazards from the PFS trial data for the Enco+Bini 450 arm. The company then identified a breakpoint on that cumulative hazards plot from which a linear trend was observed. The breakpoint was identified by (i) visually inspecting the cumulative hazards plots and (ii) by fitting multiple linear curves to the cumulative hazard plots and observing at which breakpoint the R^2 was maximum. The PFS trial data for the Enco+Bini 450 arm were then used up to the breakpoint, then, the hazard rate at the breakpoint was then applied for the remainder of the projection.

Of the 13 possible PFS curves for the Enco+Bini 450 model arm, the company used the PFS trial data for the Enco+Bini 450 arm up to month 43 plus the gamma extrapolation (PFS K-M + gamma). Clinical advice to the company was that a small proportion of patients would remain progression-free over the long-run and the company observed that the PFS K-M + gamma curve provided the most clinically plausible outcome, with the curve predicting that 10% of patients would remain progression free at 10 years.

To estimate the PFS K-M curve for the Dab+Tram model arm, the company applied the PFS HR from the NMA (see section 4.9 of this report to the PFS K-M curve for Enco+Bini 450 model arm.

5.2.6 Health-related quality of life

The EQ-5D-5L questionnaire was administered to COLUMBUS trial participants. Utility values were derived by cross-walking the EQ-5D-5L responses onto the EQ-5D-3L UK valuation set. Regression-based methods were then used to control for ECOG PS, AJCC cancer stage, healthcare provider visits, progression status (pre-progression, at disease progression and post-progression) and treatment status (on or off any antineoplastic treatment).

The company also conducted an NMA (search carried out in April 2018) to allow comparison between the utility score for patients treated with Enco+Bini 450 versus those treated with Dab+Tram at pre-progression, at 32 weeks post-treatment and at disease progression. Utility values from the COLUMBUS trial were included in the network. The NMA results showed that that mean utility score for patients treated with Dab+Tram was higher than the mean utility

score for Enco+Bini 450 at the three time-points of interest, but the differences were not statistically significant. The company considered it appropriate to apply utility values during the pre-progression states that differed by treatment (see Table 7).

Table 7 Summary of the utility values used in the company cost effectiveness analysis

Health state	Utility value, mean (SD)		Source
	Enco+Bini 450	Dab+Tram	
Progression-free	0.778 (0.015)	0.800 (0.015)	NMA
Post-progression	0.675 (0.030)	0.675 (0.030)	NMA

NMA=network meta-analysis; SD=standard deviation
Source: Company model

5.2.7 Resources and costs

The company's base case includes the cost of the following resources: drugs (first-line and subsequent lines), routine care (e.g., primary care and secondary care visits, including hospital admissions), AEs and terminal care. The company explain that they used a two-step process to inflate costs to the 2017/18 level. First, the cost was inflated to 2016/17 price level using the Hospital & Community Health Service Index[86] and then this cost was inflated by 1.243% (the average [geometric] inflation of the index between 2013 and 2016/17) to represent the 2017/18 level.

Primary treatments

Estimate of the quantity of Enco+Bini 450 or Dab+Tram used per patient per month are derived from COLUMBUS trial data. The proportion of patients in the model that receive Enco+Bini 450 and Dab+Tram are obtained from the TTD data for the Enco+Bini 450 arm of the COLUMBUS trial plus the company's log-logistic extrapolation of the trial data (TTD K-M + log-logistic). Similar to the method used by the company to identify their preferred PFS curve for the Enco+Bini 450 model arm, 13 TTD curves were also compared. TTD K-M + log-logistic was considered to be the most appropriate curve based on clinical opinion to the company (Section 3.3.1.3.3 of the CS).

Study drug treatment costs are summarised in

Table 8. The company model includes relative dose intensity (RDI) multipliers to account for the fact that not all patients on treatment receive the full dose, in order to be reflective of the conditions within trial that generated the estimates of effectiveness and safety. Both Enco+Bini 450 and Dab+Tram are administered orally. The company assumes that it takes a pharmacist 12 minutes to dispense Enco+Bini 450 or Dab+Tram and has applied a £15.22 administration cost per model cycle. A one-off treatment initiation cost of £415.89 was applied in the first model cycle to both model arms to account for the cost of hospital visits and examinations that are carried out before BRAFI+MEKi therapies are prescribed.

Table 8 Study drug costs

Drug	Dosing regimen	Cost per pack	Tablets per pack	RDI	Daily dose based on RDI	Cost per model cycle (using RDI)*
Encorafenib	450mg once a day	[redacted]	42 x 75mg	[redacted]	[redacted]	[redacted]
Binimetinib	45mg twice a day	[redacted]	84 x 15mg	[redacted]	[redacted]	[redacted]
Dabrafenib	150mg twice a day	£1,400.00	28 x 75mg	0.92	276.00	5,648.81
Trametinib	2mg once a day	£1,120.00	7 x 2mg	0.96	1.92	4,692.86

mg=milligram; RDI=relative dose multiplier; tab=tablet
* model cycle=30.42 days
Source: CS Table 46, Table 47 and Table 48

Subsequent treatments

A number of subsequent therapy options are available to people with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The company considers that a single weighted subsequent therapy cost sufficiently reflects the cost of all subsequent therapies. This cost is applied to all patients who discontinue either Enco+Bini 450 or Dab+Tram. The company states that there are insufficient data to simulate the spread of the subsequent therapy cost across discrete time-points.[87,88] The company considers that applying a one-off subsequent therapy cost is unlikely to have a large impact on the ICER per QALY gained since the mean treatment duration with subsequent therapy is short. The company notes that its approach to modelling the cost of subsequent therapy is consistent with a previous technology appraisal (TA369[13]) that evaluated the cost effectiveness Dab+Tram for advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

The company weighted subsequent therapy cost, by multiplying the per-cycle cost (that is drug cost and administration cost) for each therapy by the mean treatment duration for that therapy. For example, when costing pembrolizumab as a subsequent therapy, the company multiplied the estimated per-cycle cost (£8,039) by the mean treatment duration (6.642 month) leading to a subsequent therapy cost of £53,391. For both arms of the model, the company weighted the total cost for each subsequent therapy by the proportion of patients in the Enco+Bini 450 arm of COLUMBUS trial that received that particular therapy (**Error! Reference source not found.**). The one-off subsequent therapy cost was calculated as the sum of the weighted total cost for each subsequent therapy.

parameter estimate by plus/minus 20%. Results from the OWSAs show that the company model is most sensitive to the variation in the base case TTD HR (see Figure 3).

Figure 3 Tornado diagram showing OWSA results for treatment with Enco+Bini 450 versus treatment with Dab+Tram

Admin=administration; HR=hazard ratio; NMB=net monetary benefit; OS=overall survival; QALY=quality adjusted life year; RDI=relative dose intensity; TTD=time to treatment discontinuation; Tx=treatment
Source: CS, Figure 31

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (10,000 iterations) to assess the effect of uncertainty surrounding the parameter values used in the model. The company model probabilistic results (increment cost of *[redacted] and incremental QALY gain of +0.432) are similar to the model deterministic results (the cost effectiveness plane is presented in **Error! Reference source not found.**). The cost effectiveness acceptability curve is provided in **Error! Reference source not found.** and shows that the probability of treatment with Enco+Bini 450 being cost effective at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained is 100%.

5.4 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

For the comparison of treatment with Enco+Bini 450 versus Dab+Tram, the ERG's preferred scenario assumes there is no difference in efficacy (PFS or OS), utility values or AEs between treatments and the RDI multipliers for Enco+Bini 450 and Dab+Tram are both set to 1 (Table 9, Scenario B). At list prices, the ERG's preferred scenario results in estimated costs and QALYs being identical for Enco+Bini 450 and Dab+Tram. Using PAS prices for Enco+Bini 450, Enco+Bini 450 generates the same QALYs as Dab+Tram and leads to a [redacted] per person.

The ERG considers that the evidence for using different RDI multipliers for Enco+Bini 450 and Dab+Tram is not robust. However, the ERG, whilst assuming no difference in efficacy (PFS or OS), utility values or AEs between the two treatment combinations, has generated results from a scenario analysis (Table 9, B1) using the differential RDI multipliers that the company uses for the two drug combinations. Results from this scenario show that, using list prices, treatment with Enco+Bini 450 is £14,562 per person less expensive than treatment with Dab+Tram, whilst using PAS prices for Enco+Bini 450, treatment with Enco+Bini 450 is [redacted] than treatment with Dab+Tram.

Results generated by the ERG's changes to the company model are provided in Table 9. The ERG model adjustments to the company base case analysis are described in Appendix 8.3 of this ERG report.

Table 9 Results from ERG adjustments to the company base case (PAS prices for Enco+Bini 450, list prices for Dab+Tram)

Scenario/ERG amendment	Enco+Bini 450		Dab+Tram		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company's base case (RDI values corrected): PAS prices for Enco+Bini 450 and list prices for Dab+Tram	[redacted]	4.22	£353,603	3.77	[redacted]	0.45	Dominant	
B. ERG preferred scenario (cost-minimisation analysis: PAS prices for Enco+Bini 450 and list prices for Dab+Tram)	[redacted]	4.22	£373,318	4.22	[redacted]	0.00	-	-
B1. ERG preferred scenario with RDI multipliers for Enco+Bini 450 and Dab+Tram as in company base case (PAS prices for Enco+Bini 450 and list prices for Dab+Tram)	[redacted]	4.22	£356,094	4.22	[redacted]	0.00	-	-

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=patient access scheme; QALY=quality adjusted life year gained; RDI=relative does intensity

5.5 Conclusions of the cost effectiveness section

Clinical advice to the ERG is that, in the NHS, the first-line treatment prescribed to most of the population recruited to the COLUMBUS trial, who had ECOG PS 0 or 1, would be a PD-1 inhibitor immunotherapy. Further, clinical advice to the ERG is that, in the NHS, only the minority of patients with highly symptomatic disease or rapidly progressing disease (i.e., those with poor PS) would be prescribed first-line treatment with a targeted therapy. The ERG, therefore, considers that the results from the company model may be of limited relevance to patients in the NHS.

Results from the company's NMAs suggest that there are no statistically significant differences in terms of PFS, OS, utility values or incidence in Grade ≥3 AEs for the comparison of treatment with Enco+Bini 450 versus Dab+Tram. Despite reservations about the reliability of results from the company's NMAs, the ERG considers that a cost-minimisation analysis is an appropriate approach for comparing the cost effectiveness of these two treatments.

Using list prices for Enco+Bini 450 and Dab+Tram, there is no difference in total costs between the drug combinations.

Using the ERG's preferred scenario (equivalent OS, PFS, utility values, AEs and RDI multipliers) and PAS prices for Enco+Bini 450 results in treatment with Enco+Bini 450 costing *[redacted] than treatment with Dab+Tram. As estimated total QALYs are also assumed to be equal, this means that results show that treatment with Enco+Bini 450 [redacted] alternative to treatment with Dab+Tram.

6 OVERALL CONCLUSIONS

The objective of this appraisal, as outlined in the decision problem described in the final scope issued by NICE, is to compare the clinical (and cost effectiveness) of treatment with Enco+Bini 450 versus Dab+Tram for adults with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The main source of clinical effectiveness data used by the company to address the decision problem is the COLUMBUS trial; this trial was designed to compare the efficacy of treatment with Enco+Bini 450 versus vemurafenib, and Enco+Bini 450 versus Enco 300. As 94% of patients in the COLUMBUS trial had had no previous treatment and, at baseline, ≥70% had an ECOG of 0 (the remainder had an ECOG of 1), the clinical evidence for Enco+Bini 450 is predominantly in the first-line setting for patients with good performance status (ECOG PS 0/1).

As treatment with Dab+Tram was not a comparator in the COLUMBUS trial, the company carried out a series of NMAs to compare treatment with Enco+Bini 450 versus Dab+Tram in terms of efficacy (PFS and OS), safety outcomes and HRQoL. The results of these NMAs show that there is no statistically significant difference between the two treatments for any of these four outcome measures. However, as the NMAs are methodologically limited, the ERG considers that there are some doubts about the reliability of these conclusions.

In the NHS, there are several immunotherapies (pembrolizumab, nivolumab, ipilimumab and the combination of nivolumab+ipilimumab) that are recommended options for treating advanced (unresectable or metastatic) melanoma that has not been previously treated. This means that an immunotherapy is a first-line treatment option for all patients with advanced BRAF V600 mutation-positive melanoma. Dab+Tram is also recommended for treating advanced (unresectable or metastatic) melanoma in adults with a BRAF V600 mutation (as are two monotherapies: dabrafenib and vemurafenib). Clinical advice to the ERG is that, in the first-line setting, patients in the NHS with ECOG PS 0-1 with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma are usually treated with an immunotherapy (often pembrolizumab). This means that, for the majority of untreated patients with advanced BRAF V600 mutation-positive melanoma in the NHS, the comparison of Enco+Bini 450 versus Dab+Tram is not relevant.

Furthermore, clinical advice to the ERG is that, in the first line setting, treatment with Dab+Tram is usually reserved for patients with highly symptomatic or rapidly progressing disease as treatment with Dab+Tram tends to be effective more quickly than an immunotherapy (although duration of response is limited). However, as Dab+Tram is recommended by NICE for all patients with advanced BRAF V600 mutation-positive

melanoma, not only for patients with highly symptomatic or rapidly progressing disease, comparing Enco+Bini 450 with Dab+Tram for the small subgroup of patients not treated with an immunotherapy is appropriate. The ERG, however, notes that none of the patients in the COLUMBUS trial appear to have highly symptomatic or rapidly progressing disease; indeed, most patients (≥70%) have an ECOG PS of 0 and the remainder have an ECOG of 1. Therefore, the clinical evidence presented in the CS is of limited relevance to the decision problem faced by clinicians in the NHS.

Clinical advice to the ERG is that, in the NHS, the first-line treatment prescribed to most of the population recruited to the COLUMBUS trial, who had ECOG PS 0 or 1, would be a PD-1 inhibitor immunotherapy. Further, clinical advice to the ERG is that, in the NHS, only the minority of patients with highly symptomatic disease or rapidly progressing disease (i.e., those with poor PS) would be prescribed first-line treatment with a targeted therapy. The ERG, therefore, considers that the results from the company model may be of limited relevance to patients in the NHS.

Results from the company's NMAs suggest that there are no statistically significant differences in terms of PFS, OS, utility values or incidence in Grade ≥3 AEs for the comparison of treatment with Enco+Bini 450 versus Dab+Tram. Despite reservations about the reliability of results from the company's NMAs, the ERG considers that a cost-minimisation analysis is an appropriate approach for comparing the cost effectiveness of these two treatments.

Using list prices for Enco+Bini 450 and Dab+Tram, there is no difference in total costs between the drug combinations.

Using the ERG's preferred scenario (equivalent OS, PFS, utility values, AEs and RDI multipliers) and PAS prices for Enco+Bini 450 results in treatment with Enco+Bini 450 costing *[redacted] than treatment with Dab+Tram. As estimated total QALYs are also assumed to be equal, this means that results show that treatment with Enco+Bini 450 [redacted] alternative to treatment with Dab+Tram.

Consistently across all analyses, ORR and DCR is highest for Enco+Bini 450, followed by Enco 300 and lowest for Vemurafenib. Results for ORR and DCR are very similar for the analyses at the two data cut-off dates. At both analysis times and across all treatment arms, ORR and DCR rates are higher from investigator assessment than from BIRC.

For confirmed CR, The median time to CR in the Enco+Bini 450 arm, Enco 300 and vemurafenib [redacted] respectively by BIRC and was [redacted] respectively for investigator review.

Time to objective response

At data-cut off time 19th May 2016, the median TTR per BIRC, calculated for responding patients only (patients with CR or PR, confirmation not required), corresponded to the time of the first post-baseline at Cycle 3, Day 1 and was 1.9 months for all three treatment arms. Results were the same for median TTR per investigator assessment and were [redacted] per BIRC and per investigator assessment in the updated analysis (data cut-off 7th November 2017).

Duration of response

The Kaplan-Meier estimate of median DOR per BIRC, calculated for confirmed responses, was longer in the Enco+Bini 450 arm versus vemurafenib and Enco 300 at the data cut-off date 19th May 2016:

- Enco+Bini 450 arm: per BIRC 16.6 months; 95% CI: 12.2 to 20.4; range [redacted] month and per investigator assessment [redacted]; with [redacted] responders ongoing at the time of data cut-off
- Vemurafenib arm: per BIRC 12.3 months; 95% CI: 6.9, 16.9; range [redacted] months and per investigator assessment [redacted]; with [redacted] responders ongoing
- Enco 300 arm: per BIRC 14.9 months; 95% CI: 11.1, NE; range [redacted] months and per investigator assessment [redacted] with responders ongoing.

The most common reason for censored DOR was [redacted] in the Enco+Bini 450 and Enco 300 arms and [redacted] in the vemurafenib arm.

Results of the updated analysis (data cut-off 7th November 2017) [redacted] K-M curves for duration of response are presented in Appendix L, Section L.2.3 of the CS.

8.2 Appendix 2 Additional results of key secondary efficacy outcomes

8.2.1 Additional results of PFS for Enco+Bini 450 vs Enco 300

In the updated analysis (data cut-off 7th November 2017), the median follow-up was 32.3 months (95% CI 31.7 to 34.9 months) in the Enco+Bini 450 arm and 32.0 months (95% CI 24.0 to 34.9 months) in the Enco 300 arm. A statistically significant difference in PFS was observed in the Enco+Bini 450 arm versus Enco 300: 0.77 (95% CI: 0.59 to 1.00, one-sided p=0.0249). PFS by investigator assessment showed numerically similar (and statistically significant) results to those reported for PFS by BIRC (data cut-off 19th May 2016: HR 0.68; 95% CI: 0.52 to 0.90; nominal one-sided p=0.003 and data cut off 7th November 2017: [redacted].

Concordance of PFS events per BIRC and investigator assessment was presented in the CS (see Section **Error! Reference source not found.** of this ERG report for further description and further details of discordance for the Enco+Bini 450 arm). At data cut-off time 19th May 2016, an "event type" discordance occurred for [redacted] in the Enco 300 arm (see Table 12 of the CS). The ERG asked the company for clarification regarding discordance between investigator and BIRC for [redacted] 'death' events in the Enco 300 arm. For [redacted], progression, as assessed by the investigators, was not confirmed by the BIRC and for [redacted], progression had not been assessed by the investigator whereas PD was concluded by the BIRC. All [redacted] subsequently died before the other review confirmed progression. Further, at data cut-off time 7th November 2017, an "event type" discordance occurred for *[redacted]* in the Enco 300 arm (see Appendix L.3.2, Table 35 of the CS). In terms of "timing discordance" a [redacted] between the Enco+Bini 450 and Enco 300 arms was observed at both dates of data cut-off (see Table 13 and Appendix L.3.2, Table 36 of the CS).

As for the primary efficacy outcome (see Section **Error! Reference source not found.** of this ERG report), the ERG notes that the proportion of discordance is relatively high for both treatment arms. However, PFS results for Enco+Bini 450 vs Enco 300 are very similar across the two data-cut off times and according to BIRC or investigator review, therefore the discordance present between investigator review and BIRC does not seem to have impacted on the overall results.

Event-free probability estimates, K-M curves, sensitivity, subgroup and supportive analyses of PFS for Enco+Bini 450 versus Enco 300 are provided in Section 2.6.3 and Appendix L.3.5 of the CS and numerical subgroup analysis results in the company response to the ERG

clarification letter. Results of sensitivity and supportive analyses were consistent with results of the primary analysis of PFS for Enco+Bini 450 versus Enco 300. Subgroup analyses were

performed at both dates of data cut-off and at both data cut-off dates, all subgroups with at least than 10 patients contributing demonstrated HRs for PFS in favour of Enco+Bini 450 over Enco 300 except for the subgroups of patients with [redacted]. Further details of subgroup analysis results can be found in Appendix E.1 of the CS.

8.2.2 Additional results for OS

Event-free probability estimates, K-M data, sensitivity, subgroup and supportive analyses of OS for Enco+Bini 450 versus vemurafenib and versus Enco 300 are presented in Section 2.6.5.1 of the CS and in the company response to the ERG clarification letter. Results of sensitivity and supportive analyses are consistent with results from the primary analysis of OS for Enco+Bini 450 versus vemurafenib and versus Enco 300.

Subgroup analyses were performed at data cut-off date 7th November 2017. Most subgroups demonstrated [redacted]. As noted in Section **Error! Reference source not found.** of this ERG report, numbers of patients within some subgroups are small, CIs around HRs of small subgroups are wide and therefore results should be interpreted with caution. Further details of subgroup analysis results can be found in Section 2.7 and Appendix E.2 of the CS.

Multivariate Cox regression of OS was also performed. The ERG highlights that efficacy results are interpreted in the CS in terms of relative risk rather than hazard and that the correct interpretation is that treatment with Enco+Bini 450 treatment was associated with a longer OS compared with treatment with vemurafenib ([redacted]) and compared with Enco 300 ([redacted]). The only other pre-specified covariate that reached nominal significance in both analyses was a [redacted], which was associated with a shorter OS ([redacted], for analyses of Enco+Bini 450 versus vemurafenib and versus Enco 300).

8.3 Appendix 3: ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model.

Table 10 ERG revisions to submitted company model

ERG revisions	Implementation instructions
Setting all efficacy parameters and RDI to be the same for Dab+Tram and Enco+Bini 450	In Sheets 'Exec summary' Select value in cell K26 = "Do not include RDI" In Sheets 'Clinical' Set G75=F77, L75=K77, Q75=P77, V75=U77 and AA75=Z77 Select value in box 'Drop Down 5': 'Assign HR and OR = 1' In Sheets 'QoL' Set value in cell E11 = 0.80