NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanomang [ID923]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma [ID923]

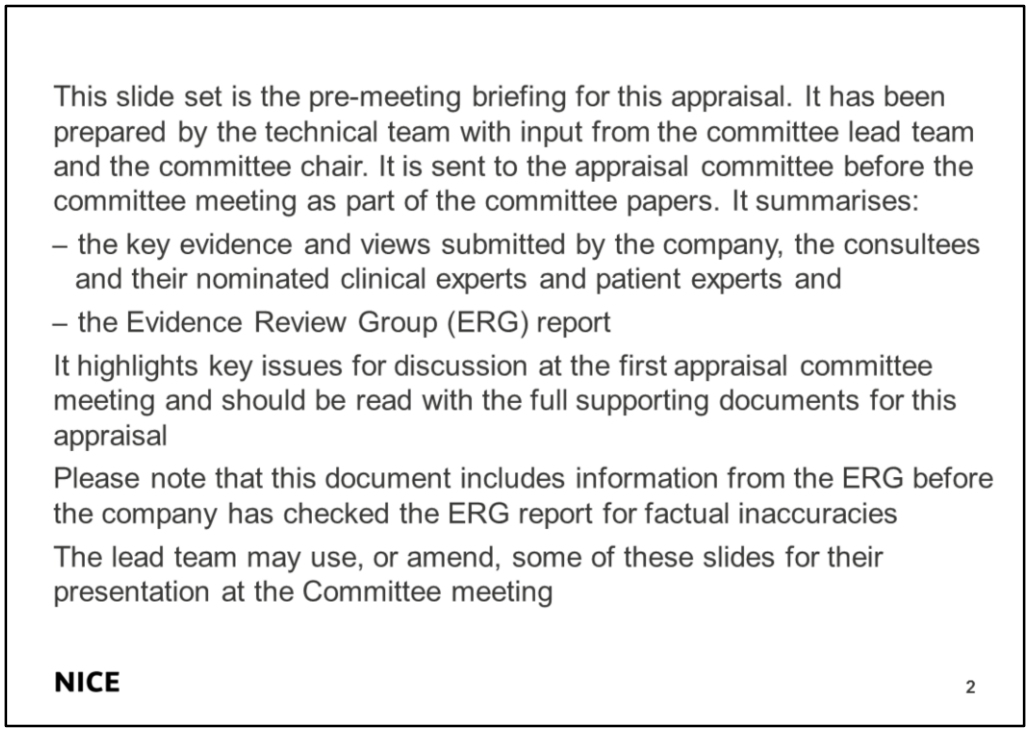
Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Encorafenib in combination with binimetinib for advanced (unresectable or metastatic) BRAF V600 mutation-positive

Pre-meeting briefing



It is advised that the PMB slides are shared with the lead team and committee as a **PDF file** (not PowerPoint), to avoid confusion with the lead team slide file

Tips for formatting slide notes

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- Don't worry if slide notes go off the bottom of the page – new pages will be inserted when you pdf/print
- Use notes to provide context, additional explanation or evidence about something on that slide or issue
- No confidential information should be included in the notes
- Give sources. Example: Source: ERG Report: Table 6, Page 51

Note for formatting slides

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When the lead team are ready to create their slides for committee using the PMB slides

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Key issues - clinical effectiveness

- How generalisable are the COLUMBUS results?
  - Is COLUMBUS population representative of those who would receive a targeted therapy for a BRAF V600 mutation-positive melanoma in the NHS?
  - In the COLUMBUS trial only 6% of patients had prior immunotherapy. Does this reflect current practice in the NHS or are targeted therapies given after immunotherapy in the metastatic setting?
- What is committee's view on the indirect clinical evidence provided by the company?
  - Are the network meta-analyses comparing encorafenib + binimetinib with dabrafenib + trametinib robust?
  - Is there a clinically meaningful difference in the clinical effectiveness of encorafenib + binimetinib with dabrafenib+ trametinib?
- Does the committee consider that encorafenib+binimetinib has a more favourable safety profile than dabrafenib+ trametinib?

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Key issues - cost effectiveness

- What is the committee's view of the company's model?
- What is the committee's view of the company's data and assumptions?
- Is the committee minded to consider that encorafenib plus binimetinib and dabrafenib plus trametinib are similar?
  - If so is the ERG's suggestion of a cost minimisation approach reasonable?

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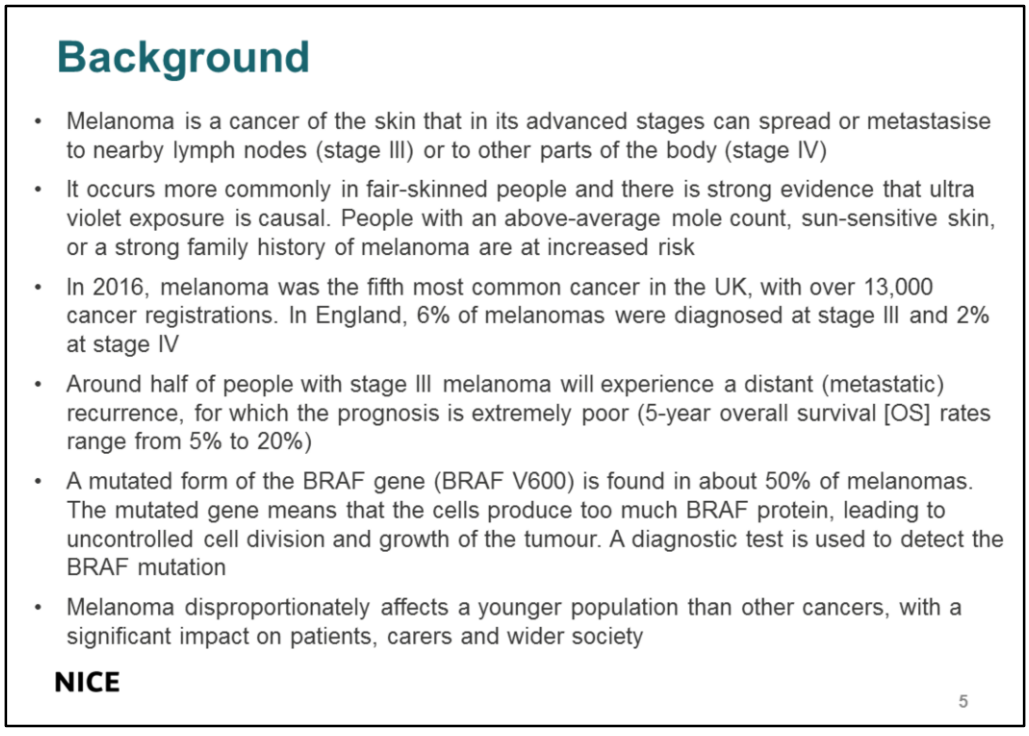

Please see pages 10-11 of the company submission for more information.

The prognosis of melanoma varies according to the stage of the disease at clinical presentation and health related quality of life (HRQoL) has shown to deteriorate particularly with later stages of disease.

Patients with lymph node involvement (stage III melanoma) are at a higher risk of disease recurrence (which can be loco-regional or metastatic) compared with stage I or stage II patients, and therefore have lower 5 and 10-year relapse free survival (RFS) rates.

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Details of the technologies

	Encorafenib (Braftovi; Pierre Fabre)	Binimetinib (Mektovi; Pierre Fabre)
Marketing authorisation	Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	
Mechanism of action	Selective RAF kinase activity inhibitor that suppresses RAF/MEK/ERK pathway in tumour cells expressing mutant BRAF kinase causing the cancer cells to stop growing and die	Inhibitor of MEK1 and MEK2 kinases and blocks the action of the abnormal BRAF protein, with the aim of slowing growth and spread of the cancer
Administration & dosage	Oral, 450 mg (six 75 mg capsules) once daily	45 mg (three 15 mg tablets) twice daily 12 hours apart
Cost	List price for 42 capsules of encorafenib 75 mg: £1,400 (7 day treatment) List price for 28 capsules of encorafenib 50 mg: £622.22 (3.11 day treatment)	List price for 84 tablets of trametinib 15 mg: £2,240 (14 days treatment)
	Patient access schemes agreed for each technology involving a single confidential discount applied to the list price of encorafenib and binimetinib	
Average cost of course of treatment	Based on median dose exposure from COLUMBUS (11.8 months): List price: £[redacted] PAS price: £[redacted]	

Please see pages 9-10 of the company submission for more information.

In order to initiate treatment with encorafenib in combination with binimetinib, patients must have confirmation of the BRAF V600 mutation using a validated test. This is in line with NG14 for the management of melanoma, which specifies that genetic testing should be offered to all patients if a targeted systemic therapy, such as encorafenib plus binimetinib, is a possible treatment option. BRAF testing is already part of routine clinical care in the NHS for high-risk patients, which includes all stage III patients and those with unresectable or metastatic melanoma, therefore no new or additional diagnostic tests are required for the proposed indication.

Current management

- Treatment options for patients with unresectable or metastatic melanoma are guided by the presence of BRAF mutations, prior treatment history and patient/disease characteristics
- NICE clinical guideline 14 recommends that people with unresectable or metastatic melanoma should be treated with either targeted therapies or immunotherapies

Immunotherapies recommended by NICE (irrespective of BRAF V600 mutation)	Targeted therapies recommended by NICE (people with BRAF V600 mutation
1. nivolumab in combination with ipilimumab (TA400) 2. nivolumab monotherapy (TA384) 3. pembrolizumab monotherapy (TA366, TA357), and 4. ipilimumab monotherapy (TA319, TA268)	BRAF inhibitor (BRAFi) monotherapies: 1. vemurafenib (TA269) 2. dabrafenib (TA321) BRAFi/MEK inhibitor (MEKi) combination therapy: 1. dabrafenib and trametinib (TA396)*

*BRAFi/MEKi combinations considered standard of care (SOC) demonstrating efficacy gains relative to BRAF monotherapy with a favourable safety profile

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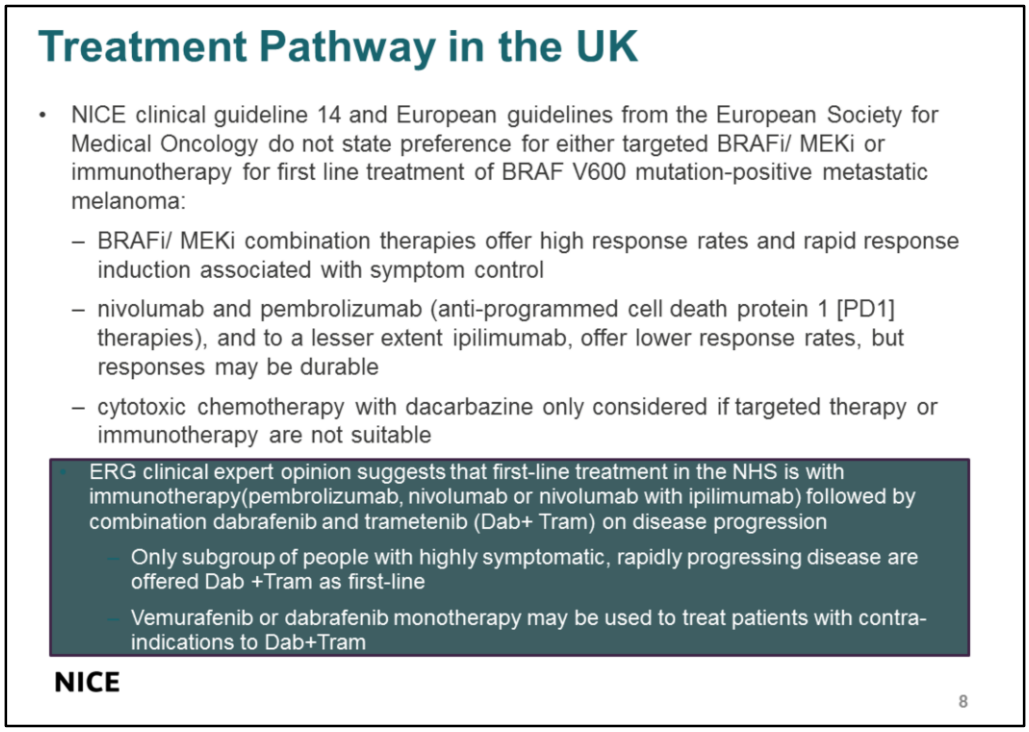
Please see pages 11-12 of the company submission for more information.

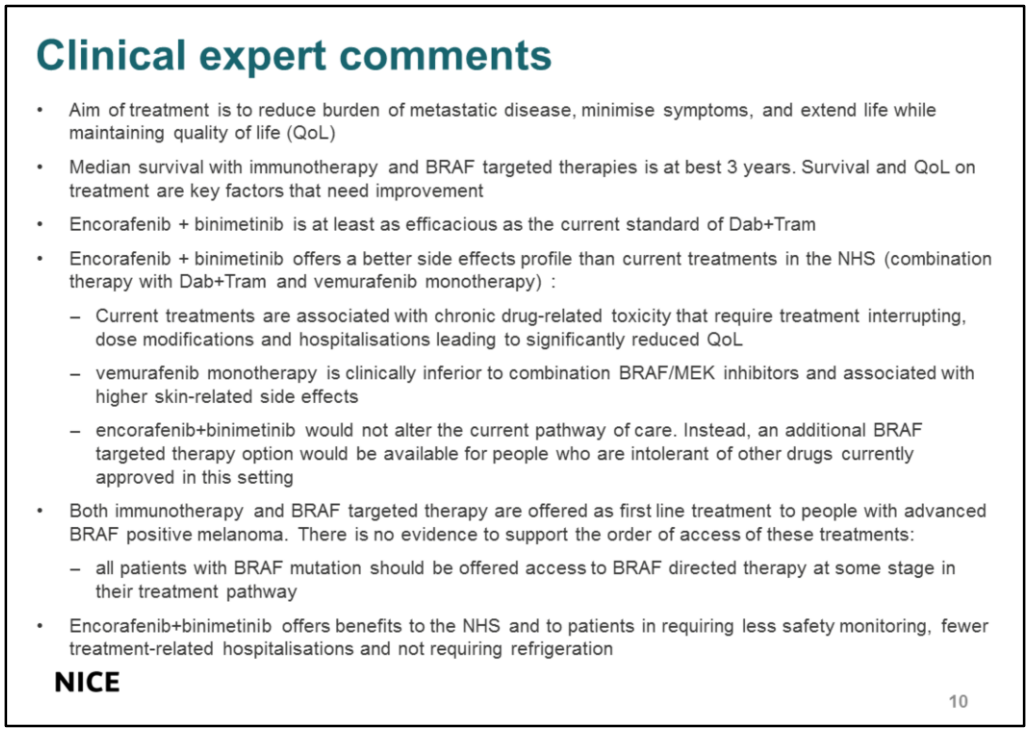


Please see pages 11-12 of the company submission for more information.

Decision problem

	NICE scope	Company submission
Population	Adults with un-resectable or metastatic BRAF V600 mutation-positive melanom	As per scope
Intervention	Encorafenib plus binimetinib	Encorafenib plus binimetinib
Comparator	Dabrafenib with trametinib	Dabrafenib with trametinib
Outcomes	Progression free survival Overall survival Response rate Adverse effects of treatment Health-related quality of life	As per scope
Subgroups	Where the evidence allows, the following subgroups will be considered: • people with previously untreated disease • people with previously treated disease that progressed on or after first line immunotherapy	Subgroups based on prior treatment experience in the metastatic setting not considered in company's economic evaluation due to small patient numbers (6% of people in COLUMBUS trial received prior therapy with immunotherapy in the metastatic setting)

Source: Table 1 (page 8) of the company submission.



Clinical expert comments

- Aim of treatment is to reduce burden of metastatic disease, minimise symptoms, and extend life while maintaining quality of life (QoL)
- Median survival with immunotherapy and BRAF targeted therapies is at best 3 years. Survival and QoL on treatment are key factors that need improvement
- Encorafenib + binimetinib is at least as efficacious as the current standard of Dab+Tram
- Encorafenib + binimetinib offers a better side effects profile than current treatments in the NHS (combination therapy with Dab+Tram and vemurafenib monotherapy) :
  - Current treatments are associated with chronic drug-related toxicity that require treatment interrupting, dose modifications and hospitalisations leading to significantly reduced QoL
  - vemurafenib monotherapy is clinically inferior to combination BRAF/MEK inhibitors and associated with higher skin-related side effects
  - encorafenib+binimetinib would not alter the current pathway of care. Instead, an additional BRAF targeted therapy option would be available for people who are intolerant of other drugs currently approved in this setting
- Both immunotherapy and BRAF targeted therapy are offered as first line treatment to people with advanced BRAF positive melanoma. There is no evidence to support the order of access of these treatments:
  - all patients with BRAF mutation should be offered access to BRAF directed therapy at some stage in their treatment pathway
- Encorafenib+binimetinib offers benefits to the NHS and to patients in requiring less safety monitoring, fewer treatment-related hospitalisations and not requiring refrigeration

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Trametinib is required to be refrigerated at all times, whereas binimetinib does not; this makes makes encorafenib+ binimetinib a much more manageable treatment for patients

Compared with dabrafenib+trametinib, encorafenib+binimetinib appears to be better tolerated, recommended doses are maintained more easily and risk of hospital admissions are considerably lower.

Patient perspective

- No patient expert comments received to date

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Clinical effectiveness

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Company's clinical evidence: COLUMBUS

Design	**2 part, phase III open-label RCT (only part 1 of the trial relevant to appraisal)**
Population (Part 1 relevant to decision problem only) (n= 577)	Adults with histologically confirmed locally advanced unresectable or metastatic BRAF V600E and/or V600K-mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC or IV). Patients were either treatment naïve or had progressed on or after previous first-line immunotherapy
Intervention	Enco+Bini 450 arm: encorafenib 450 mg QD plus binimetinib 45 mg BID (n=192)
Comparator	Vemurafenib arm: vemurafenib 960 mg BID monotherapy (n=191) Enco 300 arm: encorafenib 300 mg QD monotherapy (n=194)
Location	162 international study sites in 28 countries from Europe (including 8 sites in the UK), North America and selected other countries. 14 patients from the UK were included in the analysis of the trial
Primary outcome	Progression free survival (PFS) for Enco+Bini 450 vs vemurafenib
Other outcomes	• Overall survival (OS) • Overall response rate (ORR),Duration of response (DOR) • Disease control rate (DCR) • Time to objective response (TTR) • Patient reported outcomes • Adverse events
Duration of study and follow-up	Median follow-up time was 32.3 months (range 31.7-34.9) in the encorafenib plus binimetinib arm and 22.2 months (range 11.1-32.3) in the vemurafenib arm at data cut-off of 7th November 2017)

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Please see pages 15-35 of the company submission for more information.

The primary objective of COLUMBUS was to determine whether treatment with Enco+Bini 450 prolongs PFS compared with vemurafenib in patients with BRAF V600 mutant locally advanced unresectable or metastatic melanoma

As study was open-label, investigators and patients knew the study treatment assigned. To minimise bias, confirmation of progression had to be confirmed by independent review committee blinded to patient treatment assignment. Personnel responsible for data analysis and interpretation were also blinded to data that would systematically unblind patient treatment assignments until database lock for the primary analysis.

The primary efficacy endpoint (Enco+Bini 450 versus vemurafenib) and key secondary endpoint (Enco+Bini 450 versus Enco 300) was PFS, defined as the time from the date of randomisation to the date of the first documented progression or death due to any cause,

whichever occurred first. If a patient did not have an event at the time of the analysis cut-off or at the start of any new antineoplastic therapy, PFS was censored at the date of the last adequate tumour assessment

OS was defined as the time from the date of randomisation to the date of death due to any cause. If a death was not observed by the date of analysis cut-off, OS was to be censored at the date of last contact

COLUMBUS trial contd.

Key eligibility criteria	Adults with one measurable lesion as per RECIST version 1.1, an ECOG performance status (PS) of 0–1 and adequate organ and cardiac function Patients with any untreated central nervous system (CNS) lesion, uveal and mucosal melanoma, a history of leptomeningeal metastases, PS>2, history or current evidence of, or current risk factors for retinal vein occlusion, or a history of Gilbert's syndrome were excluded.
Baseline characteristics	Patient characteristics (age, gender, race, weight, ECOG status, BRAF mutation status, disease stage, time from diagnosis to metastatic disease, number of organs involved at baseline and lactate dehydrogenase [LDH] levels) were similar across the three arms of the trial 72% of trial population were ECOG PS 0 and the remaining 28% were of ECOG PS 1
Subgroups	Subgroup analyses performed for OS and PFS for baseline stratification factors and other relevant baseline variables provided at least 10 patients were available in the considered sub-group.

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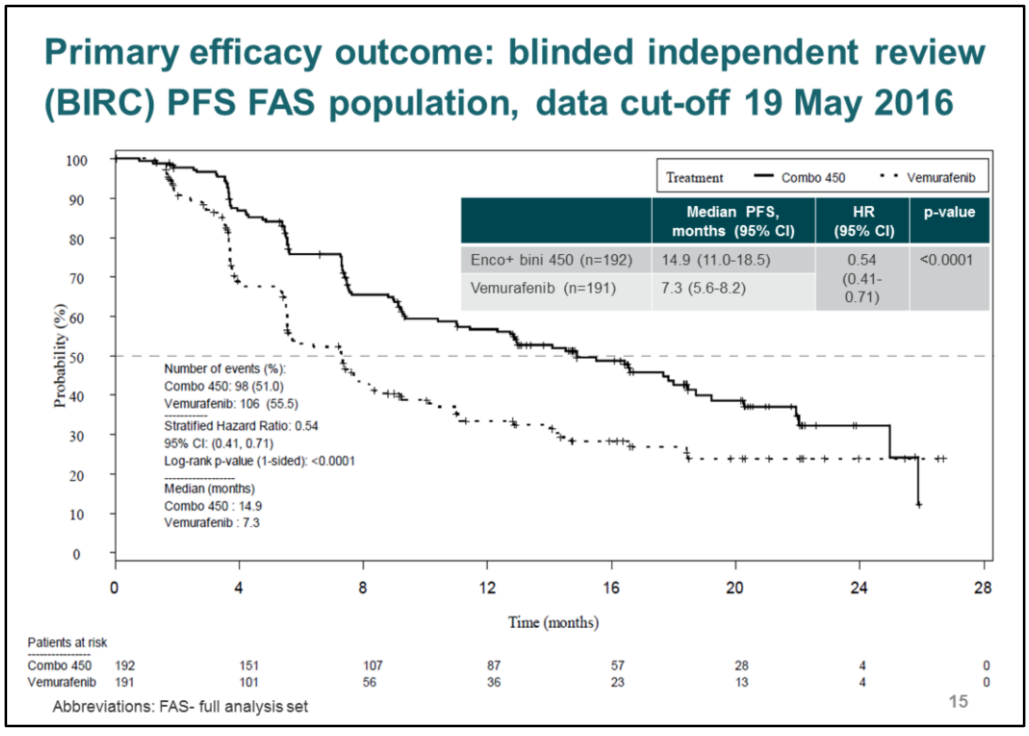
Please see pages 15-35 of the company submission for more information.

The ERG notes that the patients recruited to the COLUMBUS trial appear to be similar to the patients recruited to the COMBI-v and COMBI-d trials, trials in which Dab+Tram was compared with vemurafenib and dabrafenib, respectively

The ERG also 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



Source: Figure 3 (page 39) of company submission. Please see pages 37-39 for more information.

Updated analysis (data cut-off 7 November 2017): The HR for PFS in the Enco+Bini 450 arm relative to the vemurafenib arm was 0.51 (95% CI: 0.39, 0.67; stratified one-sided log-rank test p<0.0001)

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PFS by BIRC and local investigator review for Enco+Bini 450 compared to 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)	16.7 (16.3 to 18.4)	14.4 (10.1 to 16.6)
Median PFS (95% CI)	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)	14.8 (10.4 to 18.4)	7.3 (5.7 to 8.5)
HR (95% CI), stratified one-sided log-rank p-value	0.49 (0.37 to 0.64);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)	32.3 (31.7 to 34.9)	22.2 (11.1 to 32.3)
Median PFS (95% CI)	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)	[redacted]	[redacted]
HR (95% CI), stratified one-sided log-rank p-value	[redacted]	

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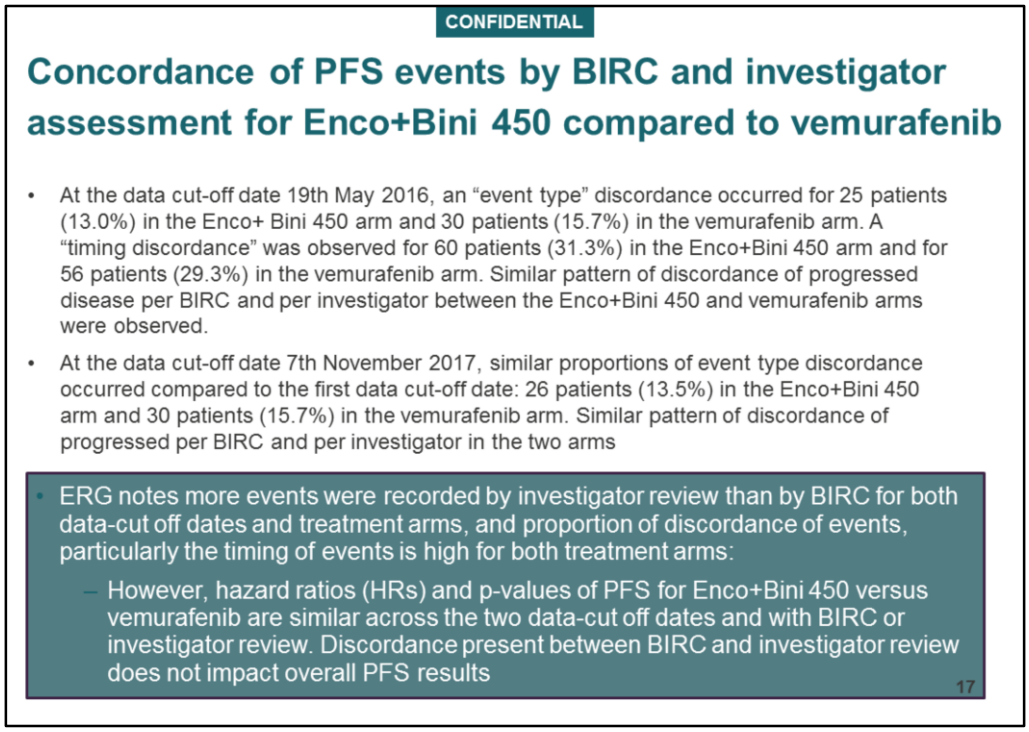
Source: Table 8 (page 38) of ERG report. Please see pages



Please see pages 39-43 of the company submission and pages 42-44 of the ERG report for more information

Investigator assessment of response was used to estimate PFS as a supportive analysis

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).

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Sensitivity and supportive analyses of PFS for Enco+Bini 450 compared to vemurafenib

Analysis (all Part 1)	Data cut-off date	HR (95% CI), stratified one-sided log-rank p-value
BIRC, FAS (primary analysis)	19 May 2016	0.54 (0.41 to 0.71); p<0.0001
BIRC, FAS (updated primary analysis)	7 November 2017	0.51 (0.39 to 0.67); p<0.0001
Investigator review, FAS	19 May 2016	0.49 (0.37 to 0.64); p<0.0001[a]
	7 November 2017	[redacted]
BIRC, per protocol set (PPS)[b,c]	19 May 2016	0.53 (0.40 to 0.70); p<0.0001[a]
BIRC, FAS, unstratified log-rank tests and Cox PH regression[c]	19 May 2016	0.58 (0.44 to 0.77); unstratified p<0.001[a]
BIRC, FAS, by electronic case report form(eCRF) stratification factors [c,d]	19 May 2016	[redacted]
BIRC, FAS, 'actual event' sensitivity analysis	19 May 2016	[redacted]
	7 November 2017	[redacted]
BIRC, FAS, 'backdating' sensitivity analysis[f]	19 May 2016	[redacted]
	7 November 2017	[redacted]
BIRC, FAS, 'further anti-cancer treatment' sensitivity analysis	19 May 2016	[redacted]
	7 November 2017	[redacted]

[a] P-values are nominal and for descriptive purposes only
[b] Number of patients included in PPS: 188 for Enco+Bini and 184 for vemurafenib
[c] Analysis in PPS, unstratified log-rank test and Cox PH regression analyses and analysis by eCRF stratification factors available only for data-cut off 19th May 2016
[d] Discordance rates ranging from 0.3% to 11.1% between randomisation stratification factors and eCRF stratification factors due to a time window of up to three weeks between registering randomisation factors and the registering stratification factors on the eCRF

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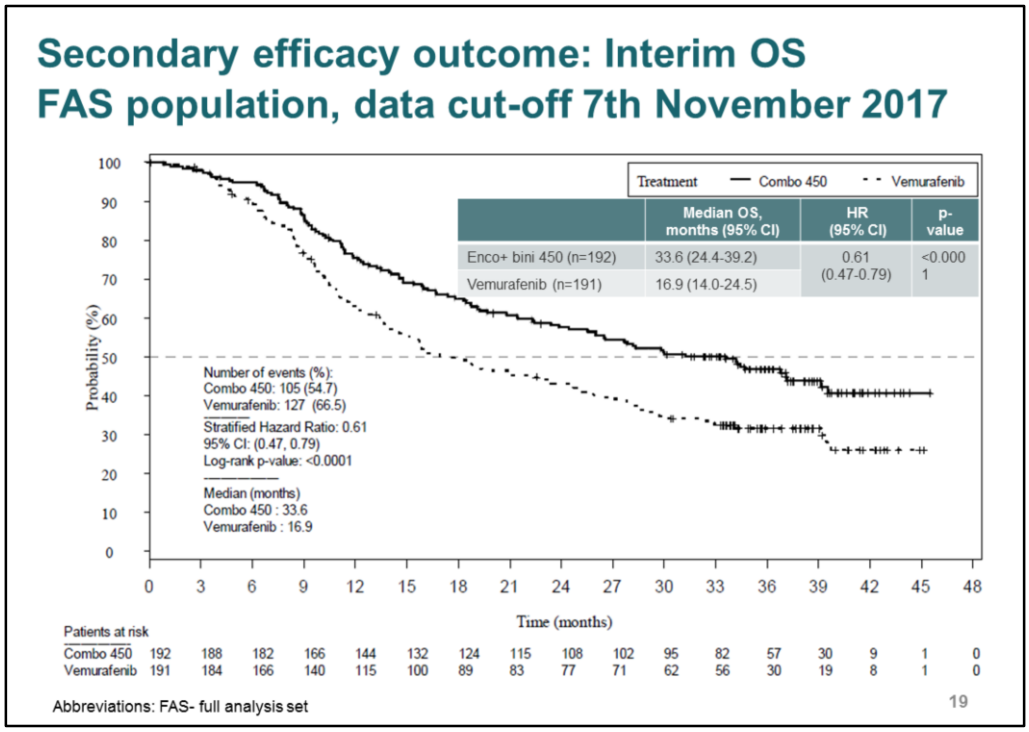
Source: Table 9 (page 45) of the ERG report . Please see pages 45-47 of the ERG report and 43-50 of company submission for more information



Source: Figure 7 (page 52) of company submission. Please see pages 51-55 for more information.

A 39% reduction in the risk of death was observed for patients treated with Enco+Bini 450 compared with those treated with vemurafenib

OS estimates (95% CI) at 12 and 24 months were 75.5% (68.8, 81.0) and 57.6% (50.3, 64.3) for Enco+Bini 450 compared with 63.1% (55.7, 69.6) and 43.2% (35.9, 50.2) for vemurafenib, respectively.

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Adverse events (data cut off 9th November 2016)

Category	Enco+Bini 450 (N=192) Median duration of exposure: [redacted]		Vemurafenib (N=186) Median duration of exposure: [redacted]	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n(%)
On-treatment deaths[a]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose interruption/adjustment	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy[b]	[redacted]	[redacted]	[redacted]	[redacted]

- People in the Enco+Bini 450 arm had longer time on treatment compared with other 2 arms of trial but frequency of AEs was similar in all groups of patients
- The most common any grade AEs in Enco+Bini 450 arm were nausea [redacted], diarrhoea [redacted], vomiting [redacted], fatigue [redacted], arthralgia [redacted] increased creatine phosphokinase [redacted], headache [redacted], constipation [redacted], and asthenia [redacted]
- The most common all grade SAEs were pyrexia [redacted], abdominal pain [redacted], acute kidney injury [redacted] and anaemia [redacted] in the Enco+Bini 450 arm and general physical health deterioration [redacted] in the vemurafenib arm

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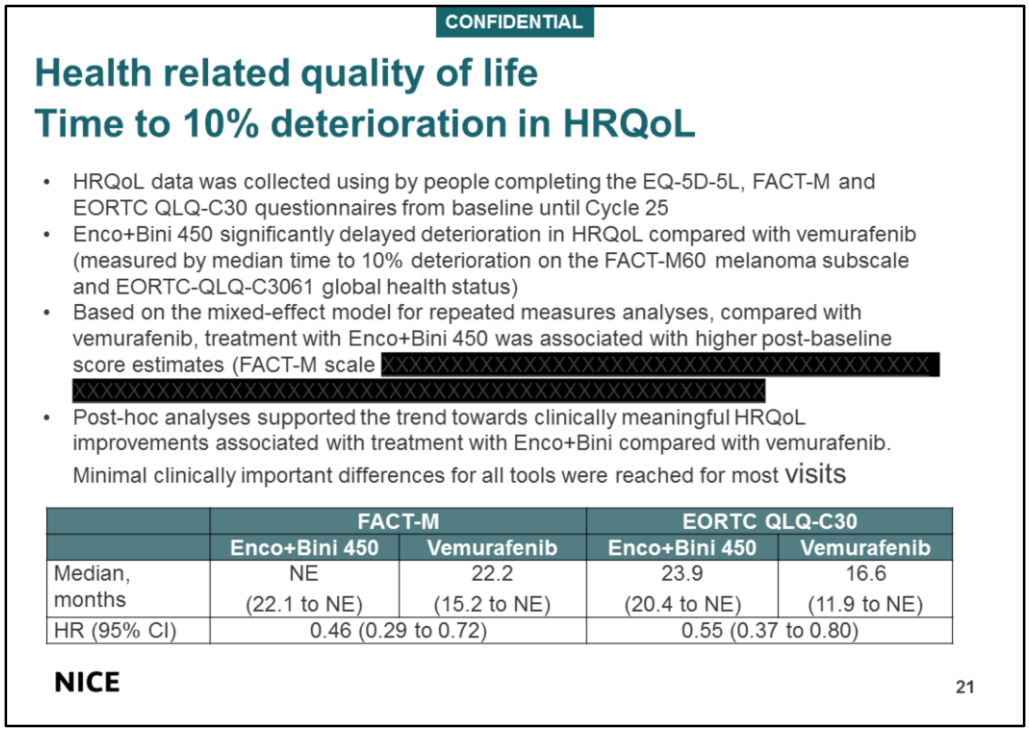
Source: Table 12 (page 49) of ERG report. Please see pages 48-51 of the ERG report and pages 75-84 of the company submission for more information

Safety data includes 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.

Company notes that the addition of binimetinib to encorafenib allows patients to tolerate treatment with encorafenib at the higher dose of 450mg.

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 of Enco+Bini 450 versus Dab+Tram. The ERG notes, from the appraisal of



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Health related quality of life
Time to 10% deterioration in HRQoL

- HRQoL data was collected using by people completing the EQ-5D-5L, FACT-M and EORTC QLQ-C30 questionnaires from baseline until Cycle 25
- Enco+Bini 450 significantly delayed deterioration in HRQoL compared with vemurafenib (measured by median time to 10% deterioration on the FACT-M60 melanoma subscale and EORTC-QLQ-C3061 global health status)
- Based on the mixed-effect model for repeated measures analyses, compared with vemurafenib, treatment with Enco+Bini 450 was associated with higher post-baseline score estimates (FACT-M scale [redacted]
- Post-hoc analyses supported the trend towards clinically meaningful HRQoL improvements associated with treatment with Enco+Bini compared with vemurafenib. Minimal clinically important differences for all tools were reached for most visits

	FACT-M		EORTC QLQ-C30	
	Enco+Bini 450	Vemurafenib	Enco+Bini 450	Vemurafenib
Median, months	NE (22.1 to NE)	22.2 (15.2 to NE)	23.9 (20.4 to NE)	16.6 (11.9 to NE)
HR (95% CI)	0.46 (0.29 to 0.72)		0.55 (0.37 to 0.80)	

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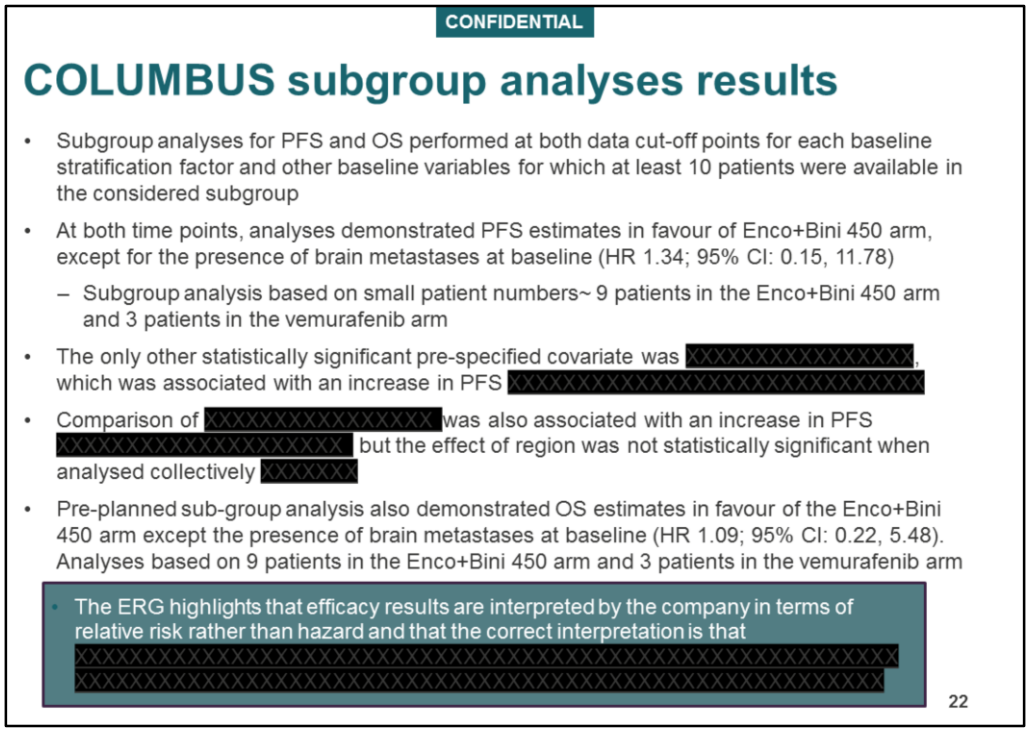
Source: Table 13 (page 451) of ERG report. Please see pages 57-60 of the company submission and pages 51-52 of ERG report for more information

The COLUMBUS trial protocol included collecting HRQoL data using three tools (the Functional Assessment of Cancer Therapy-Melanoma(FACT-M) subscale, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EuroQol-5 dimensions-5 levels (EQ-5D-5L) questionnaire

Company reports that compliance was high in each arm from baseline to Cycle 25, with majority of evaluated patients completing the questionnaires.



Please see pages 61-62 of the company submission for more information

ERG critique: overview of clinical evidence

- COLUMBUS is a good quality, well conducted trial that included blinded independent review of PFS outcomes and collection of HRQoL data
- Patients recruited to the trial largely representative of patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma in the NHS.
  - However, very few people in COLUMBUS had brain metastases and none had a poor PS (i.e., PS ≥2)
- Although outcomes of COLUMBUS favour the use of Enco+Bini 450 and show that it has a favourable safety profile, the trial does not provide direct evidence for the clinical effectiveness of Enco+Bini 450 versus Dab+Tram
- Only descriptive OS data from COLUMBUS provided due to the limitations imposed by the hierarchical approach to statistical testing used to analyse the COLUMBUS trial data

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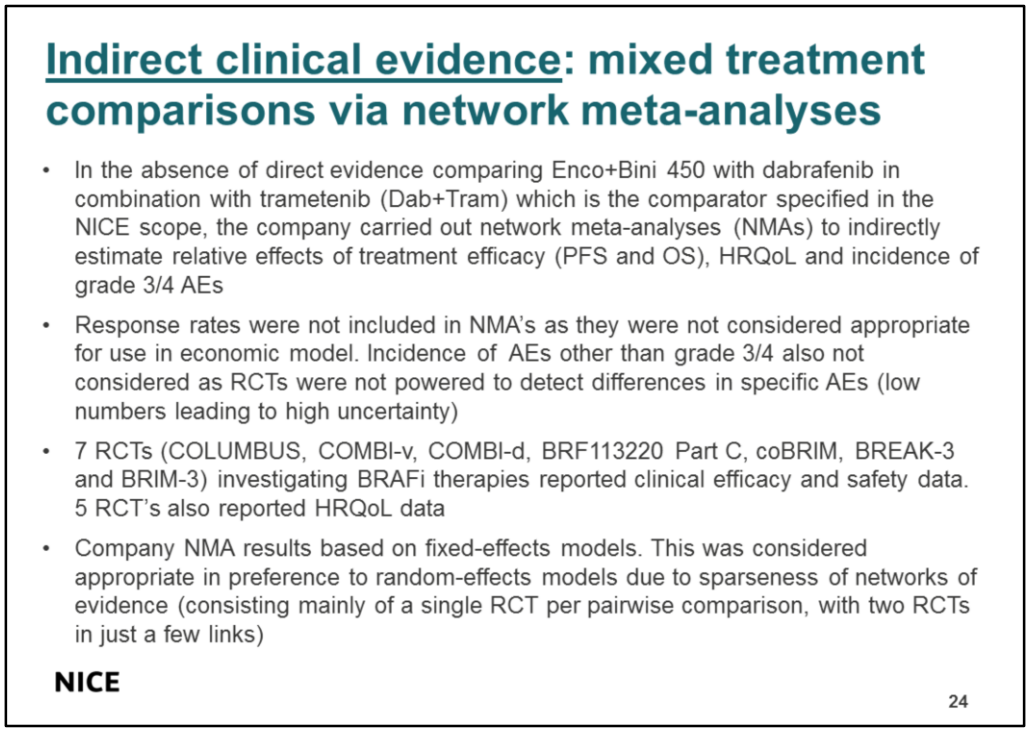

Please see pages 63-66 of the company submission for more information

Fixed-effects models assume that each study is estimating the same treatment effect, with variability induced by sampling error alone. Random effects models assume that the trial-specific treatment effects come from a common distribution and takes into account between-study heterogeneity.

The company considered the random effects approach would likely provide a poor estimate of the distribution of intervention effects and noted that the fixed effects model yielded a lower or similar deviance information criterion (DIC) than the random effects model for the majority of investigated outcomes.

NMA results

NMA results for OS	HR (95% CrI)	
	Enco+Bini 450 vs Dab +Tram	Dab+Tram vs Enco+Bini 450
Base-case	0.89 (0.65,1.23)	1.12 (0.81,1.53)
NMA results for PFS	**HR (95% CrI)**	
	Enco+Bini 450 vs Dab+Tram	**Dab+Tram vs Enco+Bini 450**
Base-case	0.77 (0.57,1.04)	1.30 (0.96,1.77)
NMA results for EQ-5D utility score	**Dt (95% CrI)**	
	Enco+Bini 450 vs Dab+Tram	**Dab+Tram vs Enco+Bini 450**
EQ-5D utility score, pre-progression	-0.02 (-0.05, 0.01)	0.02 (-0.01, 0.05)
EQ-5D utility score, DCFB at Week 32	-0.04 (-0.10, 0.02)	0.04 (-0.02, 0.10)
EQ-5D utility score, DCFB at disease progression	-0.04 (-0.12, -0.04)	0.04 (-0.04, 0.12)
NMA results for any grade ≥3 AEs	**OR (95% CrI)**	
	Enco+Bini 450 vs Dab+Tram	**Dab+Tram vs Enco+Bini 450**
	1.18 (0.70, 1.98)	0.85 (0.51, 1.43)

- The results of the company's NMAs comparing Enco+Bini 450 with Dab+Tram showed no statistically significant difference between the two treatment combinations for investigator-assessed PFS, OS, AEs and HRQoL. For all base case and sensitivity analyses, credible intervals (CrIs) were wide and crossed 1

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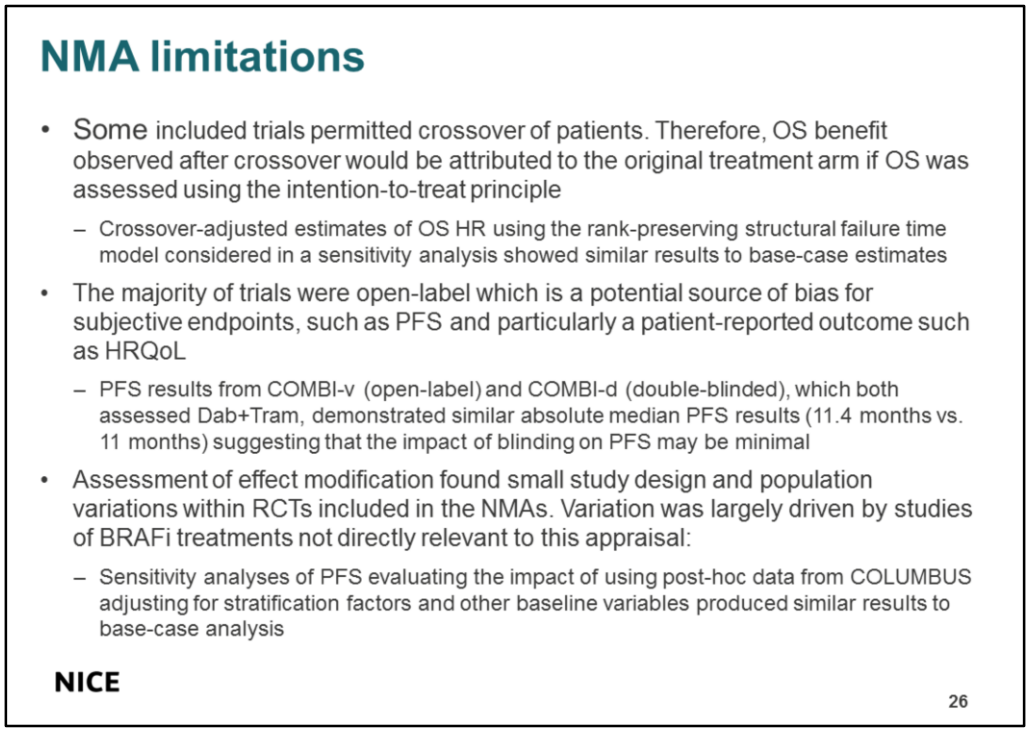
Please see pages 66-71 of the company submission for more information

OS: All 7 of the included studies in the NMAs reported OS and the most recent, mature data was used wherever available in all analyses across different outcomes.

PFS: The base-case analysis incorporated investigator assessed PFS (reported in all seven included studies) as it was not possible to generate a network for PFS assessed by BIRC (the primary endpoint of the COLUMBUS trial)

HRQoL: Double-blinded RCTs were not included in networks of HRQoL outcomes as COLUMBUS was an open-label study and inclusion of both open-label and double-blinded studies in the same network was considered methodologically inappropriate. Availability of EQ-5D data and restricting to open-label studies meant that the network consisted of COLUMBUS and COMBI-v only. The results of the NMA were consistent with those reported in the original

publications.



Please see pages 71-75 of the company submission for more information

The base-case analysis considered a network including BRAFi studies, which were found to be generally comparable in terms of study design and patient baseline characteristics, with the exception of LDH status (proportion of patients with LDH>ULN).

Although crossover was initially not planned in COLUMBUS, patients in BRAFi monotherapy arms were offered the possibility to add a MEKi to their regimen after the data monitoring committee reviewed the interim OS results in May 2016. The adjustment for Enco+Bini 450 versus vemurafenib from COLUMBUS confirmed the trend of the base-case, with an HR (95% CI) of 0.57 (0.40; 0.77), using a Cox proportional hazard mode

The base-case networks included predominantly open-label RCTs (COLUMBUS, COMBI-v, BRIM-3, BREAK-3 , and BRF113220 Part C) and two double-blinded RCTs (COMBI-d and CoBRIM)

For PFS, base-case estimates of comparative efficacy were based on locally assessed progression, which in open-label studies may also be subject to bias. Although COLUMBUS reported blinded independent review results, no other BRAFi studies within the evidence network reported on blinded independent assessment of PFS.

Sensitivity analyses were considered to evaluate the impact of using post-hoc data from COLUMBUS adjusting for stratification factors; controlling for imbalances in terms of study design or patient characteristics may reduce between-study

ERG critique: NMAs

- The patient population in COLUMBUS 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.
- However results from the NMAs should be viewed with caution due to numerous methodological limitations. These include:
  - sparsity of evidence in the networks (particularly HRQoL network),
  - variability in lengths of trial follow-up (2 years to 6 years),
  - differences between trials in median follow-up for OS (11 months to 33.3 months),
  - inclusion of dacarbazine within the networks,
  - NMA of PFS by local investigator review (rather than BIRC) was only feasible.
  - 5 of the 7 trials included within the NMAs were open-label; therefore investigator assessment of PFS in open-label trials may be subject to bias.
- Clinical expert opinion however highlights that the clinical effectiveness outcomes for patients who are treated with Enco+Bini 450 and Dab+Tram are likely to be similar

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Cost effectiveness

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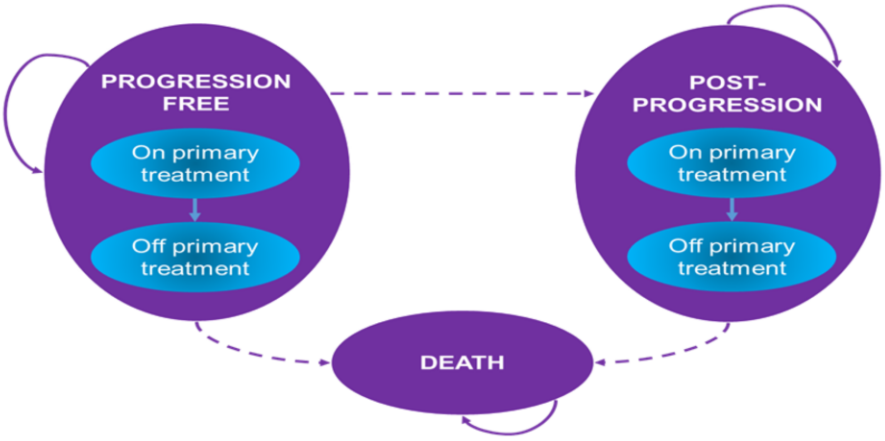
Company 3 state partitioned survival model comparing Enco+Bini 450 with Dab+Tram



Factor	Chosen values
Time horizon	30 years (lifetime assumed)
Perspective	NHS and PSS
Discount rate	3.5% per year
Cycle length	One month (half cycle correction included)

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Source: Figure 17, page 97 of the company submission

The partitioned survival analysis model is the most commonly used modelling approach within NICE health technology assessments for interventions treating advanced or metastatic cancers. The advantages of such an approach in modelling this disease are:

1)Overall survival (OS) and progression-free survival (PFS) data from the clinical trial can be used directly in the model.

2)Time dependencies and treatment effects are reflected within the survival curves (whereas a Markov model for example would require cumbersome tunnel states).

3) Hazard ratio's (HRs) from NMAs can be easily incorporated by applying these to the OS and PFS curves

Company model details

- The 3 mutually exclusive health states in the model are: progression-free (PF), post-progression (PP) and death
- PF and PP health states include tunnel states which are designed to account for primary treatment status (i.e. on or off primary treatment). Primary treatment refers to the treatment being assessed in each arm of the model (i.e. Enco+Bini 450 or Dab+Tram)
- The sub-states are used ***only*** to derive the differential costs within the health state and no differential treatment effect or HRQoL are applied in the sub-states.
- Time to treatment discontinuation (TTD) was used to define the proportion of the model population on primary treatment over time
  - TTD instead of PFS was used because in clinical practice patients may either discontinue treatment pre-progression due to tolerability or toxicity issues or continue treatment post-progression if the clinician believes the primary treatment may still provide benefit

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Please see pages 96-99 of the company submission for more information

The proportion of the cohort remaining in the PF health state over time is derived directly from the PFS curve. State membership for the death state is calculated as 1 minus the OS curve and state membership for the PP health state is derived as the difference between the OS and the PFS curve (the proportion of patients who are alive but not progression-free).

In the COLUMBUS trial, 26.0% of patients discontinued treatment pre-progression in the Enco+Bini 450 arm for reasons including AEs (November 2017 data cut-off and 12% continued treatment beyond both central and local progression (November 2017 data cut-off). The TTD approach ensures that the proportion of patients assumed to be on primary treatment with Enco+Bini 450 at any given time is reflective of the treatment taken to achieve the clinical outcomes observed within COLUMBUS and subsequently utilised within the model. The approach is also consistent with NICE TA396, in which the ERG considered that PFS was a poor proxy for time on treatment and thus treatment costs, and that time to treatment discontinuation would provide a more clinically plausible and accurate measure of

time on treatment

Clinical inputs to company model

Efficacy and clinical data inputs used in the model derived from COLUMBUS:

- Patient baseline characteristics
- OS rates from the observed trial period for the Enco+Bini 450 arm
- Probability of PFS during the observed trial period for Enco+Bini 450 arm
- Time on treatment from post-hoc analysis of COLUMBUS for the Enco+Bini 450 arm
- Health related quality of life
- Adverse events

Efficacy and clinical data inputs for the Dab+Tram arm:

- Company NMAs

Clinical data from other sources:

- Extrapolation of OS using survival observations from American Joint Committee on Cancer (AJCC) registry data (then validated by clinical expert opinion)
- General population mortality rates derived from National Life-Tables for England and Wales

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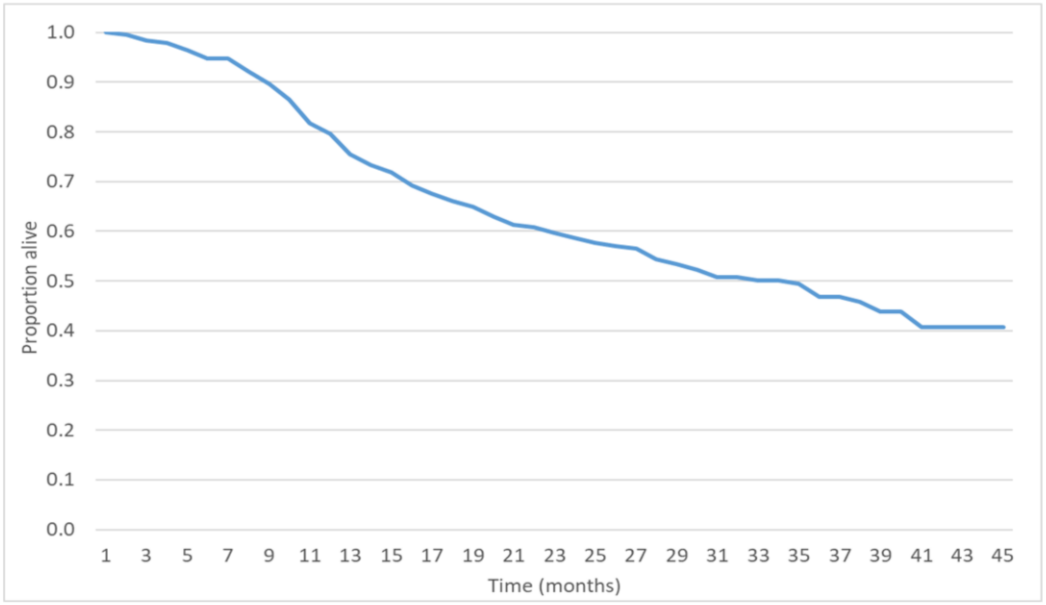
Please see pages 97-99 of the company submission for more information

Local review of progression was used to inform the model, based on the relative availability of data for the NMA

Estimates of TTD are derived from TTD data from the Enco+Bini 450 arm of the COLUMBUS trial and TTD data for the Dab+Tram model arm was assumed to be equivalent to that for the Enco+Bini 450 model arm.

Company model: OS (1)

Kaplan-Meier curve for Enco+Bini 450 from COLUMBUS



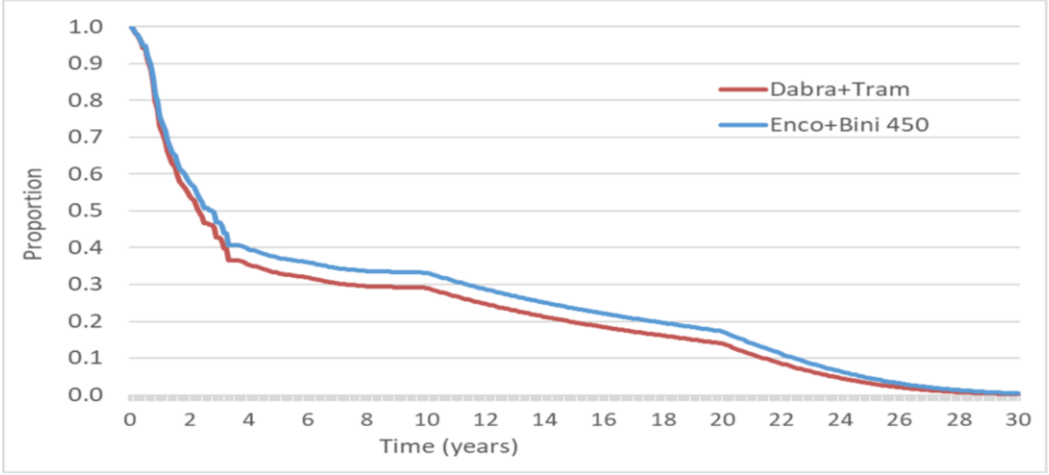
Source: Figure 13 (page 71 of the company submission)

The OS Kaplan-Meier data from the Enco+Bini 450 arm of COLUMBUS was used directly in the model up to month 44

Company model: OS (2)

Enco+Bini 450: COLUMBUS K-M OS data till 44 months + adjusted OS K-M curves from AJCC data from 44 months to year 10 + constant hazard extrapolation of OS K-M curves from AJCC during year 10-20 + general population mortality uplifted by increased risk of death in melanoma patients

Dab +Tram: HR estimate from NMA applied to Enco+ Bini 450 survival curve



Source: Figure 19 (page 103 of the company submission). Please see pages 71-75 for more information

Enco+Bini 450 curve:

- OS survival curves for Enco+Bini 450 were generated using patient level data from the latest data cut-off from COLUMBUS up till month 44
- From month 44 to year 10, OS K-M curves from the AJCC melanoma registry data were used to account for the availability of newer treatments
- A constant extrapolation of the OS K-M curves from the AJCC 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 scaled up proportionally to account for the increased relative risk of mortality in this population.

The scale-up multiplier used by the company was calculated as the HR between the mortality hazard rate from the AJCC case-mixed adjusted survival at 20 years and the corresponding rate from the general population (matched for age and gender distribution) to take

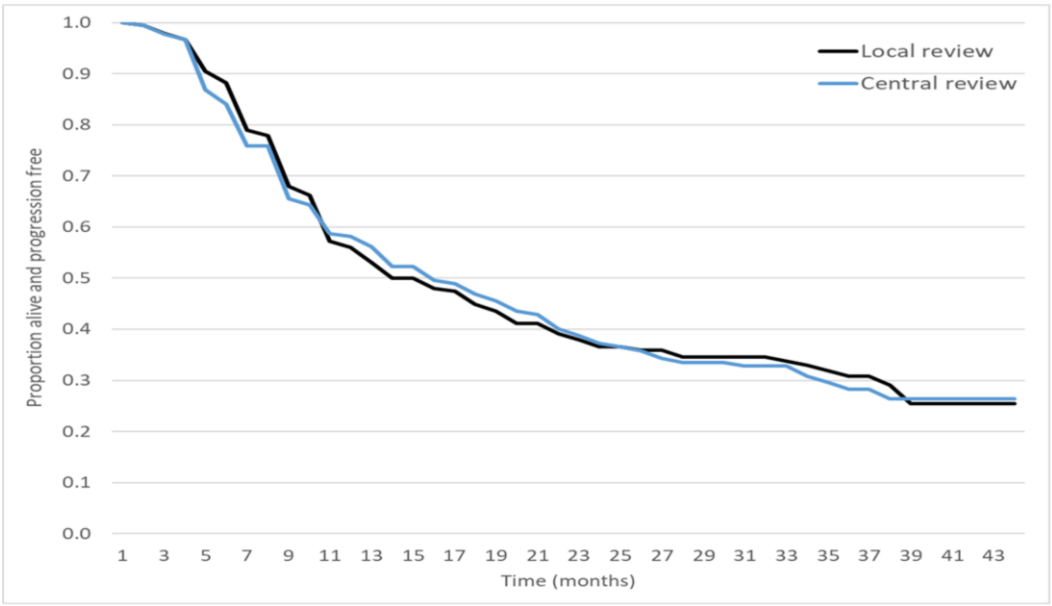
into account that the model population cannot be cured throughout the entire time horizon of the analysis. . The resulting HR (scale-up multiplier) was 2.2

Dabra+Tram curve:

Numerical estimate of HR derived from the company NMAs is applied to the entire OS curve for the Enco+Bini 450 model arm.

Company model: PFS (1)

Kaplan-Meier curve for Enco+Bini 450 from COLUMBUS



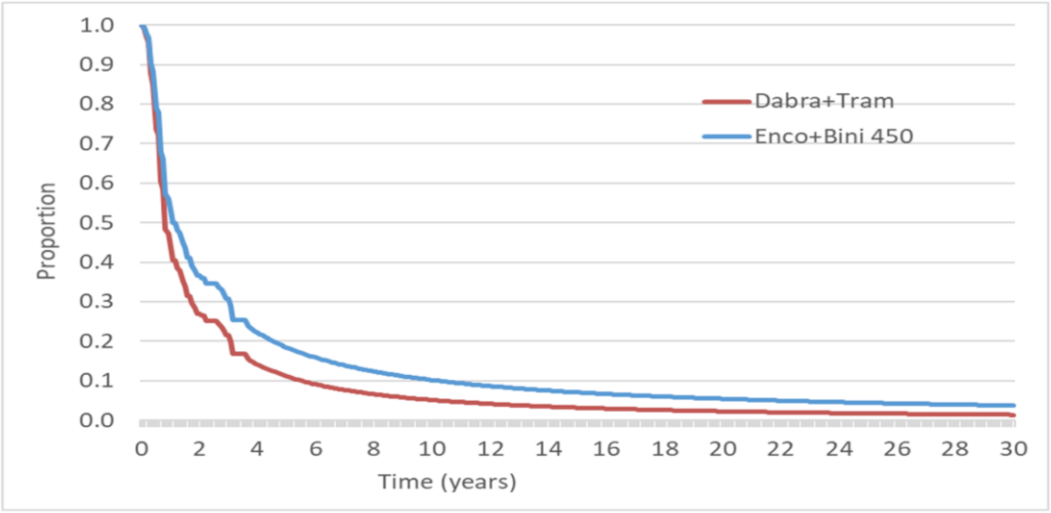
Source: Figure 18 (page 102 of the company submission)

PFS survival curves for Enco+Bini 450 were generated using patient level data from the latest data cut-off from COLUMBUS. Since all other BRAFi targeted comparator therapies included in the NMA reported PFS from study investigator assessment, PFS failure times from the local review were used in the base-case analysis for comparative purposes. A PFS analysis comparing Enco+Bini 450 with Dabra+Tram via central independent review of progression was not feasible and hence was not considered further for inclusion in the mode

Company model: PFS (2)

Enco+Bini 450: COLUMBUS K-M PFS data by local review until 43 months + gamma parametric extrapolation

Dab +Tram: HR estimate from NMA applied to Enco+ Bini 450 survival curve



Source: Figure 18 (page 102 of the company submission).

Progression was assessed in COLUMBUS by BIRC and locally by study investigators (local review). Local review of progression was used to inform the model, based on the relative availability of data for the NMA

Enco+Bini 450 model arm:

PFS data for the Enco+Bini 450 arm of the COLUMBUS trial (November 7th, 2017 data cut) was available till 43 months. In the base-case, K-M data followed by the Gamma extrapolation was used.

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 COLUMBUS . The next six curves were pairwise PFS curves using a constant hazard approach. Cumulative hazards from the PFS trial data for the

Enco+Bini 450 arm were plotted and then a breakpoint on the hazards plot identified 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.

Dabra+Tram model arm:

Numerical estimate of HR vs Enco+Bini 450 derived from the NMA (PFS by local review) applied to the entire Enco+Bini 450 survival curve.

ERG critique: OS and PFS

- Values for OS, PFS, TTD, utility values in different heath states and AE rates were derived from COLUMBUS. COLUMBUS is a well-conducted trial and trial data has been correctly included in the company model
- In the absence of direct evidence comparing the clinical effectiveness of Enco+Bini 450 versus Dab+Tram, NMAs were carried out by the company which showed no statistically significant difference between Enco+Bini 450 versus Dab+Tram for investigator-assessed PFS, OS, AEs and HRQoL
- Therefore, it is inappropriate to model any difference in efficacy or utility as the results of the NMAs indicate that there are no statistically significant differences in these outcomes

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Company model: TTD (1)

Kaplan-Meier curve for Enco+Bini 450 from COLUMBUS

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Source: Figure 23 (page 106 of the company submission)

The company carried out a post-hoc analysis of COLUMBUS patient level data to obtain TTD K-M data for Enco+Bini 450. Two different definitions of discontinuation were used:

- 1) discontinuation due to any reason and
- 2) discontinuation censoring on death and loss to follow up (LFU), which does not consider death and LFU as treatment discontinuation events.

TTD censoring death and LFU was used in the base-case to avoid double counting of deaths. As deaths are already captured as an event within PFS, they should not also be captured as discontinuation events

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Company model: TTD (2)

Enco+Bini 450: COLUMBUS K-M TTD data until available+ log-logistic parametric extrapolation

Dab +Tram: same as Enco+ Bini 450

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Source: Figure 18 (page 102 of the company submission).

Progression was assessed in COLUMBUS by BIRC and locally by study investigators (local review). Local review of progression was used to inform the model, based on the relative availability of data for the NMA

Enco+Bini 450 model arm:

PFS data for the Enco+Bini 450 arm of the COLUMBUS trial (November 7th, 2017 data cut) was available till 43 months. In the base-case, K-M data followed by the Gamma extrapolation was used.

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 COLUMBUS . The next six curves were pairwise PFS curves using a constant hazard approach. Cumulative hazards from the PFS trial data for the

Enco+Bini 450 arm were plotted and then a breakpoint on the hazards plot identified 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.

Dabra+Tram model arm:

Numerical estimate of HR vs Enco+Bini 450 derived from the NMA (PFS by local review) applied to the entire Enco+Bini 450 survival curve.

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Company model: adverse events

- AEs are applied in the model as one-off costs and not associated with any particular health state. QoL decrements due to AEs are taken into account within utility values estimated for COLUMBUS patients; therefore no additional AE disutilities are included in the model
- The model incorporates AEs likely to have a notable impact on costs (Grade 3/4 with incidence of at least 5% in either the Enco+Bini 450 arm of COLUMBUS, or the Dabra+Tram arms of COMBI-v and COMBI-d)
  - weighted average of incidence rates from COMBI-v and COMBI-d using data from the latest available data cut-offs used for Dab+Tram, arm

Grade 3/4 AEs	Enco+Bini 450	Dabra+Tram		
	COLUMBUS Nov 2016 cut-off	COMBI-v March 2015 cut-off N=350†	COMBI -d 15 Feb 2016 cut-off N=209†	COMBI-d/ COMBI-v weighted average
Hypertension	[redacted]	15.4% (54)	5.7% (12)	11.8%
Pyrexia	[redacted]	4.6% (16)	6.7% (14)	5.4%
Blood CK increased	[redacted]	NR (set to 0%)	NR (set to 0%)	0.0%
GGT increased	[redacted]	5.4% (19)	NR (set to 0%)	3.4%
ALT increased	[redacted]	2.6% (9)	2.4% (5)	2.5%

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Source: Figure 42 (page 116 of the company submission). Please see pages 115-116 of the company submission for more information

The company acknowledges that although there are limitations associated with modelling AE incidence rates from a naïve comparison of COLUMBUS, COMBI-v and COMBI-d, it allows for differences in specific AE rates to be captured. In contrast, if the OR from the NMA is used, a numerial 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. In addition, the base case approach allows all relevant AEs from COMBI-d and COMBI-v to be included as well as those from COLUMBUS.

A scenario analysis in which AE rates were assumed to be equal for Enco+Bini 450 and Dabra+Tram (this scenario considered all effectiveness to be equal including OS, PFS and utilities, based on results of the NMA which generated results where the CrI always crossed the boundary of equivalence) was also explored

ERG critique: adverse events

- NMA AE results not used in the company model and data relating to specific Grade 3 and 4 AEs with an incidence of at least 5% in either the Enco+Bini 450 arm of COLUMBUS or in the Dab+Tram arms of the COMBI-v and COMBI-d trials included:
  - this simple analysis is not robust as it fails to account for differences in patient baseline characteristics between the three trials
  - impact of AEs on utility values has been captured by utility values included in model. Therefore differences in incidence of Grade ≥3 AEs between Enco+Bini 450 and Dab+Tram model arms do not affect the estimate of incremental QALYs
  - in the company base case, the cost per patient of treating AEs was only £3 higher for patients in the Enco+Bini 450 arm than for patients in the Dab+Tram arm
- As there is no statistically significant difference in incidence of Grade ≥3 AEs, and the impact of the cost of treating AEs on model cost effectiveness results is negligible, the AE costs associated with Enco+Bini 450 and Dab+Tram can be assumed to be equal

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Company model: health state utilities

- EQ-5D-5L data collected during COLUMBUS. Utility values derived by mapping EQ-5D-5L responses onto the EQ-5D-3L UK valuation set
  - Regression-based method 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)
- Company NMA compared 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.
- 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.

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

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Source: Table 21 (page 71 of the ERG report). Please see pages 119-121 of the company submission for more information

The utility values used in the model have been derived directly from data collected as part of COLUMBUS and, as such, they consider the negative QoL associated to any treatment related AEs. Hence, no further separate one-off disutility for AEs was included in the model.

Utility values pre-progression are assigned to the cohort in the PF health state and in the base-case are applied as treatment specific using the numerically different but not statistically different results from the company NMA

Utility values for the PP health state (from post-hoc analysis of COLUMBUS QoL data) are implemented as non-treatment specific. There is no evidence to justify a different subsequent treatment mix following progression and therefore it is expected that the QoL would also be equal. This approach is in line with the approach suggested by the ERG in the cost-effectiveness analysis of Dab+Tram for TA396. In addition, it maximizes the sample size for estimating a mean score, as per protocol, a limited number of patients completed EQ-5D ≥30 days post-progression

A one-off disutility value was included in the model at progression to adjust for the QoL decrement typically associated with the worsening phase of the disease (obtained from post-hoc analysis of COLUMBUS). Model also adjusted to reflect declining utility with age.

Company model: costs and resource use

Drug costs for primary treatment:

- Estimate of Enco+Bini 450 or Dab+Tram used per patient per month derived from COLUMBUS
- Proportion of patients in the model receiving Enco+Bini 450 and Dab+Tram obtained from company base case projection of TTD in the model
- Relative dose intensity multipliers (RDIs) included to account that not all patients on treatment receive the full dose
- One-off treatment initiation cost of £415.89 applied in first model cycle to both arms to account for the cost of hospital visits and examinations that are carried out before BRAFI+MEKi therapies are prescribed

Administration costs:

- £15.22 administration cost per model cycle included based on assumption that it takes a pharmacist 12 minutes to dispense Enco+Bini 450 or Dab+Tram

AE costs:

- Total cost per AE calculated using the weighted average cost of inpatient and outpatient costs. Outpatient appointments and inpatient stays considered to be the proportions of people with Grade 3 and Grade 4 AEs in COLUMBUS respectively

Resource use by health state:

- One-off terminal care cost of £7,608 applied to people who transit to the death health state
- Resource use in the post progression health state was divided into routine management during antineoplastic treatment, disease management at progression and the routine management part of BSC with corresponding costs (see table 24 in the ERG report)

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Please see pages 122-138 of the company submission

Each health state is assigned relevant costs as follows:

Progression free:

- Cost of primary treatment (intervention and comparators in the model), including one-off treatment initiation cost, drug cost and dispensing and administration cost.
- Cost of subsequent treatments for the cohort switching to new antineoplastic treatment pre-progression, including drug cost and dispensing and administration cost.
- Routine management cost during antineoplastic treatment.

Post-progression:

- Cost of disease progression phase (one-off).
- Cost of primary treatment, including drug cost and dispensing and administration cost, for the cohort who continues to receive primary treatment post-progression.
- Cost of subsequent treatments.
- Routine management cost during antineoplastic treatment

for the cohort receiving any antineoplastic treatment post-progression.

- Cost of best supportive care

Company model: subsequent therapy cost

- Single, weighted subsequent therapy cost included in the model. Company considers this sufficiently reflects the cost of all subsequent therapies as there is insufficient data to simulate the spread of the cost across discrete time-points:
  - Cost is applied to all patients who discontinue either Enco+Bini 450 or Dab+Tram. Applying a one-off subsequent therapy cost unlikely to have a large impact on ICER per QALY gained since the mean treatment duration with subsequent therapy is short
  - approach is consistent with TA369 that evaluated the cost effectiveness Dab+Tram for advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma
- One-off subsequent therapy cost was calculated as the sum of the weighted total cost for each subsequent therapy (see table 52 in the company submission)
  - Subsequent therapy cost weighted by multiplying the per-cycle cost (drug cost and administration cost) for each therapy by mean treatment duration for therapy
  - For both arms of the model, the total cost for each subsequent therapy was weighted by the proportion of patients in the Enco+Bini 450 arm of COLUMBUS that received that particular therapy.

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Please see pages 72-73 of the company submission for more information

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Company model: base case results
(PAS price Enco+bini 450, list price Dab+Tram)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/ QALY)
Enco+Bini 450	[redacted]	5.884	4.223	[redacted]	0.613	0.453	Dominant
Dab+Tram	353,603	5.271	3.770				

Deterministic sensitivity analyses showed that the company model is most sensitive to variation in the base case TTD hazard ratio

Probabilistic sensitivity analyses showed that the company model probabilistic results (incremental cost of [redacted] and incremental QALY gain of +0.431) are similar to the model deterministic results. Cost effectiveness acceptability curve shows that the probability of treatment with Enco+Bini 450 being cost effective at a willingness-to-pay threshold of £20,000 per QALY gained is 100%

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Source: Table 61(page 141 of the company submission) .Please see pages 141-144 of the company submission for more information

Company model: scenario analysis

Most analyses are robust to changes to most model parameters excluding applying a [redacted] discount to the list price of Dab+Tram and assuming equal effectiveness between Enco+Bini 450 and Dab+Tram in terms of OS, PFS, PF utility and AE rates

Scenario	Incremental		ICER
	Costs	QALYs	
Base case	[redacted]	0.453	Dominant
Equal effectiveness for Dab+Tram and Enco+Bini 450 (OS, PFS, PF utility, AE rates)	[redacted]	0.000	Less costly, equal effectiveness
PF utilities equal for Dab+Tram and Enco+Bini 450	[redacted]	0.501	Dominant
HR for TTD for Dab+Tram vs Enco+Bini 450 = 0.9	[redacted]	0.453	Dominant
HR for TTD for Dab+Tram vs Enco+Bini 450 = 1.1	[redacted]	0.455	Dominant
Constant hazard approach for extrapolation of both TTD/ PFS	[redacted]	0.418	Dominant
TTD any reason (not censored)	[redacted]	0.453	Dominant
HR adjustment for AJCC =1	[redacted]	0.366	Dominant
OS crossover adjustment applied	[redacted]	0.422	Dominant
RDIs all set to 1	[redacted]	0.453	Dominant
Remove utility decrement for age	[redacted]	0.461	Dominant
Subsequent treatment option 2	[redacted]	0.453	Dominant
Subsequent treatment option 3	[redacted]	0.453	Dominant
Vial wastage excluded	[redacted]	0.453	Dominant
Exclude terminal care cost	[redacted]	0.453	Dominant
Both grade 3 and 4 AEs hospitalised	[redacted]	0.453	Dominant
List price for both Enco+Bini 450 and Dab+Tram	[redacted]	0.453	Dominant
PAS price for Enco+Bini 450 and [redacted] discount applied to Dab+Tram (threshold analysis to reach ICER of £20,000)	[redacted]	0.453	[redacted]
Discount rates 0% for both costs and outcomes	[redacted]	0.664	Dominant
Discount rates 6% for both costs and outcomes	[redacted]	0.358	Dominant

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Source: Table 27 (page 78 of the ERG report) .Please see pages 144-146 of the company submission for more information

ERG's preferred assumptions and changes to the model

- As OS, PFS, utility values and AEs can all be assumed to be equal for patients treated with Enco+Bini 450 and those treated with Dab+Tram, the only difference between the two treatment combinations that affects model results is treatment-related costs
  - In the company model, treatment-related costs are a function of time on treatment, administration costs, RDI multipliers and drug costs
  - company has assumed that the RDI multiplier associated with treatment with Enco+Bini 450 (Enco 0.91, Bini 0.88) is lower than with Dab+Tram. This analysis is not robust and multipliers should be the same for both treatments
- Time on treatment estimates for patients receiving Enco+Bini 450 and Dab+Tram are also likely to be the same as well as the administration costs of the two treatment combinations (given that they have the same mode of delivery)
- 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

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ERG adjustments to company base case
(PAS price Enco+Bini, list price Dab+Tram)

Scenario/ERG amendment	Enco+Bini 450		Dab+Tram		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A. Company's base case (RDI values corrected)	[redacted]	4.22	£353,603	3.77	[redacted]	0.45	Dominant
B. ERG preferred scenario (cost-minimisation analysis)	[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	[redacted]	4.22	£356,094	4.22	[redacted]	0.00	-

- At list prices, the ERG's preferred scenario results in estimated costs and QALYs being identical for Enco+Bini and Dab+Tram.
- Using PAS prices for Enco+Bini, this leads to a cost saving of [redacted] per person compared with Dab+Tram

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Equalities issues

- No equality issues raised by company or patient and professional groups

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

September 2018

File name	Version	Contains confidential information	Date
ID923_EncorafenibBinimetinib_NICE_DocB_ACIC	2	Yes	24/09/18

Contents

Tables and figures

Abbreviations

AE	Adverse event
AIC	Akaike's information criterion
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
BCRP	Breast cancer resistance protein
BIC	Bayesian information criterion
BID	Twice daily
BIRC	Blinded Independent Review Committee
BOR	Best overall response
BRAF	B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf
BRAFi	BRAF inhibitor
BSA	Body surface area
CBC	Complete blood count
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMP	Complete metabolic panel
CNS	Central nervous system
CR	Complete response
CRAF	Serine/threonine-protein kinase Raf-1
CrI	Credible interval
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450 (1A2, 3A4, 2C9 and 2B6 refer to isoforms)
Dabra+Tram	Dabrafenib in combination with trametinib
DCFB	Difference in change from baseline
DCR	Disease control rate
DIC	Deviance information criterion
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
Enco 300	Encorafenib 300 mg QD
Enco+Bini	Encorafenib combination with binimetinib
Enco+Bini 300	Encorafenib 300 mg QD in combination with binimetinib 45 mg BID
Enco+Bini 450	Encorafenib 450 mg QD in combination with binimetinib 45 mg BID
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-5L	EuroQoL-5 dimensions-5 levels
ERK	Extracellular signal-regulated kinase
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First patient first visit
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IRT	Interactive response technology that includes interactive voice response system and interactive web response system

ITT	Intention-to-treat
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
LFU	Lost to follow up
LY	Life years
MAA	Marketing authorisation application
MCID	Minimal clinically important difference
MEK	Mitogen-activated extracellular signal-regulated kinase
MEKi	MEK inhibitor
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
N/A	Not applicable
NE	Not estimable
NHS	National Health Service
NMA	Network meta-analysis
NTI	Narrow therapeutic index
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PD	Progressive disease
PD1	Programmed cell death protein 1
PDL1	Programmed death-ligand 1
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
P-gp	P-glycoprotein
PH	Proportional hazards
PP	Post-progression
PPS	Per-protocol Set
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QD	Once daily
RAF	Serine/threonine-protein kinase
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Standard deviation
StD	Stable disease
SLR	Systematic literature review
TA	Technology appraisal
TTD	Time to treatment discontinuation
TSD	Technical Support Document
TTR	Time to objective response
UGT	Uridine 5’-diphospho-glucuronosyltransferase (1A1 refers to isoform)
ULN	Upper limit of normal

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	As per scope	N/A
Intervention	Encorafenib with binimetinib	As per scope	N/A
Comparator(s)	Dabrafenib with trametinib	As per scope	N/A
Outcomes	• PFS • OS • Response rate • Adverse effects of treatment • HRQoL	As per scope	N/A
Subgroups to be considered	Where the evidence allows, the following subgroups will be considered: • people with previously untreated disease • people with previously treated disease that progressed on or after first line immunotherapy	Subgroups based on prior treatment experience in the metastatic setting will not be considered within the company's economic evaluation due to small patient numbers.	A relatively small proportion of patients in the metastatic treatment setting had received prior therapy with immunotherapy (6%) in the COLUMBUS trial. Due to the small numbers subgroups based on prior treatment experience will not be considered within the company's economic evaluation.

Abbreviations: BRAF, B-Raf proto-oncogene; HRQoL, health-related quality of life; OS, overall survival; PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1; PFS, progression-free survival; N/A, not applicable.

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	UK approved names: Encorafenib and binimetinib Brand names: BRAFTOVI® and MEKTOVI®
Mechanism of action	The RAF/MEK/ERK pathway regulates cellular proliferation, differentiation and survival (1). BRAF is a member of the RAF kinase family forming part of this pathway and a single point mutation in the BRAF gene, such as V600 mutations, are sufficient for this to become an oncogene (1), leading to uncontrolled cell proliferation and survival, and thus growth of the melanoma (2). Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor, which supresses the RAF/MEK/ERK pathway in melanoma tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). A slow dissociation half-life of over 30 hours results in prolonged pERK inhibition. Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of MEK1 and MEK2, which inhibits activation of MEK by BRAF and inhibits MEK kinase activity. This results in the inhibition of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models. In combination, encorafenib and binimetinib concomitantly inhibit the two kinases, RAF and MEK, of the RAF/MEK/ERK pathway, resulting in improved inhibition of intracellular signalling and higher anti-tumour activity.
Marketing authorisation/CE mark status	A regulatory submission was made to the EMA in July 2017. CHMP positive opinion was received on 27th July 2018 with marketing authorisation expected to be granted by the European Commission in September 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is as follows:† • Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation • Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Method of administration and dosage	Oral When used in combination, the recommended doses are anticipated to be encorafenib 450 mg (six 75 mg capsules) once daily and binimetinib 45 mg (three 15 mg tablets) twice daily, approximately 12 hours apart. The combination will be referred to as Enco+Bini 450 from this point throughout the submission

Additional tests or investigations	BRAF mutation testing: Before taking Enco+Bini 450, patients must have their BRAF V600 mutation-positive tumour status confirmed by a validated test. This is consistent with the comparator for this decision problem – Dabra+Tram (3, 4) – and, as such, the need for this diagnostic test would not represent a change in current clinical practice.
List price and average cost of a course of treatment	Encorafenib: • Anticipated list price £1,400 (PAS [redacted]) per pack of 42 x 75 mg capsules (7 days treatment) • Anticipated list price £622.22 (PAS [redacted]) per pack of 28 x 50 mg capsules (equivalent to 3.11 days treatment) Binimetinib: • Anticipated list price £2,240 (PAS [redacted]) pack of 84 x 15 mg tablets (14 days treatment) Prices are exclusive of VAT. The total cost per 28 days of treatment at list price would be £10,080.00 (PAS [redacted]). Based on median dose exposure in the COLUMBUS trial (11.8 months; Section B.2.10.1.1) the cost would be £129,210 (PAS [redacted] Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.
Patient access scheme (if applicable)	There is a simple PAS agreed with NHS England and the PAS price is incorporated in the submission.

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CHMP, Committee for Medicinal Products for Human Use; CRAF, serine/threonine-protein kinase Raf-1; Dabra+Tram, Dabrafenib in combination with trametinib; EMA, European Medicines Agency; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated extracellular signal-regulated kinase; PAS, patient access scheme; RAF, Serine/threonine-protein kinase.
†The draft SmPCs for encorafenib and binimetinib are presented in Appendix C.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview

Melanoma, an aggressive form of skin cancer, is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases (5); in 2016 there were 13,748 new diagnoses of melanoma registered in England (6) and 1,937 deaths (7). Melanoma incidence increases from around age 20–24, with significantly more females affected in younger age groups, while more males are affected in older age groups (5). In the

last two decades (1993/1995–2013/2015), melanoma incidence rates in the UK have increased by 128% and the rate is predicted to increase by a further 7% to 2035 (5).

Melanoma originates from skin cells called melanocytes and in its earliest form will present as benign lesions (8), which can then progress through various stages of malignancy; in its earliest stages, melanoma is often asymptomatic and the 10-year survival for stage 1A (confined to the skin) melanoma is 93% (9). However, as it spreads or metastasises to nearby lymph nodes (Regional metastases, stage III) or to more distant parts of the body (Distant metastases; stage IV) (9), survival rates are reduced, ranging from a 5-year survival of 59% for patients with stage IIIB disease through to 1-year survival as low as 33% (stage IV), depending on the site of metastasis (9). Around 9% of melanoma cases will be diagnosed at the advanced stages of disease (stage III or stage IV) (5), with more progressing from early stage disease to these later stages, despite treatment; an estimated 20% of primary melanomas will progress to metastatic disease (10).

Around 50% of melanomas express a mutated form of the B-Raf proto-oncogene (BRAF) and over 90% are at codon 600 (termed V600 mutations) (2). BRAF is a member of the serine/threonine-protein kinase (RAF) kinase family, forming part of the RAF/ Mitogen-activated extracellular signal-regulated kinase (MEK)/ Extracellular signal-regulated kinase (ERK) pathway which regulates cellular proliferation, differentiation and survival (1). A single point mutation in the BRAF gene, such as V600 mutations, are sufficient for this to become an oncogene (1), activating downstream signalling in the RAF/ERK/ERK pathway and leading to uncontrolled cell proliferation and survival, and thus growth of the tumour (2).

B.1.3.2 Clinical pathway of care

Treatment options for patients with unresectable or metastatic melanoma are guided by the presence of BRAF mutations, prior treatment history and patient/disease characteristics (11-13). NICE clinical guideline 14, published in 2015, recommends that for patients with unresectable stage III melanoma or with metastatic (stage IV) melanoma, systemic cancer treatment with either targeted treatments or immunotherapy should be considered (14). At the time of publication, targeted therapies recommended by NICE were the BRAF inhibitor (BRAFi) monotherapies, vemurafenib and dabrafenib, for patients with BRAF V600 mutation-positive melanoma (NICE technology appraisal [TA] 269; NICE TA321) (15, 16). Subsequently, NICE have recommended combination therapy with the BRAFi/ MEK

inhibitor (MEKi) combination of dabrafenib and trametinib (Dabra+Tram) (NICE TA396) (17),[a] with the expectation that this combination would replace monotherapy options. BRAFi/MEKi combinations are now preferred and considered as standard of care, having shown significant efficacy gains relative to BRAF monotherapy with a favourable safety profile (19-21) and with the European Society for Medical Oncology recommending them as a first-line option in BRAF mutation-positive patients (11, 12).

Immunotherapies currently recommended by NICE for advanced melanoma (irrespective of BRAF mutation status) include nivolumab in combination with ipilimumab (TA400), nivolumab monotherapy (TA384), pembrolizumab monotherapy (TA366, TA357), and ipilimumab monotherapy (TA319, TA268) (22-27). NICE clinical guideline 14 (14) and European guidelines from the European Society for Medical Oncology (11, 12) do not state a preference for either targeted BRAFi/ MEKi or immunotherapy for the first line treatment of BRAF V600 mutation-positive metastatic melanoma. However, it is recognised that these treatments may offer differing efficacy profiles which make them suitable for different sub-populations of patients; whereas BRAFi/ MEKi combination therapies offer high response rates and rapid response induction associated with symptom control, nivolumab and pembrolizumab (anti-programmed cell death protein 1 [PD1] therapies), and to a lesser extent ipilimumab, offer lower response rates, but responses may be durable (11). Cytotoxic chemotherapy with dacarbazine should be considered only if targeted therapy or immunotherapy are not suitable (11, 12, 14).

In this context, encorafenib 450 mg once daily (QD) in combination with binimetinib 45 mg twice daily (BID) (Enco+Bini 450) would be expected to provide clinicians and patients an additional treatment choice with a differentiated tolerability and toxicity profile to the combination of Dabra+Tram, and as such would be used in the same population of patients as this existing BRAFi/MEKi combination.

B.1.4 Equality considerations

Use of Enco+Bini 450 is not expected to raise any equality issues.

[a] In addition, NICE does not recommend the use of vemurafenib in combination with the MEKi, cobimetinib for treating BRAF V600 mutation-positive advanced melanoma (NICE TA414) (18).

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised and relevant comparators.

B.2.2 List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for Enco+Bini 450 is provided in Table 3 and Table 4.

Table 3: Clinical effectiveness evidence – pivotal trial

Study	**COLUMBUS (Study CMEK162B2301)** **Data sources:** • **May 2016 data cut-off:** CSR (28); Dummer et al 2018 (29); Gogas et al 2017 ESMO (30); Gogas et al 2018 ASCO (31). • **November 2016 safety update data cut-off:** EMA MAA safety update (32). • **November 2017 efficacy update data cut-off:** CSR OS addendum November 2017 data cut-off (33); OS topline report (34); Efficacy update report 7 November 2017 data cut-off (35); Dummer et al 2018 ASCO (36). • **Post-hoc analyses reports:** Post-hoc analyses reports (37, 38).				
Study design	A 2-part, randomised, open-label, multicentre, parallel group, Phase 3 study				
Population	Locally advanced, unresectable or metastatic BRAF V600-mutant melanoma				
Intervention(s)	Encorafenib 450 mg QD + binimetinib 45 mg BID (Enco+Bini 450)				
Comparator(s)	- Vemurafenib 960 mg BID - Encorafenib 300 mg QD (Enco 300)				
Indicate if trial supports application for marketing authorisation	Yes	***X***	**Indicate if trial used in the economic model**	Yes	***X***
	No			No	
Rationale for use/non-use in the model	Used in cost-effectiveness model: The pivotal, and only Phase 3 study supporting regulatory submission for Enco+Bini 450, providing comparative evidence versus standard of care at the time of the trial was conducted				

Reported outcomes specified in the decision problem*	**PFS** **OS** Response rate (ORR) **AEs** **HRQoL** (FACT-M subscale, **EQ-5D-5L,** and EORTC QLQ-C30)
All other reported outcomes*	TTR, DCR, DOR

Abbreviations: AE, adverse event; BID, twice daily; BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; EMA, European Medicines Agency; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQoL-5 dimensions-5 levels; FACT-M, Functional Assessment of Cancer Therapy-Melanoma; HRQoL, Health-related quality of life; MAA, marketing authorisation application; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; TTR, time to response.
* Outcomes marked in bold are used in the model.

Table 4: Clinical effectiveness evidence – supporting Phase 2 study

Study	**Study CLGX818X2109 (LOGIC-2)** **Data source: CSR (39)**				
Study design	Ongoing, 2-part, open-label, multicentre, Phase 2 study				
Population	Adult patients with locally advanced or metastatic BRAF V600-mutant melanoma, BRAFi/MEKi treatment-naive and non-naive				
Intervention(s)	Encorafenib 450 mg QD + binimetinib 45 mg BID (Enco+Bini 450)				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	***X***	**Indicate if trial used in the economic model**	Yes	
	No			No	***X***
Rationale for use/non-use in the model	Not used in cost-effectiveness model: Does not provide comparative evidence				
Reported outcomes specified in the decision problem	ORR (primary), PFS				
All other reported outcomes	TTR, DOR, DCR				

Abbreviations: BID, twice daily; BRAF(i), B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf (inhibitor); CSR, clinical study report; DCR, disease control rate; DOR, duration of response; MEK(i), mitogen-activated extracellular signal-regulated kinase (inhibitor); ORR, objective response rate; PFS, progression-free survival; QD, once daily; TTR, time to response.

The Phase 3 pivotal study COLUMBUS (Study CMEK162B2301) provides comparative evidence for Enco+Bini 450 for the treatment of locally advanced, unresectable or metastatic BRAF V600-mutant melanoma and is described in detail in Sections B.2.3 onwards. The Phase 2 study LOGIC-2 (Study CLGX818X2109) has been included in Table 4 for completeness, but does not provide any comparative evidence, and as such has not been used to inform the economic model and has not been described in Sections B.2.3 onwards. LOGIC-2 was presented in

the regulatory submission to the EMA to provide supportive efficacy evidence for the anticipated indication for Enco+Bini 450.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

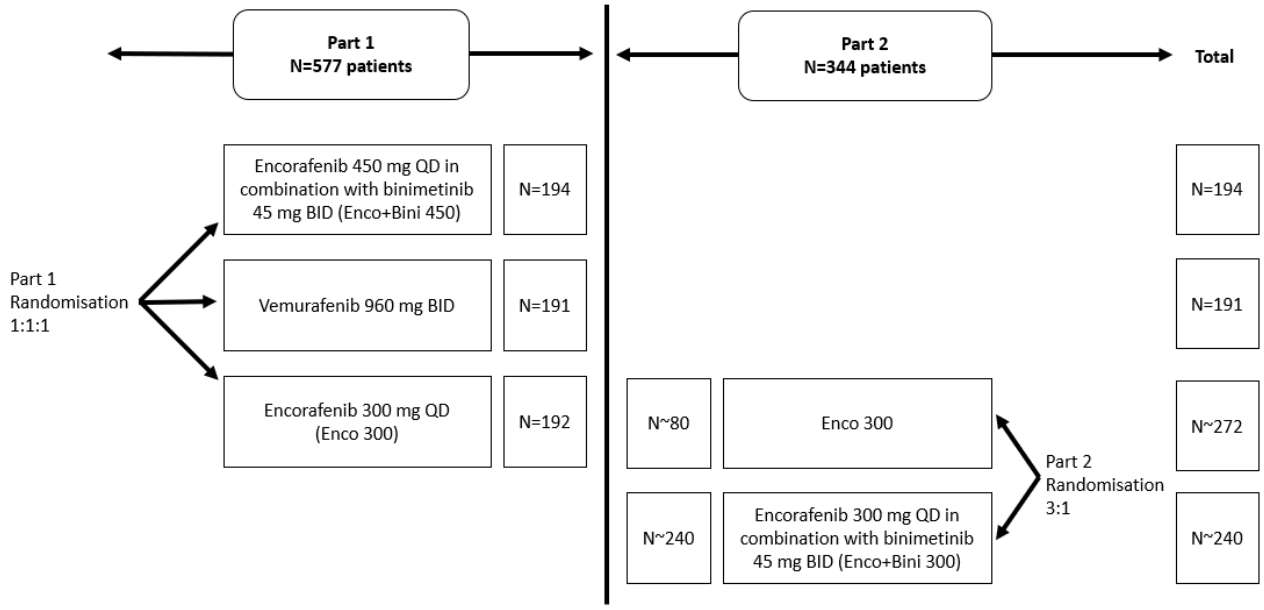
B.2.3.1 Summary of trial methodology – COLUMBUS (Study CMEK162B2301)

The COLUMBUS study was a 2-part, Phase 3 randomised, open-label, multicentre study which provides the pivotal evidence supporting the anticipated licensed indication for Enco+Bini 450.

Part 1 was a 3-arm study in which 577 patients were randomised at a 1:1:1 ratio to Enco+Bini 450, encorafenib 300 mg QD (Enco 300) or vemurafenib.

Part 2 was added based on Food and Drug Administration (FDA) feedback, via protocol amendment 3, to further quantify the contribution of binimetinib to the treatment combination by having equivalent encorafenib dosing and exposure in both treatment arms. In Part 2 (ongoing), ~320 patients were to be randomised 3:1 to encorafenib 300 mg QD in combination with binimetinib 45 mg BID (Enco+Bini 300) or Enco 300.

Figure 1: Randomisation scheme



Abbreviations: BID, twice daily; QD, once daily; Enco+Bini 300, encorafenib 300 mg QD in combination with binimetinib 45 mg BID; Enco+Bini 450, encorafenib 450 mg QD in combination with binimetinib 45 mg BID; Enco 300, encorafenib 300 mg QD.

This submission includes evidence from Part 1 only

In line with the anticipated licensed dosing regimen (Enco+Bini 450), only evidence from COLUMBUS Part 1 has been included in this submission as being relevant to the decision problem.

Evidence from Part 1, as presented in this submission, is available at three data cut-off dates, as follows:

- ***Data cut-off 19 May 2016:*** All study outcomes, except for overall survival (OS) (Part 1 primary PFS analysis)
- ***Data cut*-off 9 November 2016:** Updated safety outcomes (for European Medicines Agency [EMA] marketing authorisation application)
- ***Data cut-off 7 November 2017:***
  - Part 1 interim OS analysis
  - Updated progression-free survival (PFS) and response data

The methodology of the COLUMBUS study Part 1 is summarised in Table 5.

Table 5:Summary of trial methodology

Trial no. (acronym)	Study CMEK162B2301 (COLUMBUS)
All information relates to COLUMBUS Part 1 unless specified otherwise	
Location	Patients were randomised at 162 clinical sites in 28 countries: 20 sites in North America, 124 sites in Europe and 18 sites in selected countries from the rest of the world. Patients at 8 UK sites were randomised.
Study objective	The primary objective of COLUMBUS was to determine whether treatment with Enco+Bini 450 prolongs PFS compared with vemurafenib in patients with BRAF V600 mutant locally advanced unresectable or metastatic melanoma.
Trial design	A 2-part, randomised, open-label, international, multicentre, parallel group, Phase 3 study. In Part 1 approximately 576 patients were to be randomised in a 1:1:1 ratio to one of three treatment arms: • Enco+Bini 450 arm • Enco 300 arm • Vemurafenib arm Randomisation was stratified according to the following factors: • AJCC stage (IIIB + IIIC + IVM1a + IVM1b vs IVM1c) • ECOG PS (0 vs. 1)

Trial no. (acronym)	Study CMEK162B2301 (COLUMBUS)
	• Prior first-line immunotherapy (yes vs. no) after protocol amendment 2/BRAF mutation status (V600E vs. V600K) prior to protocol amendment 2 At protocol amendment 2 stage, stratification factors were modified such that prior first-line immunotherapy (yes vs. no) was added and BRAF mutation status (V600E vs. V600K) was removed. The BRAF mutation status was to be investigated as a covariate in the multivariate Cox-model and in a subgroup analysis if the primary endpoint was found to be significant. This was to ensure a balanced distribution among treatment arms of patients who had progressed on first-line immunotherapy and those with no prior treatment for locally advanced or metastatic melanoma. **Randomisation:** Each patient was assigned a unique patient number upon enrolment for pre-screening and randomisation numbers were generated to ensure that treatment assignment was unbiased and concealed from the Sponsor or designee's trial team. Prior to dosing, patients who fulfilled all inclusion/exclusion criteria were randomised via interactive response technology to one of the treatment arms; a patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers, and these randomisation numbers were linked to the different treatment arms. **Blinding:** As this was an open-label study, investigators and patients knew the study treatment assigned. To minimise bias, confirmation of progression had to be confirmed by independent review committee blinded to patient treatment assignment. Sponsor personnel responsible for data analysis and interpretation were also blinded to data that would systematically unblind patient treatment assignments until database lock for the primary analysis. **Study phases:** The study consisted of the following phases: pre-screening, screening and randomisation; treatment phase; end of treatment; and the follow-up period. • The treatment phase consisted of 28-day treatment cycles which continued until PD as determined by the BIRC, unacceptable toxicity, death, physician decision, early termination of the study, or discontinuation for any other reason (e.g. withdrawal of consent, lost to follow-up). • All patients were to have a safety follow-up visit 30 days after the last dose of study treatment. • Patients then had additional assessment visits depending on the reason for study drug discontinuation. • In the event of PD, patients had survival follow-up visits every 12 weeks to assess for survival and new antineoplastic treatment until death occurred. • In the event of treatment discontinuation for other reasons, patients continued to have tumour and patient reported outcome assessments, until progression, consent withdrawal, lost to follow-up or death.
Study period	• Date of first patient informed consent: 20 November 2013

Trial no. (acronym)	Study CMEK162B2301 (COLUMBUS)
	• Date of initial data cut-off: 19 May 2016 (primary PFS analysis) • Date of updated safety data cut-off: 9 November 2016 (updated safety analysis for EMA MAA) • Date of update efficacy data cut-off: 7 November 2017 (interim OS analysis, updated PFS analysis)
Eligibility criteria for participants	Patients were male or female, at least 18 years of age with histologically confirmed locally advanced unresectable or metastatic BRAF V600E and/or V600K-mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC or IV per AJCC) as determined by a Sponsor-designated central laboratory(ies), and previously untreated (treatment naïve) or had progressed on or after prior first-line immunotherapy for advanced or metastatic disease. Prior systemic treatment in the adjuvant setting was allowed, except for the administration of BRAFi or MEKi. Patients were also to have at least one measurable lesion as per RECIST version 1.1, an ECOG PS of 0–1 and adequate organ and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging. Patients with any untreated CNS lesion, uveal and mucosal melanoma, a history of leptomeningeal metastases, history or current evidence of, or current risk factors for retinal vein occlusion, or a history of Gilbert's syndrome were excluded. Full eligibility criteria are provided in Appendix L, section L.1.1.
Settings where the data were collected	Study drugs were to be taken by patients at home for all evening doses (binimetinib and vemurafenib) and for all morning doses other than when patients were scheduled for a clinic visit; in these cases, doses were to be taken under the supervision of the investigator or designee.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	**Intervention:** • Enco+Bini 450 arm: encorafenib 450 mg QD plus binimetinib 45 mg BID (N=192) **Comparators:** • Vemurafenib arm: vemurafenib 960 mg BID monotherapy (N=191) • Enco 300 arm: encorafenib 300 mg QD monotherapy (N=194) Encorafenib 50 and 100 mg were provided as capsules for oral administration QD. Binimetinib 15 mg was provided as film-coated tablets for oral administration BID, and were to be taken approximately 12 ± 2 hours apart. Patients were instructed to take encorafenib and binimetinib with a large glass of water (approximately 250 mL) daily at approximately the same time every day. On all dose administration days, patients were not to have eaten anything within 2 hours prior to the morning dose(s) of study drug intake and refrained from eating for 1 hour following encorafenib and binimetinib intake. The evening doses of binimetinib were to be taken with or without a meal but the same method was to be used consistently throughout the study. Vemurafenib 240 mg was supplied as tablets for oral administration BID, to be taken with a large glass of water (approximately 250 mL),

Trial no. (acronym)	Study CMEK162B2301 (COLUMBUS)
	approximately 12 ± 2 hours apart. Vemurafenib was to be taken either with or without a meal consistently. Patients were also instructed not to chew, crush or dissolve tablets and/or capsules.
Permitted and disallowed concomitant medications	**Permitted therapy:** Patients were to notify the investigational site of any new medications received after the start of the study drug, and all medications, other than study drug, and significant non-drug therapies administered during the study were to be listed on the electronic case report form. Patients taking concomitant medications chronically were to maintain the same dose and dose schedule if medically feasible. On the days PK blood sampling was performed, the patient was to continue their consistent use of other concomitant medication. However, if a concomitant medication was used intermittently during the study, this medication was to be avoided on these days, if medically feasible. **Permitted Concomitant Therapy Requiring Caution and/or Action:** The following were to be taken or used with caution: • Concomitant treatment with drugs that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4 and UGT1A1 or those substrates that have a NTI, or drugs that were substrates of CYP3A4 when co-administered with encorafenib • Moderate inhibitors of CYP3A4 and strong inhibitors of CYP2C19 when co-administered with encorafenib • Strong inhibitors of UGT1A1 when co-administered with binimetinib • Drugs that were known to inhibit or induce P-gp and BCRP • Co-administration of drugs that were known to be sensitive or NTI substrate of BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 • Concomitant use of warfarin with vemurafenib • Vemurafenib in combination with potent inhibitors/inducers of CYP3A4, glucuronidation and/or transport proteins (i.e., P-gp, BCRP) • Drugs with a conditional, possible or known risk to induce Torsade de Pointes • Dose adjustments for medicinal products predominantly metabolised via CYP1A2 or CYP3A4 were to be considered based on their therapeutic windows before concomitantly treating with vemurafenib • Concomitant treatments that had the potential to modify the gastric pH were to be taken at least 2 hours after the administration of binimetinib • Oral contraceptives were allowed but needed to be used in conjunction with a barrier method of contraception due to the unknown effect of study drug interactions **Prohibited Concomitant Therapy:** The following therapies were prohibited during the study:

Trial no. (acronym)	Study CMEK162B2301 (COLUMBUS)
	• Antineoplastic therapies, including chemo- or biologic-therapy or radiation therapy, covering > 30% of the red bone marrow reserve, and surgery • Strong inhibitors of the CYP3A4 substrate In addition, all patients requiring palliative radiotherapy and/or stereotactic radiotherapy were to interrupt treatment for at least 5 half-lives of the respective study drug(s) prior to and after radiotherapy or after having recovered from side effects of such a procedure.
Primary outcomes (including scoring methods and timings of assessments)	**Definition:** PFS, defined as the time from the date of randomisation to the date of the first documented disease progression or death due to any cause, whichever occurred first. **Assessments*:*** PFS was determined based on tumour assessment (RECIST version 1.1 criteria (40)) confirmed by blinded independent review (BIRC), and survival information. The local investigator's assessments were used as supportive analyses. Patients were to have at least one documented measurable lesion at study entry as per RECIST version 1.1. Any lesion that had been previously treated with radiotherapy was to be considered as a nontarget lesion, unless it was measurable and had shown clear progression since the radiotherapy, in which case, it was permitted to be considered as a target lesion. All known and suspected tumour lesions were radiographically assessed with CT or MRI, except for skin lesions, if present, which were assessed visually, by colour photography, including a metric ruler. The preferred radiologic technique was CT with IV contrast. ***Baseline:*** Baseline imaging assessments were performed during screening, within 21 days prior to randomisation, and included CT/MRI of the chest, abdomen and pelvis. A brain CT/MRI was conducted to assess CNS disease; contrast-enhanced brain MRI was preferred. Patients were to have a full body bone scan only if bone metastases were suspected. Localised CT, MRI or X-rays of all skeletal lesions identified on the screening bone scan, if not visible on the chest, abdomen and pelvis CT/MRI, were to be performed. If clinically indicated, a CT/MRI of other areas of disease were to be performed, as appropriate. Skin lesions were assessed by colour photography and a metric ruler. ***Post-screening:*** After screening, tumour assessments were performed every 8 weeks from randomisation during the first 24 months (until week 105) and every 12 weeks thereafter until BIRC progression using the same imaging modality used at baseline, irrespective of study drug interruption or actual dosing. Additional tumour assessments may have been performed if there was symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination. All patients who had disease progression determined by the local investigator required an expedited tumour response review by the BIRC, within 5 working days. The imaging vendor was to ensure that the central reviewers involved in the BIRC were blinded to the

Trial no. (acronym)	Study CMEK162B2301 (COLUMBUS)
	expedited status of the reading. Study treatment was to be continued while waiting for the results of the central review. • If the BIRC confirmed locally assessed PD, the patient discontinued study treatment and subsequent follow-up tumour assessments were no longer required. • If the BIRC did not confirm locally assessed PD, the patient continued to receive study treatment unless there was a medical need for an immediate change in therapy. Patients were to continue to have scans performed until the BIRC assessed PD. The BIRC also reviewed images from time points with no locally determined progression. Results of these readings were not communicated to the sites, even if PD was assessed by the BIRC.
Other outcomes used in the economic model/specified in the scope	• OS, calculated as the time from the date of randomisation to date of death due to any cause • ORR, calculated as the proportion of patients with a best overall response of CR or PR. ORR was to be calculated for confirmed and unconfirmed responses separately • DCR, calculated as the proportion of patients with a best overall response of CR, PR or stable disease • TTR, calculated as the time from date of randomisation until first documented CR or PR (CR or PR did not need to be confirmed) • DOR, calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer • Patient reported outcomes: o Time to definitive 10% deterioration in the FACT-M subscale and global health status/QoL score, physical functioning, emotional functioning and social functioning scale scores of the EORTC QLQ-C30 o Change from baseline in the FACT-M subscale, EQ-5D-5L, and EORTC QLQ-C30 global health status and subscale scores • Adverse events
Pre-planned subgroups	For PFS and OS, subgroup analyses were to be performed for each of the baseline stratification factors and other relevant baseline variables provided at least 10 patients were available in the considered sub-group.

Abbreviations: AJCC, American Joint Committee on Cancer; BCRP, breast cancer resistance protein; BID, twice daily; BIRC, Blinded Independent Review Committee; BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CNS, central nervous system; CR, complete response; CT, computed tomography; CYP, cytochrome P450; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQoL-5 dimensions-5 levels; FACT-M, Functional Assessment of Cancer Therapy-Melanoma; IRT, interactive response technology that includes interactive voice response system and interactive web response system; MAA, marketing authorisation application; MEK, mitogen-activated extracellular signal-regulated kinase; MRI, magnetic resonance imaging; NTI, narrow therapeutic index; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to objective response; UGT, uridine 5'-diphospho-glucuronosyltransferase.

B.2.3.2 Baseline characteristics and demographics: COLUMBUS

Patient demographics and characteristics at baseline are summarised in Table 6. Overall, baseline characteristics were similar in the 3 treatment arms. A higher percentage of patients in the Enco+Bini 450 arm compared with the Enco 300 and vemurafenib arms were ≥65 years old (31.3% Enco+Bini 450 arm, 20.6% Enco 300 arm, 26.7% vemurafenib arm); however, mean and median age were similar among the 3 treatment arms. Most patients in the 3 treatment arms were Caucasian (90.8% overall), and most were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 (72.1% overall).

The majority of patients (≥61.9%) were Stage IV M1C (metastases to all visceral sites except lungs, or distant metastases to any site) at study entry; of those Stage IV M1C patients, more patients had normal lactate dehydrogenase (LDH) levels than elevated LDH levels. At baseline, for the trial population overall, the median LDH and the percentage of patients with elevated LDH was similar among the 3 treatment arms, with 28.6%, 24.2% and 27.2% of patients classified as having high LDH in the Enco+Bini 450, Enco 300 and vemurafenib arms, respectively. However, of those patients with Stage IV M1C disease, more patients in the Enco+Bini 450 and Enco 300 arms had elevated LDH compared with the vemurafenib arm (25.0% and 25.3% vs. 18.8%).

All patients in the Enco+Bini 450 and vemurafenib arms and 99.0% of patients in the Enco 300 arm (2 patients were indeterminate) were positive for a BRAF V600 mutation at baseline; overall 88.6% were BRAF V600E mutant, 10.9% were V600K mutant, 1 patient in the vemurafenib arm was V600E&K mutant and 2 patients in the Enco 300 arm were indeterminate.

The treatment arms were balanced with respect to baseline tumour characteristics. Most patients (86.7% overall) had both target and nontarget lesions at baseline as per the Blinded Independent Review Committee (BIRC). The mean and median number of organs involved at baseline, respectively, was 2.7 and 2.0 in the Enco+Bini 450 arm, 2.5 and 2.0 in the Enco 300 arm and 2.6 and 2.0 in the vemurafenib arm. A similar percentage of patients in each treatment arm had >3 organs involved at baseline (21.9–23.6%). The frequency of involvement of liver and lung was similar in the 3 treatment arms (liver, 31.9–33.9%; lung, 49.7–55.2%). A higher percentage of patients presented with central nervous system (CNS) involvement (brain metastases) at baseline in the Enco+Bini 450 and Enco 300 arms

as compared with the vemurafenib arm (5.2% Enco+Bini 450 arm, 4.1% Enco 300 arm, 1.6% vemurafenib arm).

Table 6: Baseline characteristics and demographics – FAS, Part 1

	Enco+Bini 450 N=192	Enco 300 N=194	Vemurafenib N=191	Overall N=577
Age (years)				
Mean (SD)	56.2 (13.62)	54.6 (12.63)	55.2 (14.18)	55.3 (13.48)
Median	57.0	54.0	56.0	56.0
Min - Max	20–89	23–88	21–82	20–89
Age category (years), n (%)				
<65	132 (68.8)	154 (79.4)	140 (73.3)	426 (73.8)
≥65	60 (31.3)	40 (20.6)	51 (26.7)	151 (26.2)
Sex, n (%)				
Female	77 (40.1)	86 (44.3)	80 (41.9)	243 (42.1)
Male	115 (59.9)	108 (55.7)	111 (58.1)	334 (57.9)
Race, n (%)				
Caucasian	181 (94.3)	175 (90.2)	168 (88.0)	524 (90.8)
Asian	5 (2.6)	6 (3.1)	8 (4.2)	19 (3.3)
Native American	0	2 (1.0)	2 (1.0)	4 (0.7)
Other	3 (1.6)	2 (1.0)	2 (1.0)	7 (1.2)
Unknown [a]	3 (1.6)	9 (4.6)	11 (5.8)	23 (4.0)
Weight (kg)				
n	191	192	191	574
Mean (SD)	79.2 (17.8)	82.3 (18.4)	79.8 (17.8)	80.43 (18.010)
Median	78.1	80.3	78.7	79.0
Min - Max	46.5-143.0	46.3-151.0	42.6-150.0	42.6–151.0
Body surface area (m^2)				
n	186	188	188	562
Mean (SD)	1.9 (0.24)	1.9 (0.24)	1.9 (0.22)	1.9 (0.24)
Median	1.9	1.9	1.9	1.9
Min - Max	1.44-2.54	1.45-2.80	1.37-2.61	1.37–2.80
ECOG PS, n (%) [b]				
0	136 (70.8)	140 (72.2)	140 (73.3)	416 (72.1)
1	56 (29.2)	54 (27.8)	51 (26.7)	161 (27.9)
Primary site of cancer, n (%)				
Skin melanoma	191 (99.5)	192 (99.0)	190 (99.5)	573 (99.3)
Unknown	1 (0.5)	2 (1.0)	1 (0.5)	4 (0.7)

	Enco+Bini 450 N=192	Enco 300 N=194	Vemurafenib N=191	Overall N=577
BRAF mutation status				
V600E	170 (88.5)	173 (89.2)	168 (88.0)	511 (88.6)
V600K	22 (11.5)	19 (9.8)	22 (11.5)	63 (10.9)
V600E&K	0	0	1 (0.5)	1 (0.2)
Indeterminate	0	2 (1.0)	0	2 (0.3)
Stage at time of study entry, n (%)				
Stage IIIB	0	2 (1.0)	1 (0.5)	3 (0.5)
Stage IIIC	9 (4.7)	4 (2.1)	10 (5.2)	23 (4.0)
Stage IV M1A	26 (13.5)	29 (14.9)	24 (12.6)	79 (13.7)
Stage IV M1B	34 (17.7)	39 (20.1)	31 (16.2)	104 (18.0)
Stage IV M1C with elevated LDH	48 (25.0)	49 (25.3)	36 (18.8)	133 (23.1)
Stage IV M1C with normal LDH	75 (39.1)	71 (36.6)	89 (46.6)	235 (40.7)
Time from initial diagnosis to onset of metastatic disease (months)[c]				
n	187	191	187	565
Mean (SD)	37.02 (61.090)	36.45 (62.708)	38.14 (52.994)	37.20 (59.010)
Median	15.05	13.04	14.92	14.42
Min - Max	0.0–448.5	0.0-388.8	0.0-280.5	0.0–448.5
Number of organs involved at baseline,[d] n (%)				
1	47 (24.5)	56 (28.9)	45 (23.6)	148 (25.6)
2	58 (30.2)	52 (26.8)	59 (30.9)	169 (29.3)
3	45 (23.4)	42 (21.6)	42 (22.0)	129 (22.4)
>3	42 (21.9)	44 (22.7)	45 (23.6)	131 (22.7)
LDH at baseline (U/L)				
n	192	194	191	577
Mean (SD)	298.7 (368.93)	265.2 (251.21)	239.8 (189.27)	267.9 (280.49)
Median	173.0	188.5	174.0	179.0
Min - Max	76–3590	75–1886	57–1285	57–3590

	Enco+Bini 450 N=192	Enco 300 N=194	Vemurafenib N=191	Overall N=577
LDH at baseline,[e] n (%)				
Low	0	0	0	0
Normal	137 (71.4)	147 (75.8)	139 (72.8)	423 (73.3)
High	55 (28.6)	47 (24.2)	52 (27.2)	154 (26.7)
Missing	0	0	0	0

Abbreviations: CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FAS, full analysis set; LDH, lactate dehydrogenase; Max, maximum; Min, minimum; PS, performance status; SD, standard deviation; U, units.
[a]Unknown denotes "unknown" was selected on the eCRF if the patient's race was unknown; [b]Last non-missing ECOG PS prior to or on the start of study treatment for patients who took at least one study treatment or prior to or on Cycle 1 Day 1 for patients who didn't take any study treatment; [c]Time from initial diagnosis to onset of metastatic disease calculated only for patients with metastatic disease; [d]For patients with stage IIIB and IIIC at study entry, the number of organs involved at baseline is equal to one and presented as skin; [e]Low and high categories defined by normal ranges.
Source: CSR, with some minor adjustments for missing data from the OS top line results addendum (28, 34).

The percentage of patients who had received prior antineoplastic therapies overall was similar across the 3 treatment arms (Table 7). Among the therapy types, the percentage of patients who received prior systemic treatment or who had prior surgery was similar; however, a higher percentage of patients in the Enco 300 arm (21.6%) received prior radiotherapy as compared with either the Enco+Bini 450 (15.6%) or vemurafenib (13.1%) arms.

Prior chemotherapy was allowed only in the adjuvant setting or as local-regional treatment; 11 patients (1.9%) overall received prior chemotherapy in the adjuvant setting (3 patients [1.6%] Enco+Bini 450 arm, 4 patients [2.1%] Enco 300 arm, 4 patients [2.1%] vemurafenib arm). Two patients previously treated with chemotherapy in the metastatic setting were enrolled (1 patient Enco+Bini 450 arm and 1 patient vemurafenib arm); both received prior dacarbazine.

A similar percentage of patients (29.7% Enco+Bini 450 arm, 29.9% Enco 300 arm, 29.8% vemurafenib arm) received prior immunotherapy in any disease setting, including ipilimumab, anti-PD1/PDL1 inhibitors and interferons/interleukins. Prior use of interferons/interleukins was most common (26.7% overall) and similar among the 3 treatment groups; few patients received prior ipilimumab (4.2% overall) or anti-PD1/PDL1 inhibitors (0.5% overall).

Table 7: Prior antineoplastic therapy – FAS, Part 1

	Enco+Bini 450 N=192 n (%)	Enco 300 N=194 n (%)	Vemurafenib N=191 n (%)
Any therapy[a]	158 (82.3)	161 (83.0)	165 (86.4)
Medication	62 (32.3)	63 (32.5)	59 (30.9)
Surgery	146 (76.0)	149 (76.8)	157 (82.2)
Radiotherapy	30 (15.6)	42 (21.6)	25 (13.1)
Medication: setting at last treatment			
Adjuvant	52 (27.1)	46 (23.7)	46 (24.1)
Neoadjuvant	0	1 (0.5)	1 (0.5)
Therapeutic - Metastatic	10 (5.2)	16 (8.2)	12 (6.3)
Radiotherapy: setting at last radiotherapy			
Adjuvant	17 (8.9)	20 (10.3)	11 (5.8)
Neoadjuvant	0	1 (0.5)	0
Therapeutic - metastatic	6 (3.1)	11 (5.7)	6 (3.1)
Therapeutic	3 (1.6)	6 (3.1)	4 (2.1)
Palliative	2 (1.0)	4 (2.1)	2 (1.0)
Other	2 (1.0)	0	0
Missing	0	0	2 (1.0)

Abbreviations: FAS, full analysis set.
[a]A patient may have had multiple therapy types.
Source: CSR (28).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence: COLUMBUS

B.2.4.1 Populations analysed

The following populations were considered in the study:

- **Full Analysis Set (FAS):** defined according to the intention-to-treat (ITT) principle, and consisted of all randomised patients. Patients were analysed according to the treatment and stratification factors they were assigned to at randomisation. Efficacy outcomes were primarily assessed using the FAS.
  - At the time of the primary PFS analyses, all patients randomised to Part 1 of the study were included and analyses based on data collected up to and including 19 May 2016.

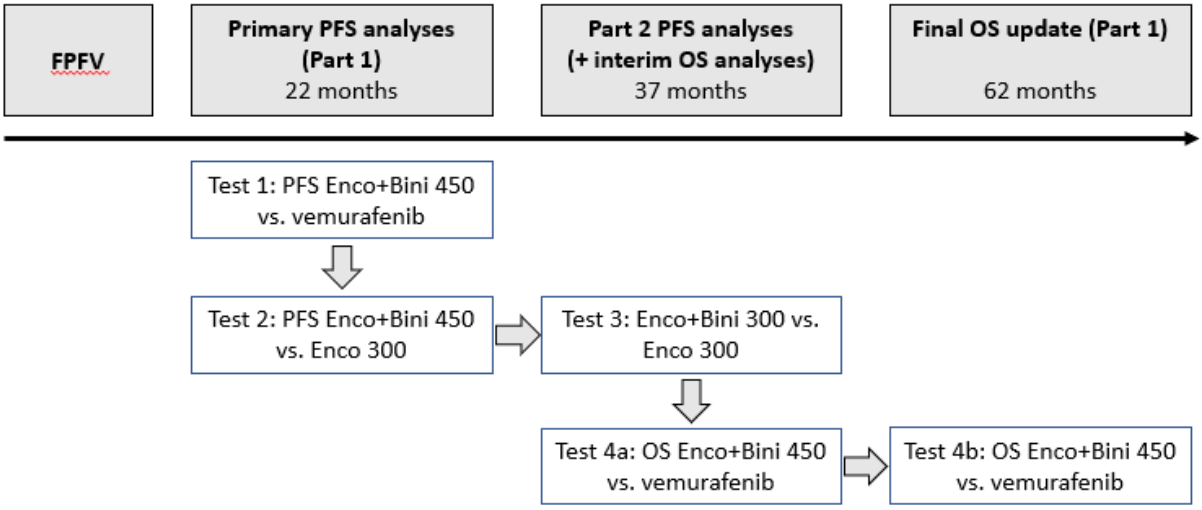
- **Per-protocol Set (PPS):** included all patients from the FAS who had no major protocol deviations and who received at least one dose of study medication.
- **Safety Set:** included patients who received at least one dose of the study medication and had at least one valid post-baseline safety evaluation. Patients were analysed according to the study treatment they actually received, defined as the treatment received during the whole treatment period. This was the analysis set for all safety evaluations.

Seven patients (5 patients in the vemurafenib arm and 2 patients in the Enco 300 arm) were randomised but did not receive study drug and were excluded from the PPS and the Safety Set.

B.2.4.2 Analysis timepoints and hierarchical statistical testing

Primary and secondary efficacy endpoints were to be tested as shown in Figure 2. A hierarchical approach was taken for statistical testing of the primary and key secondary efficacy endpoints.

Figure 2: Timing of testing of primary and secondary endpoints



Abbreviations: Enco+Bini 300, encorafenib 300 mg QD in combination with binimetinib 45 mg BID; Enco+Bini 450, encorafenib 450 mg QD in combination with binimetinib 45 mg BID; FPFV, first patient first visit; Enco 300, encorafenib 300 mg QD; OS, overall survival; PFS, progression-free survival.

⇨ Hierarchical testing sequence

The timing of the analyses refers to the analysis cut-off date, i.e. when the expected number of events or time point was reached or is expected to be reached.

Part 2 PFS analyses comparing C300 and encorafenib are not relevant to the decision problem and are not presented within this submission.

Primary PFS analysis (Part 1): The primary PFS analysis was conducted in Part 1 of the study at a data cut-off date of 19 May 2016. The analysis was to be performed

when enrolment in Part 1 was complete (i.e. when ~576 patients were randomised into Part 1) and was event driven (i.e. 145 PFS events for Enco+Bini 450 versus vemurafenib and 191 PFS events for Enco+Bini 450 versus Enco 300). A hierarchical testing procedure was adopted and the Part 1 key secondary endpoint, PFS of Enco+Bini 450 versus Enco 300, was to be tested if the primary endpoint, PFS of Enco+Bini 450 versus vemurafenib, was statistically significant.

Secondary interim OS analysis (planned to be performed at the time of Part 2 PFS analyses): The secondary Part 2 PFS analysis was designed to provide results for the Enco+Bini 300 intervention versus Enco 300. As these results are not relevant to the licensed indication for Enco+Bini 450 or the scope of this NICE appraisal, Part 2 PFS analyses are not presented. However, the hierarchical approach to statistical testing was further employed for Part 2 PFS analyses and for the interim OS analysis conducted at the time of Part 2 PFS analyses. As such the OS for Enco+Bini 450 versus vemurafenib was only to be tested if the Part 1 PFS analyses described above, **followed by** the Part 2 PFS outcome (PFS of Enco+Bini 300 versus Enco 300), were all statistically significant. The Part 1 PFS analysis of Enco+Bini 450 versus Enco 300 was shown to be numerically superior but did not reach the pre-defined level for significance of $p<0.025$ ($p=0.0256$, see Section B.2.6.3.1, data cut-off 19 May 2016), which may have reflected the improved efficacy observed with Enco 300 monotherapy compared with vemurafenib monotherapy (data not presented, nominal one-sided $p=0.004$ for PFS by BIRC). Given the above, OS analyses could not be formally tested, and nominal p-values are provided for descriptive purposes only.

The interim OS analysis was planned to be performed at the time of the Part 2 PFS analysis at approximately 37 months, but not until approximately 232 OS events had been observed across the Enco+Bini 450 and vemurafenib arms combined. The data cut off for the interim OS analysis was 7 November 2017, by which time the pre-specified events had been observed.

OS analyses were not performed at the time of primary PFS analysis to preserve Sponsor blinding and maintain integrity of the planned interim OS analysis.

Final OS update: not available; planned when 309 deaths have occurred for the comparison of Enco+Bini 450 versus vemurafenib (approximately 62 months).

B.2.4.3 Statistical hypothesis and methods of analyses

B.2.4.3.1 PFS (primary endpoint)

The primary efficacy endpoint (Enco+Bini 450 versus vemurafenib) and key secondary endpoint (Enco+Bini 450 versus Enco 300) was PFS, defined as the time from the date of randomisation to the date of the first documented progression or death due to any cause, whichever occurred first. If a patient did not have an event at the time of the analysis cut-off or at the start of any new antineoplastic therapy, PFS was censored at the date of the last adequate tumour assessment (See Section B.2.4.5 for details of censoring rules). Blinded tumour assessment data read centrally by a BIRC were used in the primary efficacy analysis, with the local Investigator's assessments being used in supportive analyses.

PFS was analysed based on data from the FAS according to the treatment arm and two of the stratification factors (cancer stage and ECOG PS) patients were randomised to. Due to the relatively low expected prevalence of patients with prior immunotherapy (~15%), the two prior immunotherapy strata (yes and no) were combined at the time of the analysis to avoid small or empty strata. The same principle applied to all stratified tests and models in this study.

The primary PFS analysis between Enco+Bini 450 and vemurafenib arms was tested using a stratified log-rank test at a one-sided 2.5% cumulative level of significance.

The null and the alternative hypothesis were defined as follows:

$H_0: \theta_{C450vs.V} \geq 0$ *vs.* $H_A: \theta_{C450vs.V} < 0,$

where $\theta_{C450vs.V}$ is the PFS log-hazard ratio (HR) for Enco+Bini 450 arm versus vemurafenib.

The distribution of PFS was described using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

A Cox regression model stratified by randomisation stratification factors was used to estimate the HR of PFS, along with 95% CI based on the Wald test. The PHREG procedure in SAS with option TIES=EXACT was used to fit the Cox proportional hazards model. To assess the validity of the proportional hazard assumption, the log-cumulative hazard plot was therefore produced for each stratum separately.

The same method of analysis and supportive analyses was used for the Part 1 key secondary objective comparing PFS for Enco+Bini 450 versus Enco 300.

For PFS endpoints that were not primary or key secondary, the distribution of PFS was estimated using the Kaplan-Meier method. The median PFS along with 95% confidence interval (CI) was presented by treatment arm. A stratified Cox regression analysis was used to estimate the HR of PFS, along with 95% CI.

B.2.4.3.2 OS

OS was defined as the time from the date of randomisation to the date of death due to any cause. If a death was not observed by the date of analysis cut-off, OS was to be censored at the date of last contact. Survival time for patients with no post-baseline survival information was to be censored on the date of randomisation.

The following statistical hypothesis for OS was to be tested:

$H0: \theta_{C450vs.V} \geq 0$ *vs. HA:* $\theta_{C450vs.V} < 0$

where $\theta_{C450vs.V}$ is the OS log-HR for the Enco+Bini 450 arm versus the vemurafenib arm.

OS was described using Kaplan-Meier methods. A Cox regression model stratified by randomisation stratification factors (cancer stage and ECOG PS) was used to estimate the HR of OS, along with 95% CI based on the Wald test (as per PFS).

Interim analysis (planned for at the time of the Part 2 PFS analysis):

- OS for Enco+Bini 450 versus vemurafenib OS was to be formally tested.
- In addition, the treatment effect of Enco+Bini 450 versus Enco 300 and Enco 300 versus vemurafenib was to be estimated on the FAS combining data regardless of the part the patients were randomised to. Log-rank test p-values were to be presented for descriptive purposes only.

B.2.4.3.3 Other outcomes

Analyses of best overall response, objective response rate (ORR), disease control rate (DCR), time to objective response (TTR) and duration of response (DOR) and were performed using BIRC assessments, with local Investigator's assessments being used for sensitivity analyses. Rates (ORR, DCR) were presented by treatment arm along with exact 95% CI. TTR and DOR were described using Kaplan-Meier methods as per PFS. No formal statistical test was performed.

For patient reported outcomes, time to definitive 10% deterioration in the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) subscale and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30) global health status and subscale scores were described using Kaplan-Meier methods and analysed using a stratified Cox regression model as per PFS. Descriptive statistics were used to summarise the FACT-M subscale, EuroQoL-5 dimensions-5 levels (EQ-5D-5L) index score and EORTC QLQ-C30 scores at each time point and change from baseline. In absence of a validated EQ-5D-5L valuation set, UK EQ-5D-3L value sets for the UK were used, using the crosswalk developed by van Hout et al (41).

A mixed-effect model for repeated measures (MMRM) was used to compare the treatment arms in terms of change from baseline in the domain score over time.

B.2.4.4 Sample size and power calculation

B.2.4.4.1 PFS

For vemurafenib, a median PFS of 7 months was assumed, based on updated results from the BRIM-3 Phase 3 study and BRIM-2 Phase 2 study (42, 43) in which previously untreated patients and patients who progressed after at least one prior systemic treatment were studied, respectively (Median PFS: 6.9 and 6.8 months, respectively). This was further corroborated by the results of two Phase 3 studies (Combi-v and coBRIM) of the combination of BRAFi and MEKi (dabrafenib plus trametinib and vemurafenib plus cobimetinib, respectively) versus single-agent vemurafenib (19, 21) and a Phase 4 study of vemurafenib (44) in patients with metastatic melanoma.

For Enco 300 the observed median PFS was 7.1 months (95% CI: 3.7, 14.7) and 7.4 months (95% CI: 7.4, not estimable [NE]), respectively, based on the dose-escalation and dose-expansion results of the ongoing Phase 1 study CLGX818X2101 (NCT ID: NCT01436656, data not reported in this submission). In the less advanced patient population recruited to COLUMBUS, the median PFS was therefore expected to be around 8 months.

Enco+Bini 450 was expected to result in a 42% reduction in HR compared with vemurafenib, corresponding to an increase in median PFS from 7 months to 12 months, based on results from the Phase 1b/2 study CMEK162X2110 (45).

In order for the study to properly address its Part 1 objectives, i.e. to evaluate Enco+Bini 450, it was required that both endpoints, the primary and the key secondary, were tested. The key secondary comparison, PFS of Enco+Bini 450 versus Enco 300, was therefore the sample size driver.

In study Part 1, patients were randomised in a 1:1:1 ratio to receive Enco+Bini 450, Enco 300 or vemurafenib. For the comparison of Enco+Bini 450 versus Enco 300, 191 PFS events were required to detect a HR of 0.667 with an 80% power using a log-rank test at a one-sided 2.5% level of significance. A statistically significant log-rank test corresponded to an observed HR<0.753, corresponding to a median PFS in the Enco+Bini 450 arm of 10.6 months if the median in the Enco 300 arm was 8 months.

For the Part 1 primary comparison, Enco+Bini 450 versus vemurafenib, 145 PFS events were required to detect a HR of 0.58 with a 90% power using a log-rank test at a one-sided 2.5% level of significance. A statistically significant log-rank test corresponded to an observed HR<0.722.

Considering the observed accrual until August 2014, an anticipated accrual rate of 50 patients per month for the following months and accounting for 15% lost to follow-up, a total of 576 patients (192 patients in each arm) were planned to be recruited in Part 1 over around 15 months. The primary analysis of PFS was to be performed when Part 1 enrolment was complete, and a sufficient number of PFS events for both the primary and key secondary comparisons were available. This was expected to occur around 22 months after first treatment of the first patient.

B.2.4.4.2 OS

Based on the Combi-v Phase 3 data (21), a 17-month median OS was expected to be observed in the vemurafenib arm. Enco+Bini 450 was expected to increase median OS to 22 months, corresponding to a HR of 0.7727.

Power calculations were conditional in the sense that OS evaluations were only to be performed if the primary and key secondary comparisons were significant. A Gamma function with parameter 1 was considered as the α-spending function to provide more chance for the trial to stop early if the alternative hypothesis was true. For OS, the lost to follow-up rate was considered to be 5%.

B.2.4.5 Data management and patient withdrawals

Disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and death (from any cause) were considered as events. If a patient did not have a documented event by the date of analysis cut-off or before they initiated treatment with further antineoplastic therapy, PFS was censored at the date of last adequate tumour assessment (i.e. at the date of last tumour assessment of complete response (CR), partial response (PR) or stable disease) prior to the cut-off date or start date of new antineoplastic therapy, whichever was earlier. In this case, the last tumour evaluation date at that assessment was used. If a PFS event was observed after ≥2 missing or non-adequate tumour assessments, then PFS was censored at the last adequate tumour assessment. However, if a PFS event was observed after a single missing or non-adequate tumour assessment, the actual date of the event was used. When a patient discontinued treatment for "disease progression" based on clinical deterioration, without documented evidence of progression based on RECIST v1.1, it was not to be considered as a PFS event.

Censoring rules applied to the PFS endpoint are described in Table 8.

Table 8: Censoring rules for PFS

	Situation	Event date	Outcome
A[a]	No baseline assessment	Date of randomisation	Censored
B	Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate tumour assessment[b]	Censored
D	No progression	Date of last adequate tumour assessment[b]	Censored
E	Treatment discontinuation due to "Disease progression" without documented progression, i.e., clinical progression based on investigator claim	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment)	Information ignored
F	New antineoplastic therapy given	Date of last adequate tumour assessment[b]	Censored

Abbreviations: PD, progressive disease, N/A, not applicable
[a]The rare exception to this is if the patient died no later than the time of the second scheduled assessment as defined in the protocol in which case a PFS event at the date of death was counted; [b]tumour assessment with non-missing and non-unknown overall lesion response.

For TTR, patients who did not achieve a PR or CR were to be censored at the last adequate tumour assessment date when they did not have a PFS event, or after a duration of time equal to the maximum follow-up when they had a PFS event. For DOR, if a patient with a CR or PR had no progression or death due to underlying cancer, the patient was censored at the date of last adequate tumour assessment.

B.2.4.6 Sensitivity analyses and other supportive analyses

Several sensitivity analyses were to be conducted to support the primary analysis of PFS and key secondary endpoints, providing nominal p-values for descriptive purposes. These included:

- Using data based on local investigator assessment
- Using PPS
- Using unstratified log-rank test/HR from unstratified Cox model
- PFS by BIRC (FAS) using stratification factors as provided in the electronic case report form (eCRF), as opposed to randomisation stratum (performed per the statistical analysis plan due to >5% discordance between randomisation strata and eCRF strata).
- "Actual event" analysis for PFS with a censoring rule that included a PFS event even if the event was recorded after two or more missing tumour assessments.
- "Backdating" analysis for PFS with a censoring rule that backdated events occurring after one or more missing tumour assessments. Events were backdated to 8 weeks (or 12 weeks if the patient had been on treatment long enough) after the last adequate tumour assessment.
- "Further antineoplastic therapy", sensitivity analysis for PFS including tumour assessments after initiation of subsequent antineoplastic therapy.

In supportive analyses, the effect of potential prognostic factors was to be investigated by using multivariate Cox regression. In addition to covariates for the stratification factors considered for randomisation (cancer stage and ECOG PS), the following factors measured at baseline could be included as covariates: tumour tissue mutation status (V600E vs. V600K); gender (male vs. female); age (continuous); baseline brain metastases (yes vs. no); LDH baseline level (continuous); geographical region (North America vs. Europe [including Russia] vs. Australia vs. others). To avoid model instabilities, these covariates were only included if there were ≥10 patients in each category.

B.2.4.7 Participant flow in the relevant randomised controlled trials

In total, 1,345 patients were screened for entry into Part 1 of the study. Of these, 577 patients were randomly assigned in a 1:1:1 ratio to receive either Enco+Bini 450 (n=192), Enco 300 (n=194) or vemurafenib (n=191). For further details, please refer to Appendix D, Section D.2.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence: COLUMBUS

A complete quality assessment for the COLUMBUS trial is provided in Table 9.

Table 9: Quality assessment results for COLUMBUS

Trial number (acronym)	COLUMBUS
Was randomisation carried out appropriately?	Yes. A patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers when applicable.
Was the concealment of treatment allocation adequate?	Yes. At the time of randomisation, treatment allocation was concealed. However, this was an open label study; investigators and patients were soon informed of the study treatment assigned. Double-blinding wasn't considered feasible on the basis of patient safety, as discussed in Section B.2.13.2.1.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A. This was an open label study; the Investigators and patients were aware of the study treatment assigned. However, an independent blinded review of study data was also performed.
Were there any unexpected imbalances in drop-outs between groups?	Not clear. For survival outcomes, the Data Monitoring Committee decided to provide the choice for patients on vemurafenib monotherapy to move to other therapies (Section B.2.9.3).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The FAS was defined according to the ITT principle, and consisted of all randomised patients. Following the ITT principle, patients were analysed according to the treatment and stratification factors they were assigned to at randomisation.

Abbreviations: FAS, full analysis set; IRT, interactive response technology; ITT, intention-to-treat; N/A, not applicable.

B.2.6 Clinical effectiveness results of the relevant trials: COLUMBUS

COLUMBUS efficacy overview

- The primary objective of the pivotal COLUMBUS study was met. Enco+Bini 450 significantly improved PFS, based on the blinded independent review (BIRC), compared with vemurafenib, by more than doubling the median duration of PFS (14.9 months vs. 7.3 months), thereby providing a statistically significant and clinically relevant improvement in PFS (HR 0.54, 95% CI: 0.41, 0.71, one-sided stratified log rank p<0.0001; [November 2017 update: HR 0.51, 95% CI: 0.39, 0.67; one-sided stratified log rank p<0.0001]).
- There was also a statistically significant and clinically relevant PFS benefit with Enco+Bini 450 compared with Enco 300 by BIRC assessment at the most recent study cut-off date of November 2017 (HR: 0.77; 95% CI: 0.59, 1.00; p=0.0249).
- PFS results by investigator assessment were consistent with those by BIRC for comparisons of Enco+Bini 450 with vemurafenib and with Enco 300.
- All unstratified subgroup analyses demonstrated PFS point estimates (by BIRC assessment) in favour of Enco+Bini 450 versus vemurafenib, with the exception of the presence of brain metastases at baseline (HR 1.34); the number of patients in this subgroup was very small (nine in the Enco+Bini 450 arm and three in the vemurafenib arm) and hence this result should be interpreted with caution.
- Overall survival was doubled with Enco+Bini 450 compared with vemurafenib monotherapy (33.6 months vs 16.9 months), representing a 39% reduction in the risk of death (HR: 0.61, 95% CI: 0.47, 0.79; nominal one-sided p<0.0001). Sensitivity analyses of OS based on alternate stratification factors and analysis sets yielded consistent results.
- Patients treated with Enco+Bini 450 patients were more likely to achieve a clinically relevant reduction in tumour burden as defined by RECIST v1.1 compared with vemurafenib (ORR by BIRC: 63.0% vs. 40.3%; [November 2017 update: 63.5% vs. 40.8%]). Responses on Enco+Bini 450 treatment were durable, lasting a median of 16.6 months compared with a DOR of 12.3

months for vemurafenib treatment (By BIRC; [November 2017 update: 18.6 vs. 12.3 months]).

- Health-related quality of life (HRQoL) findings were consistent with the observation of clinical benefit and improved tolerability of Enco+Bini 450 compared with single-agent Enco 300 and vemurafenib; Enco+Bini 450 significantly delayed deterioration in HRQoL, as measured by median time to 10% deterioration on the FACT-M melanoma subscale and EORTC-QLQ-C30 global health status.
- Enco+Bini 450 treatment was also associated with clinically meaningful and statistically significant HRQoL gains over time, compared with both monotherapy treatments (vs. vemurafenib [FACT-M melanoma scale [redacted]; QLQ-C30 global health status +[redacted]]; vs. Enco 300 [FACT-M melanoma scale [redacted]; QLQ-C30 global health status [redacted]).

COLUMBUS included three study arms: Enco+Bini 450, vemurafenib and Enco 300. As the primary efficacy outcome, PFS results have been presented for Enco+Bini 450 versus vemurafenib; these results are directly relevant to the NICE scope and decision problem and are also utilised in the network meta-analysis (NMA). Enco+Bini 450 versus Enco 300 results for PFS are included as the key secondary efficacy outcome. Comparisons of vemurafenib and Enco 300 are also available but have not been presented as they are not directly relevant to the scope and are not used in the cost-effectiveness model. Enco 300 monotherapy will not be licensed for BRAF V600-mutant melanoma.

Data are presented as follows:

- ***Data cut-off 19 May 2016:*** All study outcomes, except for OS (Part 1 primary PFS analysis)
- ***Data cut-off 7 November 2017:***
  - Part 1 interim OS analysis
  - Updated PFS and response outcomes

B.2.6.1 Primary efficacy outcome: PFS Enco+Bini 450 vs vemurafenib

- The primary objective of the study was met as Enco+Bini 450 significantly improved PFS, based on blinded independent review (BIRC), compared with

vemurafenib, by more than doubling the duration of PFS (median 14.9 months [95% CI: 11.0, 18.5] vs. 7.3 months [95% CI: 5.6, 8.2]; stratified one-sided log-rank test p<0.0001) (Table 10).

- The HR for PFS in the Enco+Bini 450 arm relative to the vemurafenib arm was 0.54 (95% CI: 0.41, 0.71), equating to an estimated 46% risk reduction in disease progression or death (i.e. an increase in PFS).
- There were 98 PFS events (51% of patients) in the Enco+Bini 450 arm and 106 events (56% of patients) in the vemurafenib arm.
- Estimates of PFS at 12 months and 24 months were [redacted] for Enco+Bini 450 compared with [redacted] for vemurafenib. No imputations were used for start or end dates for the primary PFS analysis.
- **Updated analysis (data cut-off 7 November 2017):** The HR for PFS in the Enco+Bini 450 arm relative to the vemurafenib arm was 0.51 (95% CI: 0.39, 0.67; stratified one-sided log-rank test p<0.0001) (see Appendix L, section L.3.1 for detailed results).

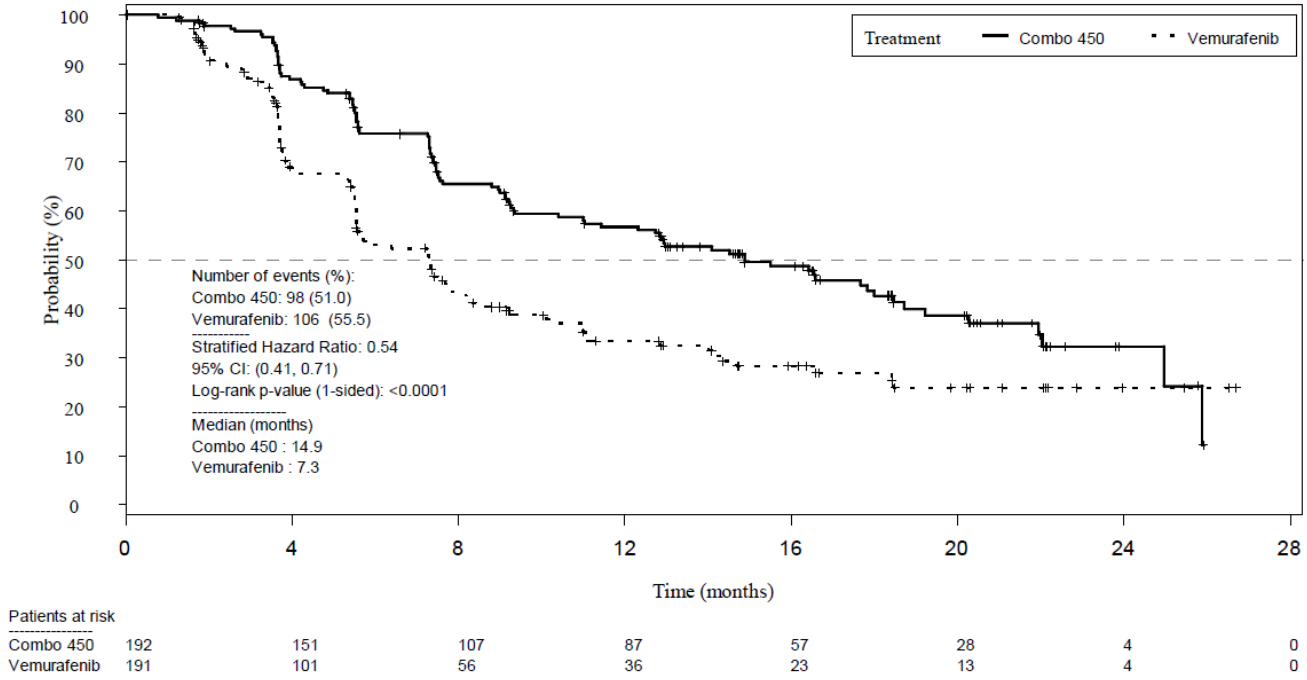
Table 10: Kaplan-Meier summary of PFS based on BIRC for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016

	Enco+Bini 450 N=192	Vemurafenib N=191
Patients with events/Patients included in analysis (%)	98/192 (51.0)	106/191 (55.5)
Percentiles (95% CI)[a]		
25th	[redacted]	[redacted]
50th (median)	14.9 (11.0, 18.5)	7.3 (5.6, 8.2)
75th	[redacted]	[redacted]
Event-free probability estimates (95% CI)[b]		
4 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
16 months	[redacted]	[redacted]
20 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; NE, not estimable; PFS, progression-free survival.
[a] Represents the estimated time (95% CI), reported in months, at which the specified percentiles occur based on the Kaplan-Meier analysis. Note that the 50th percentile is the same as the median time to event. Values were calculated using the Brookmeyer and Crowley method in PROC LIFETEST; [b] Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups. Greenwood formula is used for CIs of Kaplan-Meier estimates.
Source: CSR (28), Dummer et al 2018 (29).

- The PFS Kaplan-Meier curves (Figure 3) separate early (approximately 1-2 months into treatment) and do not intersect until the end of follow-up where the number of patients in each arm is ≤4.

Figure 3: Kaplan-Meier estimate of PFS based on BIRC for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; FAS, full analysis set; PFS, progression-free survival.
Source: CSR (28), Dummer et al 2018 (29).

B.2.6.2 Secondary analysis of primary outcome

B.2.6.2.1 PFS by investigator assessment: PFS Enco+Bini 450 vs vemurafenib

Investigator assessment of response was used to estimate PFS as a supportive analysis and had almost identical results to those based on BIRC (Table 11; Figure 4). The median PFS values based on Kaplan-Meier estimates were 14.8 months (95% CI: 10.4, 18.4) and 7.3 months (95% CI: 5.7, 8.5) for Enco+Bini 450 and vemurafenib arms, respectively, corresponding to a 51% reduction in risk of disease progression or death with Enco+Bini 450 (HR 0.49; 95% CI: 0.37, 0.64; one-sided nominal p<0.0001).

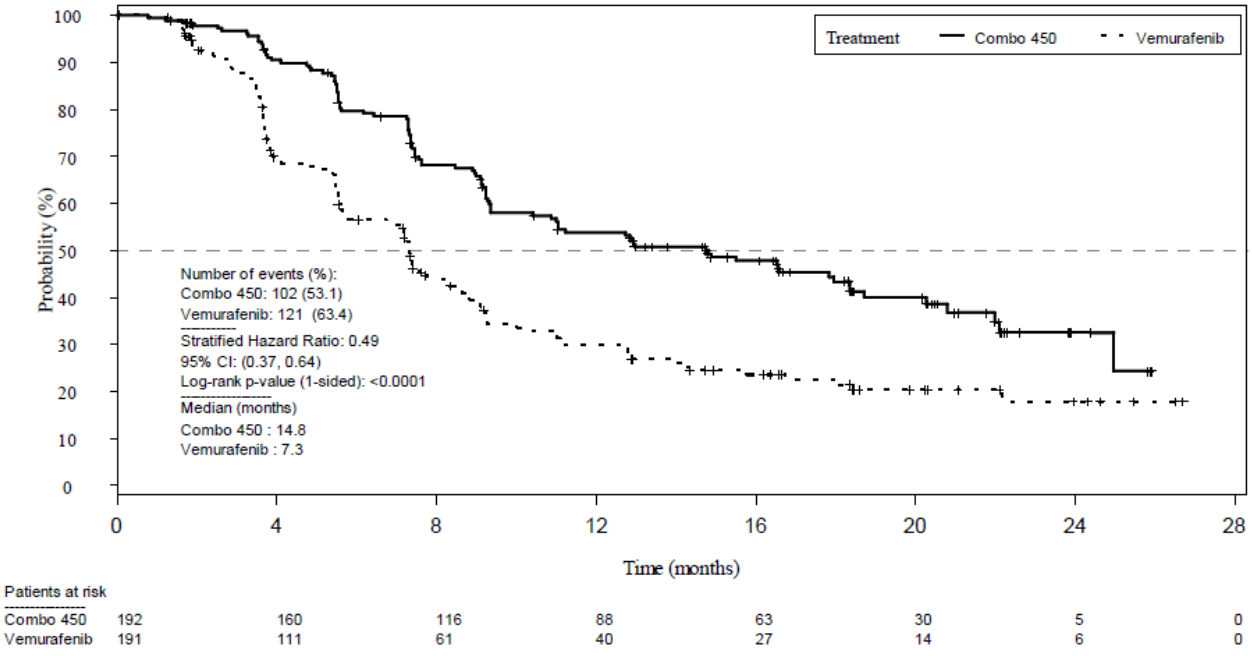
Updated analysis (data cut-off 7 November 2017): The HR for PFS in the Enco+Bini 450 arm relative to the vemurafenib arm was [redacted] (see Appendix L, section L.3.2 for detailed results).

Table 11: Kaplan-Meier summary of PFS based on investigator assessment for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016

	Enco+Bini 450 N=192	Vemurafenib N=191
Patients with events/Patients included in analysis (%)	102/192 (53.1)	121/191 (63.4)
Percentiles (95% CI)[a]		
25th	[redacted]	[redacted]
50th	14.8 (10.4, 18.4)	7.3 (5.7, 8.5)
75th	[redacted]	[redacted]
Event-free probability estimates (95% CI)[b]		
4 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
16 months	[redacted]	[redacted]
20 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival.
[a] Represents the estimated time (95% CI), reported in months, at which the specified percentiles occur based on the Kaplan-Meier analysis. Note that the 50th percentile is the same as the median time to event. Values were calculated using the Brookmeyer and Crowley method in PROC LIFETEST; [b] Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups. Greenwood formula is used for CIs of Kaplan-Meier estimates.
Source: CSR (28), Dummer et al 2018 (29).

Figure 4: Kaplan-Meier estimate of PFS based on investigator assessment for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: CI, confidence interval; FAS, full analysis set; PFS, progression-free survival.
Source: CSR (28), Dummer et al 2018 (29).

B.2.6.2.2 Comparison of PFS by BIRC and investigator assessment: PFS Enco+Bini 450 vs vemurafenib

Concordance of PFS events per BIRC and investigator assessment was reviewed.

- Comparison between BIRC and investigator assessments of PFS by event type (progressive disease [PD] or death) or censoring, showed the events identified (PD or death) [redacted] (Table 12).
- Comparison of PFS event or censoring and PFS timing were also compared:
  - In the Bini+Enco 450 arm, [redacted] had "type" discordance (i.e., disagreement that patient had an event or did not have an event) and [redacted] (i.e., agreed that the patient had an event but disagreed on the timing).
  - In the vemurafenib arm, [redacted] had "type" discordance and [redacted] had "timing" discordance.
  - Some patients had both type and timing discordance.
- Timings of PD events for PFS were also compared (Table 13) showing that there was a [redacted] between the Enco+Bini 450 and vemurafenib arms. PD was found earlier:
  - per BIRC than per investigator in [redacted] of patients with PD in the Enco+Bini 450 and vemurafenib arms, respectively.
  - per investigator than per BIRC in [redacted] of patients with PD in the Enco+Bini 450 and vemurafenib arms, respectively.

Table 12: Comparison of PFS event type/censor and PFS date between BIRC and investigator review – FAS, Part 1, data cut-off 19 May 2016

Enco+Bini 450 N=192 n (%)[a]				
		BIRC Assessment		
		PD	Death	Censored
Investigator Assessment	PD	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Censored	[redacted]	[redacted]	[redacted]
Enco 300 N=194 n (%)[a]				
		BIRC Assessment		
		PD	Death	Censored
Investigator Assessment	PD	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Censored	[redacted]	[redacted]	[redacted]
Vemurafenib N=191 n (%)[a]				
		BIRC Assessment		
		PD	Death	Censored
Investigator Assessment	PD	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Censored	[redacted]	[redacted]	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; FAS, full analysis set; PD, progressive disease; PFS, progression-free survival.
[a] Percent rates are calculated as the number of patients in the corresponding category divided by the total number of patients in each treatment group.
Source: CSR (28).

Table 13: Comparison of PFS event of PD and PFS date between BIRC and investigator review – FAS, Part 1, data cut-off 19 May 2016

Analysis Set	Enco+Bini 450 N=80 n (%)	Enco 300 N=78 n (%)	Vemurafenib N=95 n (%)
PD at the same time[a]	[redacted]	[redacted]	[redacted]
PD per investigator was earlier than by BIRC	[redacted]	[redacted]	[redacted]
PD per BIRC was earlier than by investigator	[redacted]	[redacted]	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; FAS, full analysis set; PD, progressive disease; PFS, progression-free survival.
[a] Percent rates are calculated as the number of patients in the corresponding category divided by the number of patients in each treatment group who had PD as per both BIRC and investigator.
Source: CSR (28).

Updated analysis (data cut-off 7 November 2017): See Appendix L, section L.3.2 for detailed results).

B.2.6.2.3 Additional PFS analyses: PFS Enco+Bini 450 vs vemurafenib

B.2.6.2.3.1 PFS by BIRC – Per Protocol Analysis Set

Analyses only available for data cut-off 19 May 2016.

PPS results were reflective of the FAS analysis of PFS for Enco+Bini 450 versus vemurafenib (median PFS by BIRC 15.5 months (95% CI: 11.0, 18.7) vs 7.3 months (95% CI: 5.6, 8.3); HR 0.53 (95% CI: 0.40, 0.70; nominal p<0.0001).

B.2.6.2.3.2 PFS by BIRC – Unstratified tests

Analyses only available for data cut-off 19 May 2016.

An analysis of PFS by BIRC was conducted with data from the FAS using unstratified log-rank and Cox regression tests. The HR for PFS of the Enco+Bini 450 arm versus the vemurafenib arm was [redacted]).

B.2.6.2.3.3 PFS by BIRC – Additional sensitivity analyses

To assess the robustness of the primary analysis, further sensitivity analyses of PFS based on BIRC were performed, as described in Section B.2.4.6. Results were consistent with the primary PFS analysis (Table 14), yielding similar HRs ([redacted]), median PFS values ([redacted] [Enco+Bini 450] vs [redacted] [vemurafenib]) and p values ([redacted]).

Table 14: Analysis of PFS by BIRC, sensitivity analyses – FAS, Part 1, data cut-off 19 May 2016

	Median (95% CI) [a]	HR (95% CI) [b]	P value [c]
Primary PFS analysis (FAS)			
Enco+Bini 450	14.9 (11.0, 18.5)		
Vemurafenib	7.3 (5.6, 8.2)	0.54 (0.41, 0.71)	< 0.001
PFS by eCRF stratification factors			
Enco+Bini 450	[redacted]		
Vemurafenib	[redacted]	[redacted]	[redacted]
PFS by "Actual Event" analysis			
Enco+Bini 450	[redacted]		
Vemurafenib	[redacted]	[redacted]	[redacted]
PFS by "Backdating" analysis			
Enco+Bini 450	[redacted]		
Vemurafenib	[redacted]	[redacted]	[redacted]
PFS by "Further Anti-cancer Treatment" analysis			
Enco+Bini 450	[redacted]		
Vemurafenib	[redacted]	[redacted]	[redacted]

Abbreviations: AJCC, American Joint Committee on Cancer; BIRC, blinded independent review committee; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FAS, full analysis set; HR, hazard ratio; IVRS, interactive voice response system; PFS, progression-free survival; PS, performance status.
[a] Median (time to event) and its 95% CI are generated by Kaplan-Meier estimation with Brookmeyer & Crowley CI; [b] For overall analyses, both Log-rank test and Cox PH model are stratified by IVRS AJCC stage and ECOG PS. Within stratum, the analyses are not stratified; [c] The p-values are nominal, 1-sided and are based on the log rank score test. The HRs and CIs are derived from the Cox proportional hazards model using the Wald test. Analyses comparing Enco+Bini 450 vs. vemurafenib only consider data from patients randomised to those treatment groups. Vemurafenib is the reference group for the HR.
Source: CSR (28).

Updated analysis (data cut-off 7 November 2017): As per the earlier analysis (May 2016), sensitivity analysis of the November 2017 data cut-off yielded results that were consistent with the primary PFS analysis, yielding similar HRs [redacted], median PFS values [redacted] and p values [redacted]. See Appendix L, section L.3.2 for detailed results.

B.2.6.2.3.4 PFS by BIRC – Multivariate Cox Regression

Analyses only available for data cut-off 19 May 2016.

The effect of potential prognostic factors was investigated using a multivariate Cox regression model stratified by the study stratification factors (American Joint

Committee on Cancer [AJCC] stage and ECOG PS). The objective of this analysis was to explore the sensitivity of the statistical significance of treatment effect on PFS when adjusting for main prognostic factors.

[redacted]). The only other pre-specified covariate that reached statistical significance was [redacted], which was associated with an increase in the relative risk of disease progression or death ([redacted]). The comparison of [redacted] was also associated with an increase in the relative risk of disease progression or death ([redacted]), but region was not significant when analysed collectively ([redacted]). No other covariates were found to have a significant effect on PFS.

B.2.6.3 Secondary efficacy outcome relevant to HE model and/or scope: PFS Enco+Bini 450 vs Enco 300

B.2.6.3.1 PFS by BIRC: PFS Enco+Bini 450 vs Enco 300

- An estimated 25% risk reduction in disease progression or death was observed with Enco+Bini 450 compared with Enco 300 (HR 0.75, 95% CI: 0.56, 1.00), and median PFS estimates were 14.9 months (95% CI: 11.0, 18.5) and 9.6 months (95% CI: 7.5, 14.8), respectively (Table 15 and Figure 5).
- Approximately half the patients in each arm had a PFS event (Enco+Bini 450, 51.0%; Enco 300, 49.5%).
- The PFS difference between the Enco+Bini 450 arm and the Enco 300 arm was not statistically significant (one-sided p=0.0256) by the one-sided stratified log-rank test according to the threshold for significance per protocol of p<0.025.
- Estimates of PFS at 12 months and 24 months were [redacted] for Enco+Bini 450 compared with [redacted] for Enco 300.

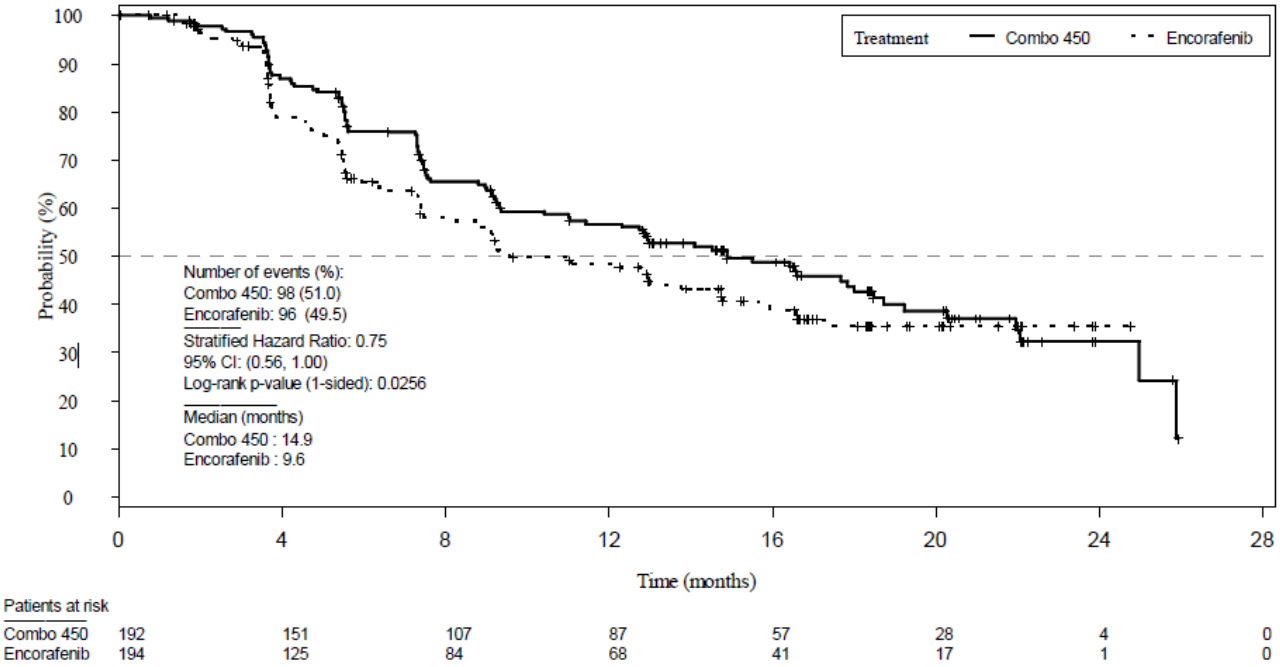
- **Updated analysis (data cut-off 7 November 2017):** The HR for PFS in the Enco+Bini 450 arm relative to Enco 300 was 0.77 (95% CI: 0.59, 1.00). The PFS difference was statistically significant (one-sided p=0.0249) by the one-sided stratified log-rank test according to the threshold for significance per protocol of p<0.025) (see Appendix L, section L.3.3 for detailed results).

Table 15: Kaplan-Meier summary of PFS based on BIRC for Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 19 May 2016

	Enco+Bini 450 N=192	Enco 300 N=194
Patients with events/Patients included in analysis (%)	98/192 (51.0)	96/194 (49.5)
Percentiles (95% CI)[a]		
25th	[redacted]	[redacted]
50th	14.9 (11.0, 18.5)	9.6 (7.5, 14.8)
75th	[redacted]	[redacted]
Event-free probability estimates (95% CI)[b]		
4 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
16 months	[redacted]	[redacted]
20 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; NE, not estimable; PFS, progression-free survival.
[a] Represents the estimated time (95% CI), reported in months, at which the specified percentiles occur based on the Kaplan-Meier analysis. Note that the 50th percentile is the same as the median time to event. Values were calculated using the Brookmeyer and Crowley method in PROC LIFETEST; [b] Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups. Greenwood formula is used for CIs of Kaplan-Meier estimates.
Source: CSR (28), Dummer et al 2018 (29).

Figure 5: Kaplan-Meier estimate of PFS based on BIRC for Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: BIRC, Blinded Independent Review Committee; CI, confidence interval; FAS, full analysis set; PFS, progression-free survival.
Source: CSR (28), Dummer et al 2018 (29).

B.2.6.3.2 PFS by investigator assessment: PFS Enco+Bini 450 vs Enco 300

The PFS difference between the Enco+Bini 450 arm and the Enco 300 arm based on investigator assessment of response was consistent with that reported by the BIRC (Table 16; Figure 6).

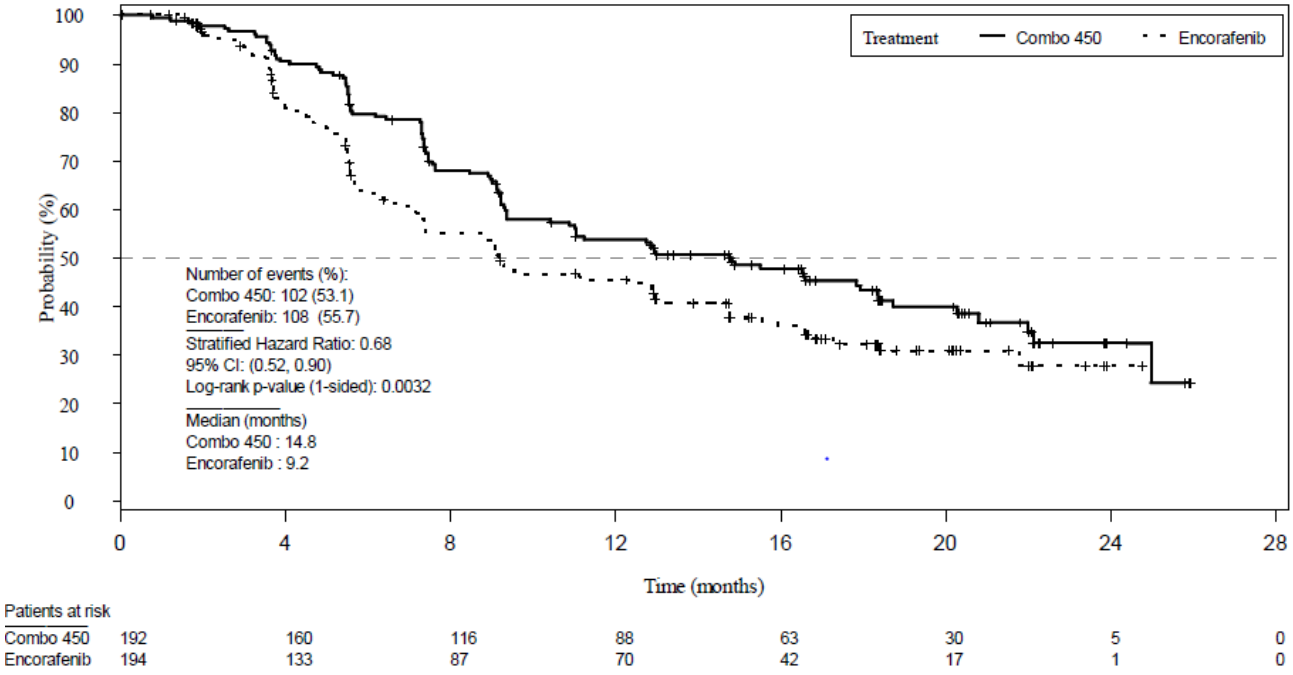
- Statistically significant 32% risk reduction in disease progression or death with Enco+Bini 450 compared with Enco 300 (HR 0.68; 95% CI: 0.52, 0.90; nominal one-sided p=0.003).
- Median PFS estimates were 14.8 months (95% CI: 10.4, 18.4) and 9.2 months (95% CI: 7.4, 12.9) for Enco+Bini 450 and Enco 300, respectively.
- **Updated analysis (data cut-off 7 November 2017):** The HR for PFS in the Enco+Bini 450 arm relative to Enco 300 was [redacted] (see Appendix L, section L.3.3 for detailed results).

Table 16: Kaplan-Meier summary of PFS based on investigator assessment for Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 19 May 2016

	Enco+Bini 450 N=192	Enco 300 N=194
Patients with events/Patients included in analysis (%)	102/192 (53.1)	108/194 (55.7)
Percentiles (95% CI)[a]		
25th	[redacted]	[redacted]
50th	14.8 (10.4, 18.4)	9.2 (7.4, 12.9)
75th	[redacted]	[redacted]
Event-free probability estimates (95% CI)[b]		
4 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
16 months	[redacted]	[redacted]
20 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival.
[a] Represents the estimated time (95% CI), reported in months, at which the specified percentiles occur based on the Kaplan-Meier analysis. Note that the 50th percentile is the same as the median time to event. Values were calculated using the Brookmeyer and Crowley method in PROC LIFETEST; [b] Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups. Greenwood formula is used for CIs of Kaplan-Meier estimates.
Source: CSR (28), Dummer et al 2018 (29).

Figure 6: Kaplan-Meier estimate of PFS based on investigator assessment for Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: CI, confidence interval; FAS, full analysis set; PFS, progression-free survival.
Source: CSR (28), Dummer et al 2018 (29).

B.2.6.3.3 Comparison of PFS by BIRC and investigator assessment: PFS Enco+Bini 450 vs Enco 300

Concordance of PFS events per BIRC and investigator assessment was reviewed (Table 12; Table 13).

- Type of PFS event or censoring and PFS timing [redacted] between BIRC and investigator assessments:
  - In the Bini+Enco 450 arm, [redacted] had "type" discordance (i.e., disagreement that patient had an event or did not have an event) and [redacted] had "timing" discordance (i.e., agreed that the patient had an event but disagreed on the timing).
  - In the Enco 300 arm, [redacted] had "type" discordance and [redacted] had "timing" discordance.
  - Some patients had both type and timing discordance.
- PD was found earlier:
  - per BIRC than per investigator in [redacted] of patients with PD in the Enco+Bini 450 and Enco 300 arms, respectively
  - per investigator than per BIRC in [redacted] of patients with PD in the Enco+Bini 450 and Enco 300 arms, respectively.

Updated analysis (data cut-off 7 November 2017): See Appendix L, section L.3.2 for detailed results).

B.2.6.3.4 Additional PFS analyses: Enco+Bini 450 vs Enco 300

BIRC PFS analyses conducted for the PPS and using unstratified log-rank and Cox regression tests [redacted] for Enco+Bini 450 versus Enco 300 (Analyses only available for data cut-off 19 May 2016).

Several additional sensitivity PFS analyses, as described in Section B.2.4.6 yielded results that were consistent with the primary PFS analysis, with similar HRs ([redacted]), median PFS values and p values. Similar consistency was found for the November 2017 data cut-off, yielding similar HRs [redacted], median PFS values and p values.

B.2.6.4 Censoring for primary and secondary PFS analyses

PFS based on BIRC: [redacted] were censored for the primary PFS analysis based on BIRC ([redacted] across the study). The most common reason for censoring was because [redacted] in the Enco+Bini 450 arm

([redacted] and the Enco 300 arm ([redacted]) versus [redacted] in the vemurafenib arm and because patients had [redacted] in the vemurafenib arm ([redacted] in the Enco+Bini 450 arm and [redacted] in the Enco 300 arm). The distribution of censoring was evaluated by a reverse Kaplan-Meier analysis and [redacted] between the Enco+Bini 450 and vemurafenib arms, with [redacted].

PFS based on investigator assessment: As with the BIRC analysis of PFS, the most common reason for censoring of PFS by investigator assessment in the Enco+Bini 450 and Enco 300 arms [redacted], and because [redacted]) in the vemurafenib arm. [redacted] in the Enco+Bini 450 arm were censored for PFS analysis per investigator assessment compared with vemurafenib arm ([redacted]

Updated analysis based on BIRC (data cut-off 7 November 2017): By the time of the updated analysis [redacted] of patients overall were censored ([redacted]), with [redacted] and [redacted] remaining on treatment in the Enco+Bini 450 and vemurafenib arms, respectively. [redacted] was the most common reason for censoring in the Enco+Bini 450 arm, whereas [redacted] was the most common reason in the Enco 300 arm and vemurafenib arm ([redacted], respectively vs. [redacted] in the Enco+Bini 450 arm).

Full details of reasons for censoring for data cut-off May 2016 are provided in Appendix L, section L.2.1 and for data cut-off November 2017 are provided in Appendix L, section L.3.4.

B.2.6.5 Other secondary efficacy outcomes relevant to HE model and/or scope

Based on the hierarchical testing procedure adopted for the trial, as the Part 1 key secondary endpoint (PFS for Enco+Bini 450 versus Enco 300) was not found to be statistically significant,[b] all alpha for the study has been spent. As a result, the

[b] Although the PFS difference between the Enco+Bini 450 arm and the Enco 300 arm was on the verge of statistical significance (one-sided p=0.0256) by the stratified log-rank test based on data at the May 2016 data cut-off, the result was significant in the updated analysis (November 2017 data cut-off; p=0.0249).

subsequent secondary efficacy endpoints were summarised using nominal p-values for descriptive purposes only.

B.2.6.5.1 Overall survival

B.2.6.5.1.1 Overall survival: Enco+Bini 450 versus vemurafenib

- A 39% reduction in the risk of death was observed for patients treated with Enco+Bini 450 compared with those treated with vemurafenib (HR 0.61, 95% CI: 0.47, 0.79; nominal one-sided p<0.0001) (Table 17, Figure 7).
- The median OS (95% CI) was 33.6 months (24.4, 39.2) in patients treated with Enco+Bini 450 in comparison to 16.9 months (14.0, 24.5) in patients treated with vemurafenib monotherapy.
- OS estimates (95% CI) at 12 and 24 months were 75.5% (68.8, 81.0) and 57.6% (50.3, 64.3) for Enco+Bini 450 compared with 63.1% (55.7, 69.6) and 43.2% (35.9, 50.2) for vemurafenib, respectively.

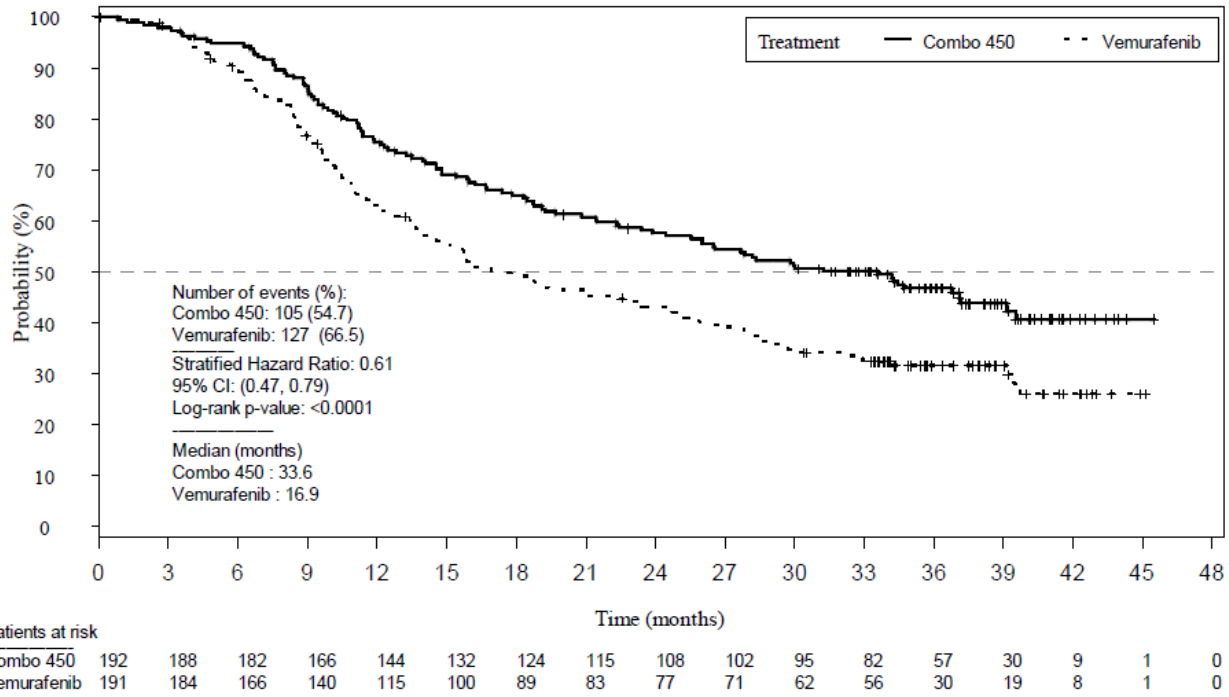
As the results of the Part 1 key secondary analysis (PFS, Enco+Bini 450 vs. Enco 300) were not statistically significant (Section B.2.6.3.1), the OS analysis is considered only descriptive in nature. If this comparison had been a formal interim analysis conducted as part of the testing hierarchy, the results would have been compared to the critical p value (i.e., the efficacy superiority boundary) defined by the Gamma function with parameter=1 specified in the study protocol to control the overall Type I error rate. The observed p<0.0001 would have been less than the critical p value of 0.021.

Table 17: Overall Survival, Enco+Bini 450 versus vemurafenib and Enco 300 – FAS, Part 1, data cut-off 7 November 2017

	Event / N (%)	Median (95% CI)[a]	HR (95% CI)[b]	P value (one-sided)[c]
Enco+Bini 450	105/192 (54.7)	33.6 (24.4, 39.2)		
Vemurafenib	127/191 (66.5)	16.9 (14.0, 24.5)	0.61 (0.47, 0.79)	<0.0001
Enco 300	106/194 (54.6)	23.5 (19.6,33.6)	0.81 (0.61, 1.06)	0.0613

Abbreviations: CI, confidence interval; HR, hazard ratio.
Log-rank test and Cox proportional hazards model are stratified by AJCC stage and ECOG PS per randomisation. [a] Median (time to event) and its 95% CI are generated by Kaplan-Meier estimation with Brookmeyer & Crowley confidence intervals. [b]HR and CIs are derived from the Cox proportional hazards model using the Wald test. [c]P value is based on the log-rank score test.
Source: CSR OS addendum (33), Dummer et al 2018 ASCO (36).

Figure 7 Kaplan-Meier Plot of OS, Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 7 November 2017



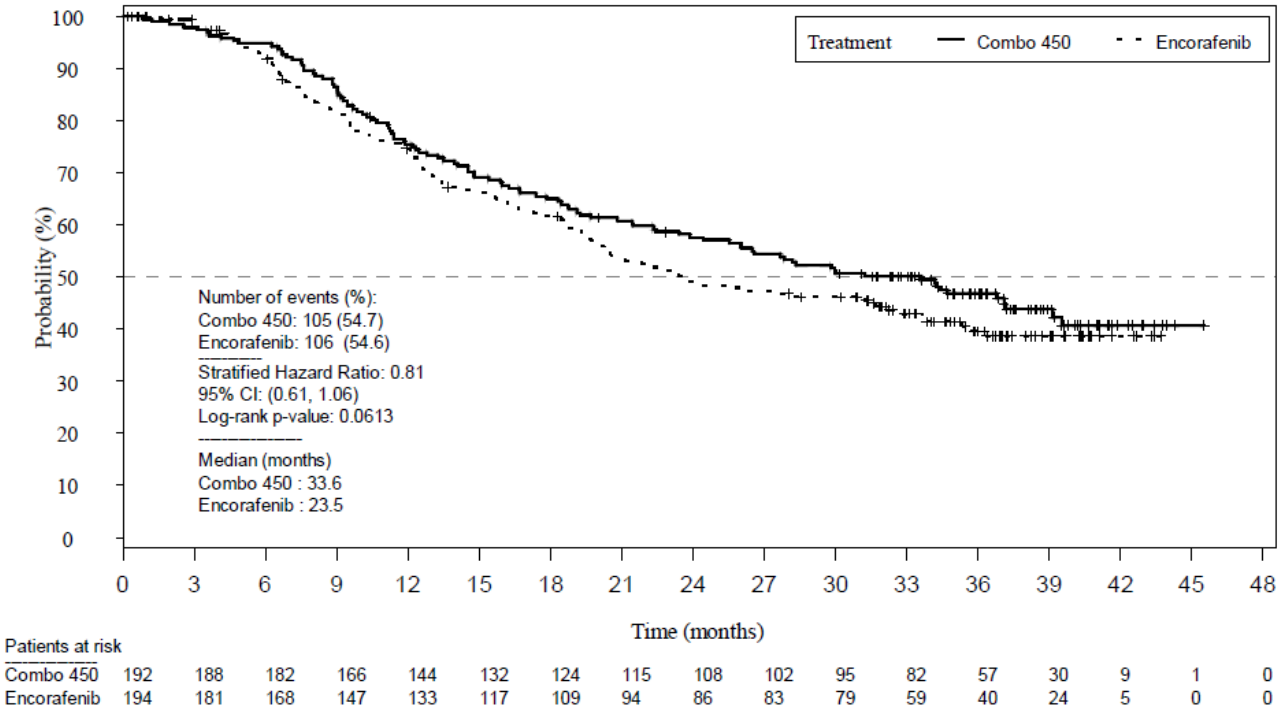
Abbreviations: CI, confidence interval.
Source: CSR OS addendum (33), Dummer et al 2018 ASCO (36).

B.2.6.5.1.2 Overall survival: Enco+Bini 450 versus Enco 300

Formal OS analysis of Enco+Bini 450 versus Enco 300 was not planned but was performed and summarised descriptively.

- An estimated 19% reduction in the risk of death was observed for patients randomised to Enco+Bini 450 versus Enco 300 (HR 0.81, 95% CI: 0.61, 1.06).
- Median OS (95% CI) was 33.6 months (24.4, 39.2) in patients treated with Enco+Bini 450 and 23.5 months (19.6, 33.6) in patients treated with Enco 300 (Table 17, Figure 8).
- OS (95% CI) estimates at 12 months and 24 months were 75.5% (68.8, 81.0) and 57.6% (50.3, 64.3) for Enco+Bini 450 compared with 74.6% (67.6, 80.3) and 49.1% (41.5, 56.2) for Enco 300.

Figure 8 Kaplan-Meier Plot of OS, Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 7 November 2017



Abbreviations: CI, confidence interval.
Source: CSR OS addendum (33), Dummer et al 2018 ASCO (36).

B.2.6.5.1.3 Sensitivity analysis of OS

The primary OS analyses for Enco+Bini 450 versus vemurafenib and versus Enco 300 was repeated with the following modifications to methodology:

- Stratified log-rank test and Cox regression model using stratification factors as provided in the case report form, as opposed to randomisation strata.
- Stratified log-rank test and Cox regression model to evaluate the treatment effect using the PPS.
- Unstratified log-rank test and Cox regression model.

Results of these sensitivity analyses were consistent with the primary OS analysis, yielding similar HRs ([redacted] versus vemurafenib; [redacted] versus Enco 300), median OS values and p values ([redacted] versus vemurafenib) for analyses performed on all study subjects.

B.2.6.5.1.4 Supportive analyses of OS

A multivariate Cox regression model stratified by the study stratification factors was used to explore the sensitivity of the statistical significance of treatment effect on OS when adjusting for main prognostic factors.

- Enco+Bini 450 treatment was associated with a decrease in the relative risk of death compared with vemurafenib ([redacted]) and compared with Enco 300 ([redacted]).
- The only other prespecified covariate that reached nominal significance in both analyses was a [redacted], which was associated with an increase in the relative risk of death ([redacted], for analyses of Enco+Bini 450 versus vemurafenib and versus Enco 300)

B.2.6.5.1.5 Censoring and potential follow-up of OS

Enco+Bini 450 versus vemurafenib: The proportion of patients censored for the OS analysis in the Enco+Bini 450 arm ([redacted] than that observed in the vemurafenib arm ([redacted] were alive and ongoing for survival follow-up in the Enco+Bini 450 and vemurafenib arms, respectively. The majority of censored patients in both groups who were alive and ongoing had a last contact within the 12 weeks prior to data cut-off (See Appendix L, section L.4 for tabulated data).

Enco+Bini 450 versus Enco 300: The proportion of patients censored for the OS analysis in the Enco+Bini 450 arm ([redacted] that observed in the Enco 300 arm ([redacted]); [redacted] were alive and ongoing for survival follow-up in the Enco+Bini 450 and Enco 300 arms, respectively. A majority of censored patients in both groups who were alive and ongoing had a last contact within the 12 weeks prior to data cut-off (See Appendix L, section L.4 for tabulated data).

B.2.6.5.2 Best overall response: ORR and DCR

ORR:

- Confirmed ORR per BIRC was 63.0% (95% CI: 55.8, 69.9) in the Enco+Bini 450 arm compared with 50.5% (95% CI: 43.3, 57.8) in the Enco 300 arm and 40.3% (95% CI: 33.3, 47.6) in the vemurafenib arm (Table 18).

DCR:

- The DCR per BIRC was 92.2% (95% CI: 87.4, 95.6) in the Enco+Bini 450 arm compared with 84.0% (95% CI: 78.1, 88.9) in the Enco 300 arm and 81.7% (95% CI: 75.4, 86.9) in the vemurafenib arm (Table 18).

The most frequent reason for a best overall response (BOR) of unknown was [redacted]Enco+Bini 450 arm, [redacted]Enco 300 arm, [redacted]vemurafenib arm).

Results per investigator review are presented in Appendix L, section L.2.2.

Updated analysis (data cut-off 7 November 2017): updated results were consistent with those from the May 2016 cut-off (see Appendix L, section L.3.5 for detailed results).

Table 18: BOR by BIRC – FAS, Part 1, data cut-off 19 May 2016

	Enco+Bini 450 N=192 n (%)	Enco 300 N=194 n (%)	Vemurafenib N=191 n (%)
Patients with measurable disease at baseline[a]	[redacted]	[redacted]	[redacted]
Patients with non-measurable disease only at baseline[a]	[redacted]	[redacted]	[redacted]
Confirmed ORR: CR + PR	121 (63.0)	98 (50.5)	77 (40.3)
95% CI	(55.8, 69.9)	(43.3, 57.8)	(33.3, 47.6)
Confirmed BOR[b,c]			
CR	15 (7.8)	10 (5.2)	11 (5.8)
PR	106 (55.2)	88 (45.4)	66 (34.6)
StD	46 (24.0)	53 (27.3)	73 (38.2)
Non-CR/Non-PD[d]	10 (5.2)	12 (6.2)	6 (3.1)
PD	2 (1.0)	6 (3.1)	13 (6.8)
DCR: CR+PR+StD+Non-PD/Non-CR	177 (92.2)	163 (84.0)	156 (81.7)
95% CI[e]	(87.4, 95.6)	(78.1, 88.9)	(75.4, 86.9)
Unknown[f]	11 (5.7)	25 (12.9)	22 (11.5)
Not assessed[g]	2 (1.0)	0	0

Abbreviations: BIRC, blinded independent review committee; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; ORR, overall response rate; PD, progressive disease; PR, partial response; StD, stable disease.
[a] Does not include the 2 patients who were not assessed by BIRC; [b] Best overall response is based on central reviewer's assessment using RECIST v1.1; [c] CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met; [d] Non-CR/non-PD applies only to patients with non-target lesions at baseline who did not achieve a CR or have PD; [e] The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson's method; [f] Unknown response: Not included in BOR assessment but included in denominator for ORR and DCR. Progression has not been documented and one or more lesions have not been assessed or have been assessed using a different method than baseline; [g] Not included in BOR assessment but included in denominator for ORR and DCR. No assessment has occurred by BIRC; not included in patients with measurable or non-measurable disease at baseline.
Source: CSR (28), Dummer et al 2018 (29).

B.2.6.5.3 Time to objective response

B.2.6.5.3.1 Complete response

- A confirmed CR by BIRC was achieved by a slightly higher percentage of patients in the Enco+Bini 450 arm versus Enco 300 and vemurafenib (7.8%, 5.2% and 5.8%, respectively), and their median time to CR [redacted], respectively (Table 18).
- A confirmed CR by investigator review was achieved by 16.1%, 8.8% and 7.3% of patients in the Enco+Bini 450, Enco 300 and vemurafenib arms, respectively, and their median time to CR [redacted], respectively.
- **Updated analysis (data cut-off 7 November 2017):** A confirmed CR by BIRC was achieved by 11.5%, 7.2% and 8.4% of patients in the Enco+Bini 450, Enco 300 and vemurafenib arms, respectively. A confirmed CR by investigator review was achieved by 19.3%, 9.8% and 8.4% of patients in the Enco+Bini 450, Enco 300 and vemurafenib arms, respectively.

B.2.6.5.3.2 TTR

- 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.

- **Updated analysis (data cut-off 7 November 2017):**
  - Median TTR per BIRC, calculated for responding patients only (patients with CR or PR, confirmation not required), [redacted] for all three treatment arms.
  - [redacted].

B.2.6.5.4 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:

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

Kaplan-Meier estimates of median DOR per investigator, calculated for confirmed response, were similar to those by BIRC:

- Enco+Bini 450 arm: [redacted]
- Vemurafenib arm: [redacted]
- Enco 300 arm: [redacted]

See Appendix L, section L.2.3 for Kaplan-Meier curves.

Updated analysis (data cut-off 7 November 2017): updated results were consistent with those from the May 2016 cut-off (see Appendix L, section L.3.6 for detailed results).

B.2.6.5.5 Patient-reported outcomes

Analyses only available for data cut-off 19 May 2016.

B.2.6.5.5.1 Compliance to questionnaire completion

The compliance level was high in each arm throughout the study, with ≥80% of evaluated patients (i.e. still receiving treatment or in post-treatment follow-up visit) completing the FACT-M (~85–90%), EORTC QLQ-C30 (~85–90%) and the EQ-5D-5L [redacted] questionnaires from baseline until Cycle 25. Completion rates ranged from [redacted] at the safety follow-up, 30 days after treatment discontinuation.

B.2.6.5.5.2 FACT-M, EORTC QLQ-C30 and EQ-5D-5L

Baseline scores were similar across the treatment arms (higher is better). Baseline mean score range +/- standard deviation (SD) was [redacted] for the FACT-M melanoma subscale, [redacted] for the QLQ-C30 global health score and [redacted] for the EQ-5D-5L index score. The baseline scores reflect the substantial HRQoL impairment in this patient population.

B.2.6.5.5.3 Time to definitive deterioration (primary analysis)

Patients in the Enco+Bini 450 arm showed a significantly delayed deterioration in HRQoL compared with the vemurafenib and Enco 300 arms. Based on a definitive 10% deterioration in patient-reported outcomes scores, the results were as follows:

- FACT-M melanoma subscale: median (95% CI) was not reached (NE) (22.1, NE) in the Enco+Bini 450 arm versus 22.1 months (15.2, NE) in the vemurafenib arm and 20.3 months (15.0, NE) in the Enco 300 arm. The corresponding HRs (95% CI) were 0.46 (0.29, 0.72) versus vemurafenib and 0.48 (0.31, 0.75) versus Enco 300.
- EORTC QLQ-C30 global health status:
  - Median time to 10% deterioration was delayed by more than 7 months in the Enco+Bini 450 arm versus vemurafenib and by more than 9 months versus Enco 300:
    - ◊ Median time (95% CI) 23.9 months (20.4, NE) for Enco 450 versus 16.6 months (11.9, NE) for vemurafenib and 14.7 months (9.2, 18.4) with Enco 300.
    - ◊ Corresponding HRs (95% CI) were HR of 0.55 (0.37, 0.80) and 0.45 (0.31, 0.65).

See Appendix L, section L.2.4 for Kaplan-Meier curves.

B.2.6.5.5.4 Score change post-baseline (primary analysis)

Based on the longitudinal MMRM analyses, treatment with Enco+Bini 450 was associated with higher post-baseline score estimates, suggesting clinically meaningful HRQoL gains with Enco+Bini 450 compared with the monotherapy treatments:

- versus vemurafenib (FACT-M melanoma scale [redacted]; EQ-5D index score [redacted]; QLQ-C30 global health status [redacted])
- versus Enco 300 (FACT-M melanoma scale [redacted]; EQ-5D index [redacted]; QLQ-C30 global health status [redacted]).

B.2.6.5.5.5 Score change from baseline by visit (post-hoc analysis)

In post-hoc analyses (37), the adjusted mean score changes from baseline were compared between treatment arms at each time-point until Cycle 25 (Week 95), including time as a categorical variable in the MMRM. [redacted]

Compared with vemurafenib, the minimal clinically important difference of 2 points (46) was reached at all visits [redacted]

and the QLQ-C30 minimal clinically important difference of 5 points (47) was reached at all visits [redacted].
Overall, the difference between arms reached the minimal clinically important difference [redacted]

The difference in EQ-5D-5L index score was [redacted] (Table 19); the minimal clinically important difference for the EQ-VAS (≥7 points) [redacted]

Clinically meaningful improvements with Enco+Bini 450 versus vemurafenib [redacted]

Table 19: Mean score change from baseline at each time-point, EQ-5D-5L index scores – MMRM post-hoc analysis, data cut-off 19 May 2016

EQ-5D-5L	C3	C5	C7	C9	C11	C13	C15	C17	C19	C21	C23	C25	At DP
Utility index	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80	W88	W96	
Enco+Bini 450	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCFB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C, cycle; CI, confidence interval; DCFB, difference in mean change from baseline; DP, disease progression; EQ-5D-5L, Euroqol-5 dimensions-5 levels; MCID, minimal clinically important difference; MMRM, mixed model repeated measures; W, Week.
* MCID reached (≥ 0.08 points for EQ-5D index score) between the Enco+Bini 450 and vemurafenib arms. Results versus Enco 300 were similar.
Source: QoL post-hoc report (37).

B.2.7 Subgroup analysis: COLUMBUS

Pre-planned subgroup analyses of PFS and OS were performed for each baseline stratification factor and other relevant baseline variables for which at least 10 patients were available in the considered subgroup. Subgroups were prespecified as listed in the SAP. Subgroup analyses were performed based on gender, age, race, region, Japanese patients, LDH level at baseline, ECOG PS, BRAF mutation status, AJCC stage, primary site of cancer, number of organs involved at baseline, baseline brain metastases, prior immunotherapy and prior adjuvant therapy. The analyses were to include Kaplan-Meier summaries and HRs (+95% CI) from unstratified Cox models. A forest plot representation was also provided.

Demographics and disease characteristics for subgroups were not defined.

A summary of results for Enco+Bini 450 versus vemurafenib, based on analyses of data from the May 2016 data cut-off for PFS and the November 2017 cut-off for OS, is provided below. Full results are provided in Appendix E, including updated PFS analyses conducted at the time of the November 2017 data cut-off, which show similar results to those at the earlier data cut-off. It should be noted that for many of the analyses, the number of patients included in each subgroup was small which may affect interpretation of the data.

PFS Enco+Bini 450 versus vemurafenib: All unstratified subgroup analyses demonstrated PFS point estimates in favour of the Enco+Bini 450 arm, except for the presence of brain metastases at baseline (HR 1.34; 95% CI: 0.15, 11.78), but this analysis only included nine patients in the Enco+Bini 450 arm and three patients in the vemurafenib arm. Most of the HRs in the Enco+Bini 450 arm relative to the vemurafenib arm were in the vicinity of 0.58, the HR of the unstratified treatment effect, indicating that the effect of Enco+Bini 450 is robust across subgroups.

In subgroups of patients with poor prognosis, the relative risk reduction of disease progression or death was as follows:

- Patients with stage IV M1c disease (n=108 Enco+Bini 450; n=107 vemurafenib): median PFS [redacted]; HR 0.48, 95% CI: 0.34, 0.69.
- Patients with 3 organs involved at baseline (n=45 Enco+Bini 450; n=42 vemurafenib): median PFS [redacted]; HR 0.44, 95% CI: 0.25, 0.78.

- Patients with >3 organs involved at baseline (n=42 Enco+Bini 450; n=45 vemurafenib): [redacted]; HR 0.64, 95% CI: 0.39, 1.06.
- Patients with baseline LDH < upper limit of normal (ULN) (n=137 Enco+Bini 450; n=139 vemurafenib): [redacted]; HR 0.47, 95% CI: 0.33, 0.67.
- Patients with baseline LDH ≥ ULN (n=55 Enco+Bini 450; n=52 vemurafenib): [redacted]; HR 0.73, 95% CI: 0.47, 1.14.

OS Enco+Bini 450 versus vemurafenib: Pre-planned unstratified subgroup analyses demonstrated point estimates in favour of the Enco+Bini 450 arm except the presence of brain metastases at baseline (HR 1.09; 95% CI: 0.22, 5.48), which included nine patients in the Enco+Bini 450 arm and three patients in the vemurafenib arm. Most of the HRs in the Enco+Bini 450 arm relative to the vemurafenib arm were in the vicinity of 0.65, the HR of the unstratified treatment effect, indicating that the effect of Enco+Bini 450 is robust across subgroups.

B.2.8 Meta-analysis

COLUMBUS is the only randomised controlled trial (RCT) reporting on the efficacy and safety of Enco+Bini 450 in patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. Therefore, a meta-analysis was not required.

B.2.9 Indirect and mixed treatment comparisons

Overview

- In the absence of direct efficacy, safety and QoL data for Enco+Bini 450 versus Dabra+Tram, a Bayesian NMA was conducted to elicit estimates of relative treatment efficacy and safety. The NMA broadly considered BRAFi monotherapies and BRAFi/MEKi combination therapies, including the two combination therapies of relevance to this appraisal, Enco+Bini 450 and Dabra+Tram.
- In the base-case analysis of OS, Enco+Bini 450 was associated with a HR of 0.89 (95% credible interval [CrI]: 0.65, 1.23) compared with Dabra+Tram. The result from a sensitivity analysis adjusting for crossover was consistent with the base-case analysis (HR 0.90; 95% CI: 0.61,1.34). Similarly, an analysis of median OS returned a numerically favourable result, suggesting an additional 8.4 months in OS for Enco+Bini 450 versus Dabra+Tram (95% CrI: -2.86, 19.71).
- In the PFS (investigator assessed) base-case analysis, Enco+Bini 450 was associated with a HR of 0.77 (95% CrI: 0.57, 1.04) compared with Dabra+Tram. A comparison of PFS assessed by blinded independent assessment, which would potentially mitigate uncertainty driven by the open-label nature of the majority of studies in the network, was found to be unfeasible due to an unconnected network.
- Analysis of HRQoL outcomes were limited to an indirect comparison of Enco+Bini 450 with Dabra+Tram via the common comparator, vemurafenib, suggesting comparability of Enco+Bini 450 and Dabra+Tram for EQ-5D index scores (differences less than the minimal clinically important difference of 0.08 points).
- Incidence of any grade ≥3 adverse event (AE) was found to be numerically higher for Enco+Bini 450 versus Dabra+Tram (Odds ratio [OR]: 1.18; 95% CrI: 0.70, 1.98)
- In general, the evidence networks were relatively sparse with single RCTs feeding each link of the evidence network in most cases, driving relatively high uncertainty and associated wide CrIs. Although Enco+Bini 450 showed numeric improvements in OS and PFS, all CrIs crossed one showing that NMA results should be interpreted with caution.

B.2.9.1 Methodology

In the absence of head-to-head evidence comparing the efficacy and safety of Enco+Bini 450 with Dabra+Tram for the management of unresectable or metastatic BRAF V600 mutation-positive melanoma, an NMA was conducted to determine relative treatment effects. All priority 1 studies identified by the clinical systematic literature review (SLR) (Appendix D) and the QoL SLR (Appendix H) were assessed for NMA feasibility; i.e. publications of RCTs assessing BRAFi therapies (monotherapies and BRAFi/MEKi combinations) that are licensed for use within the EU. The scope of the NMA was broader than the scope of the appraisal hence the inclusion of evidence for all BRAFi monotherapy & BRAFi/MEKi combinations. While complete evidence networks are utilised that incorporate all the available evidence, we only present results of the NMA for Enco+Bini 450 versus Dabra+Tram.

In total, 23 records identified in the clinical SLR reported efficacy and safety data on seven RCTs investigating BRAFi; these records were assessed for inclusion in the NMA of efficacy and safety outcomes (COLUMBUS, COMBI-v, COMBI-d, BRF113220 Part C, CoBRIM, BREAK-3, and BRIM-3) (Table 20).

Five of the seven RCTs investigating BRAFi from the clinical SLR reported HRQoL data, across 12 records (COLUMBUS, COMBI-v, COMBI-d, CoBRIM, and BREAK-3), including two records of pooled HRQoL data for COMBI-v/ COMBI-d (Table 20).

Table 20: Summary of trials used to inform the NMA

References of trial	Enco+ Bini 450	Vemu	Dabra+ Tram	Dabra	Vemu+ Cobi	Dac
Studies identified in the clinical SLR						
COLUMBUS Primary: (29) Secondary: (31, 36)	✓	✓				
COMBI-v Primary: (21) Secondary: (49)		✓	✓			
COMBI-d Primary: (50) Secondary: (20, 51)			✓	✓		
BRF113220 Part C Primary: (52) Secondary: (53-56)			✓	✓		
CoBRIM Primary: (57) Secondary: (19, 58)		✓			✓	

References of trial	Enco+ Bini 450	Vemu	Dabra+ Tram	Dabra	Vemu+ Cobi	Dac
BREAK-3 Primary: (59) Secondary: (60, 61)				✓		✓
BRIM-3 Primary: (62) Secondary: (42, 63, 64)		✓				✓
Studies identified in the HRQoL SLR						
COLUMBUS (30)	✓	✓				
COMBI-v (65-68)*		✓	✓			
COMBI-d (67-69)*			✓	✓		
CoBRIM (57, 70-72)		✓			✓	
BREAK-3 (73, 74)				✓		✓

Abbreviations: Cobi, cobimetinib; Dabra, dabrafenib; Dac, dacarbazine; Enco+Bini 450, encorafenib 450 mg + binimetinib; HRQoL, health-related quality of life; NMA, network meta-analysis; SLR, systematic literature review; Tram, trametinib; Vemu, vemurafinib.
* including 2 records reporting pooled analyses of COMBI-v and COMBI-d

Full details of the methodology for the mixed treatment comparison are provided in Appendix D.

B.2.9.2 Results

The following sections report results from the NMA for outcomes which have been used to inform the economic model, namely PFS, OS, quality of life and overall incidence of Grade 3/4 AEs. Response rates were also considered but have not been included herein as they were not considered appropriate for use in the model. Analysis of the incidence of specific AEs was deemed to not be feasible given that RCTs were not powered to detect differences in specific AEs, while low numbers generate high uncertainty.

All results are based on fixed-effects models which assume that each study is estimating the same treatment effect, with variability induced by sampling error alone. This was deemed most appropriate due to the sparseness of the networks of evidence, which consist mainly of a single RCT per pairwise comparison, with two RCTs in just a few links. Given the nature of a random effects model, which assumes that the trial-specific treatment effects come from a common distribution and takes into account between-study heterogeneity, this alternative approach will likely provide a poor estimate of the distribution of intervention effects in this case. In addition, the fixed effects model yielded a lower or similar deviance information criterion (DIC) than the random effects model for the majority of investigated

outcomes. Model fit, as measured by the difference between the number of data points and total residual deviance, was generally similar between fixed and random effects models. Overall, this could be interpreted as the fixed effects model being the more parsimonious model and the model of choice (DIC and residual deviance values are provided in Appendix D, section D.1.3.2). For HRQoL outcomes, the evidence network was restricted to two trials in the base-case thus only fixed effect models were run for HRQoL endpoints.

Given the use of fixed-effects models, statistical tests for heterogeneity were not appropriate. However, assessment of inconsistency indicate that no substantial inconsistency was detected in any of the base-case analyses (See Appendix D, section D.1.3.2)

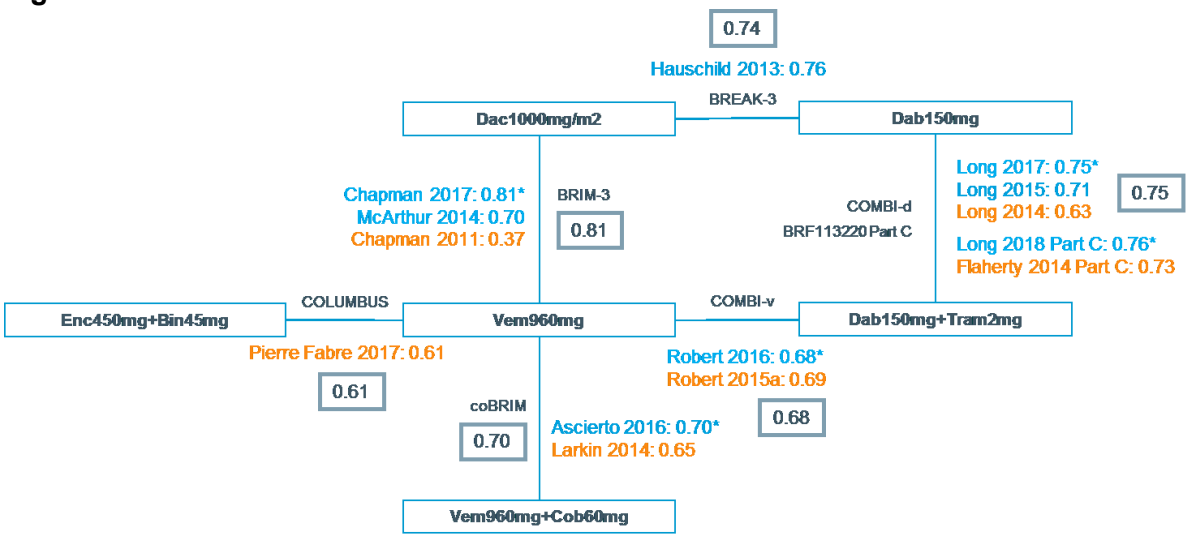
For each outcome, network diagrams are presented to illustrate the body of data that was considered for the evidence synthesis. However, NMA results are presented for Enco+Bini 450 and Dabra+Tram only as these are the treatments of relevance for this submission.

Note: HRs (95% CrIs) and other measures of efficacy/safety are presented for Enco+Bini 450 versus Dabra+Tram (for consistency with the direction of effect presented from the COLUMBUS study) and also for Dabra+Tram versus Enco+Bini 450, to allow direct utilisation within the economic model (See Section B.3.3). For comparisons of Enco+Bini 450 versus Dabra+Tram, a HR<1 indicates a result in favour of Enco+Bini 450.

B.2.9.2.1 Overall survival

The network of evidence for the OS base-case analysis is presented in Figure 9. All seven of the included studies reported OS. Estimates from studies highlighted in orange refer to the original publication, whereas those from studies highlighted in blue refer to updated results based on more mature data. The most recent, mature data was used wherever available, as indicated by a star (*).

Figure 9: Evidence network for OS – base-case



Abbreviations: Bin, binimetinib; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.
The most recent, mature data was used wherever available, as indicated by *.

Table 21 presents the base-case NMA OS results for Enco+Bini 450 versus Dabra+Tram. The result favours Enco+Bini 450 (HR<1), however the CrI crosses 1. Sensitivity analyses on the OS NMA are discussed in Section B.2.9.3.1.

Table 21: NMA results for OS – base-case

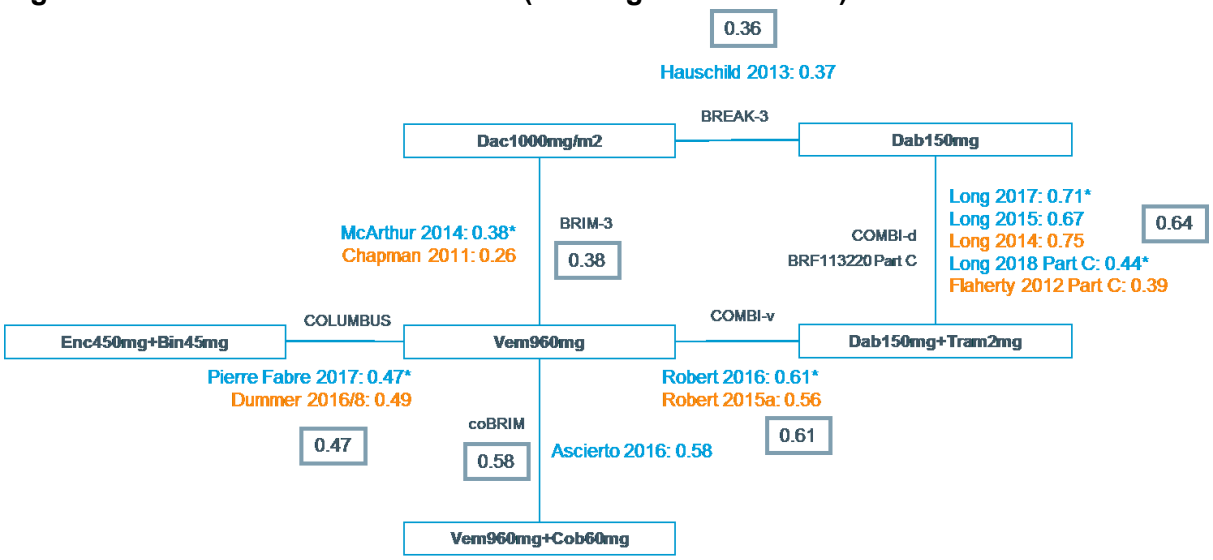
	HR (95% CrI)	
	Enco+Bini 450 vs Dabra+Tram	**Dabra+Tram vs Enco+Bini 450**
Base-case	0.89 (0.65,1.23)	1.12 (0.81,1.53)

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival.

B.2.9.2.2 PFS

The network of evidence for the PFS base-case analysis is presented in Figure 10. The base-case used investigator assessed PFS (reported in all seven included studies) as it was not possible to generate a network for PFS assessed by BIRC (the primary endpoint of the COLUMBUS trial; described in more detail in Section B.2.9.3.2). Estimates from studies highlighted in orange refer to the original publication, whereas those from studies highlighted in blue refer to updated results based on more mature data. The most recent, mature data was used wherever available, as indicated by a star (*).

Figure 10: Evidence network for PFS (investigator assessed) – base-case



Abbreviations: Bin, binimetinib; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.
The most recent, mature data was used wherever available, as indicated by *.

Table 22 presents the base-case NMA PFS results for Enco+Bini 450 versus Dabra+Tram. The result favours Enco+Bini 450 (HR<1), however the CrI crosses 1. Sensitivity analyses on the PFS NMA are discussed in Section B.2.9.3.2.

Table 22: NMA results for PFS – base-case

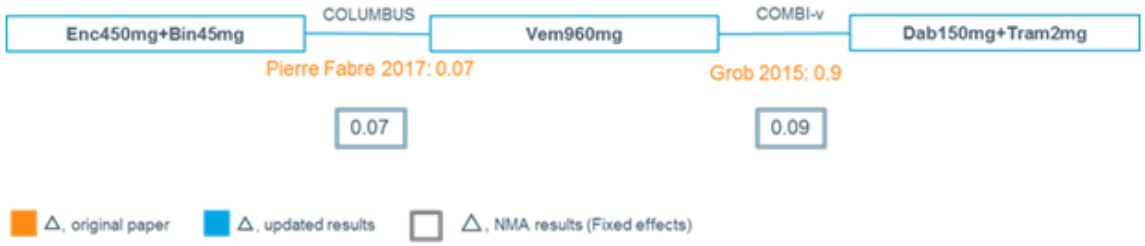
	HR (95% CrI)	
	Enco+Bini 450 vs Dabra+Tram	**Dabra+Tram vs Enco+Bini 450**
Base-case	0.77 (0.57,1.04)	1.30 (0.96,1.77)

Abbreviations: CrI, credible Interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

B.2.9.2.3 Quality of life

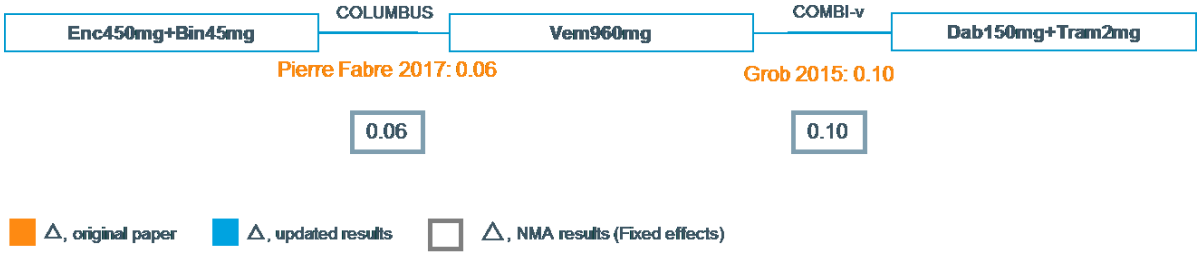
The networks of evidence for EQ-5D utility score outcomes pre-progression, at Week 32 and at disease progression are presented in Figure 11 to Figure 13. Double-blinded RCTs were not included in networks of HRQoL outcomes as COLUMBUS was an open-label study and inclusion of both open-label and double-blinded studies in the same network was deemed to be methodologically inappropriate. Based on availability of EQ-5D data and restricting to open-label studies meant that the network consisted of COLUMBUS and COMBI-v only.

Figure 11: Evidence network for EQ-5D utility score pre-progression



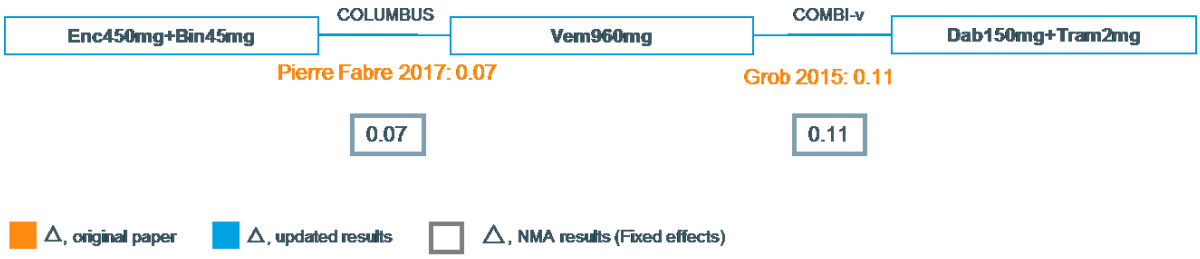
Abbreviations: Bin, binimetinib; Dab, dabrafenib; Enc, encorafenib; EQ-5D, EuroQol-5 dimensions; HR, hazard ratio; NMA, network meta-analysis; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.

Figure 12: Evidence network for EQ-5D utility score, DCFB at Week 32



Abbreviations: Bin, binimetinib; Dab, dabrafenib; DCFB, difference in change from baseline; Enc, encorafenib; EQ-5D, EuroQol-5 dimensions; HR, hazard ratio; NMA, network meta-analysis; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.

Figure 13: Evidence network for EQ-5D utility score, DCFB at disease progression



Abbreviations: Bin, binimetinib; Dab, dabrafenib; DCFB, difference in change from baseline; Enc, encorafenib; EQ-5D, EuroQol-5 dimensions; HR, hazard ratio; NMA, network meta-analysis; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.

Table 23 presents the NMA results for the difference in EQ-5D utility scores pre-progression, and the difference in change from baseline (DCFB) at Week 32 and at disease progression for Enco+Bini 450 versus Dabra+Tram. All results numerically favoured Dabra+Tram (Delta for Enco+Bini 450 vs Dabra+Tram <0), however the CrIs crossed zero in both cases while these numerical improvements were also

inferior to the minimal clinically important difference for EQ-5D utility scores (0.08 points (48)). The results of the NMA were consistent with those reported in the original publications (as indicated in Figure 11 to Figure 13).

Table 23: NMA results for EQ-5D utility score

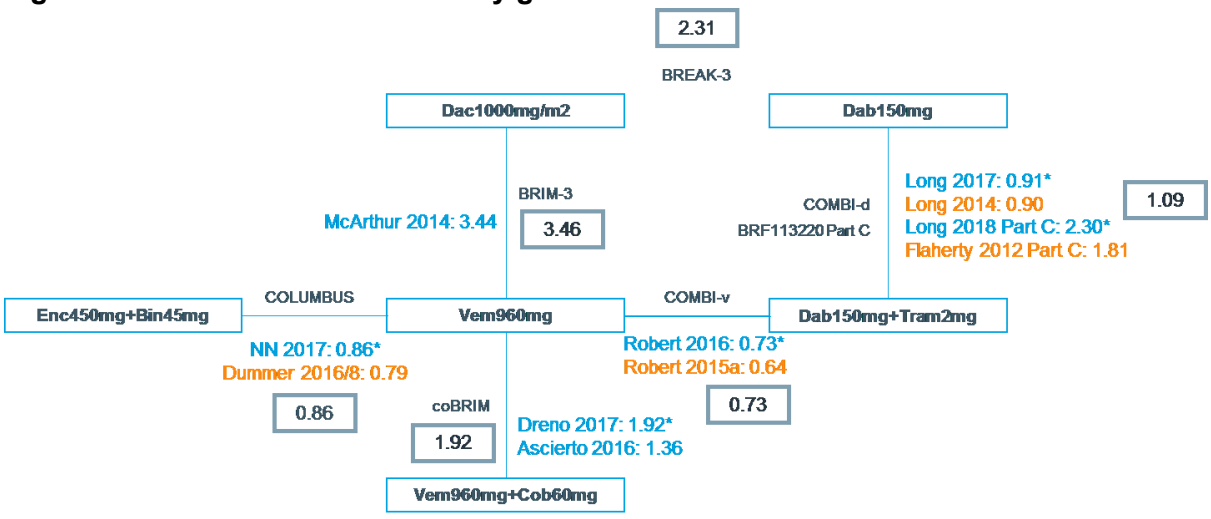
	Dt (95% CrI)	
	Enco+Bini 450 vs Dabra+Tram	**Dabra+Tram vs Enco+Bini 450**
EQ-5D utility score, pre-progression	-0.02 (-0.05, 0.01)	0.02 (-0.01, 0.05)
EQ-5D utility score, DCFB at Week 32	-0.04 (-0.10, 0.02)	0.04 (-0.02, 0.10)
EQ-5D utility score, DCFB at disease progression	-0.04 (-0.12, -0.04)	0.04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

Abbreviations: CrI, credible interval; DCFB, difference in change from baseline; Dt, delta; EQ-5D, EuroQol-5 dimensions; NMA, network meta-analysis.

B.2.9.2.4 Any grade ≥3 AEs

The network of evidence for any grade ≥3 AEs is presented in Figure 14. Estimates from studies highlighted in orange refer to the original publication, whereas those from studies highlighted in blue refer to updated results based on more mature data. The most recent, mature data was used wherever available, as indicated by a star (*).

Figure 14: Evidence network for any grade ≥3 AEs



Abbreviations: AE, adverse event; Bin, binimetinib; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; NMA, network meta-analysis; OR, odds ratio; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.
The most recent, mature data was used wherever available, as indicated by *.

Table 24 presents the NMA results for any grade ≥3 AEs for Enco+Bini 450 versus Dabra+Tram. The result favours Dabra+Tram (OR>1), however the CrI crosses 1.

Table 24: NMA results for any grade ≥3 AEs

	OR (95% CrI)	
	Enco+Bini 450 vs Dabra+Tram	**Dabra+Tram vs Enco+Bini 450**
Any grade ≥3 AEs	1.18 (0.70, 1.98)	0.85 (0.51, 1.43)

Abbreviations: AE, adverse event; CrI, credible Intervals; NMA, network meta-analysis; OR, odds ratio.

In a separate analysis (networks not shown), serious AEs were found to be numerically lower for Enco+Bini 450 versus Dabra+Tram (HR [95% CrI] for Enco+Bini 450 vs. Dabra+Tram: 0.86 [0.52, 1.43]).

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

The NMA has a number of potential limitations:

- Some of the included studies permitted crossover of patients and results adjusted for this crossover were available for analysis (COLUMBUS, COMBI-v, BRF113220 Part C, BRIM-3 and BREAK-3). If assessing OS using the intent-to-treat principle this would mean that any OS benefit observed following crossover would be attributed to the original treatment arm. Therefore, crossover-adjusted estimates of OS HR using the rank-preserving structural failure time model were considered in a sensitivity analysis, which showed similar results to the base-case estimates (results described in Section B.2.9.3.1)
  - Although crossover was initially not planned in COLUMBUS, patients in BRAFi monotherapy arms were offered the possibility to add a MEKi to their regimen after the data monitoring committee reviewed the interim OS results in May 2016.
- The base-case networks included predominantly open-label RCTs (COLUMBUS, COMBI-v, BRIM-3, BREAK-3 , and BRF113220 Part C) and two double-blinded RCTs (COMBI-d and CoBRIM); the open-label nature of the majority of trials may be a potential source of bias for subjective endpoints, such as PFS and particularly a patient-reported outcome such as QoL which may be biased due to patients' expectations towards the efficacy of an intervention.
  - For HRQoL outcomes it was deemed methodologically inappropriate to include both open-label and double-blinded studies in the same evidence

network; as such base-case analyses of HRQoL were based solely on open-label studies.

  - For PFS, base-case estimates of comparative efficacy were based on locally assessed progression, which in open-label studies may also be subject to bias. This can be controlled for by the use of blinded independent review, which was employed during the COLUMBUS study, as well as BRF113220 Part C. However, no other BRAFi studies within the evidence network reported on blinded independent assessment of PFS and therefore, a comparison of PFS by BIRC for Enco+Bini 450 with Dabra+Tram was not possible (see Section B.2.9.3.2 for evidence network).
  - Although naïve comparison of results between trials should be interpreted with caution, PFS results from COMBI-v (open-label) and COMBI-d (double-blinded), which both assessed Dabra+Tram, demonstrated similar absolute median PFS results (11.4 months vs. 11 months (21, 51)), which suggests that any potential impact of blinding on the PFS outcome may be minimal.

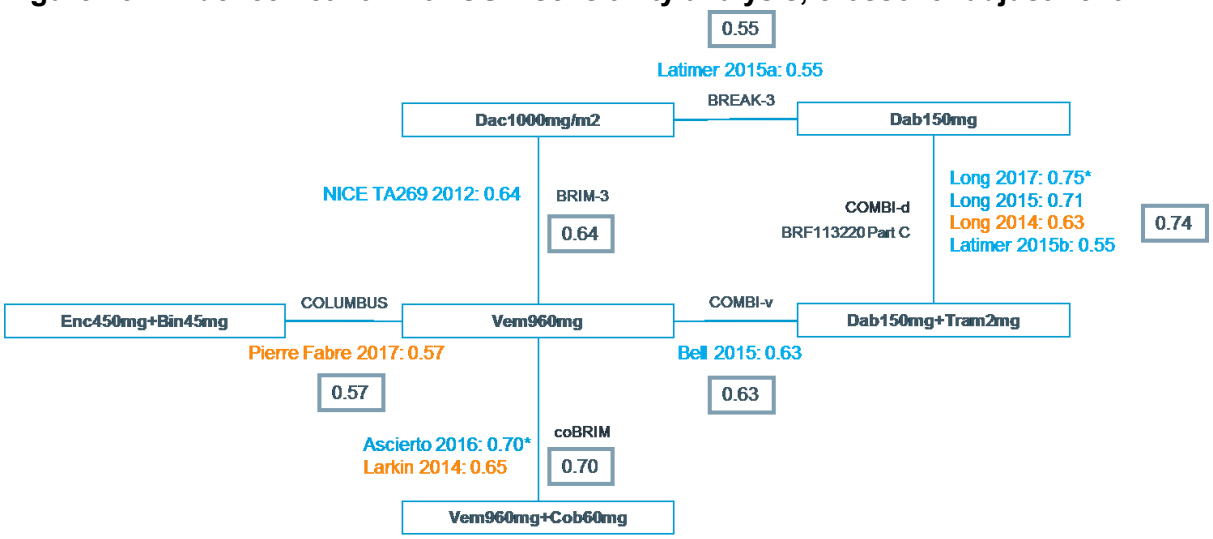
- The assessment of effect modification found modest study design and population variations within the RCTs (See Appendix D, section D.1.3.1). The base-case analysis considered a network including BRAFi studies, which were found to be generally comparable in terms of study design and patient baseline characteristics, with the exception of LDH status (proportion of patients with LDH>ULN).
  - This variation was largely driven by studies of BRAFi treatments not directly relevant to this appraisal (e.g. BRIM-3, 58% vemurafenib and dacarbazine arms), whereas the proportion of patients with LDH>ULN observed in COLUMBUS (Enco+Bini 450) and COMBI-v (Dabra+Tram) were broadly similar (28.6% vs. 34%, respectively).
  - Sensitivity analyses of PFS were conducted to evaluate the impact of using post-hoc data from COLUMBUS adjusting for stratification factors and other baseline variables, including ECOG performance status, LDH status and BRAF mutation status. Two separate analyses demonstrated limited impact, yielding similar results to those generated in the base-case.
  - Subgroup analyses were conducted to assess the impact of these potential effect modifiers

B.2.9.3.1 Overall survival

Although crossover was initially not planned in COLUMBUS, patients in BRAFi monotherapy arms were offered the possibility to add a MEKi to their regimen after the Data Monitoring Committee reviewed the interim OS results in May 2016. At the November 2017 cut-off, 43 (23%) patients from the vemurafenib arm had received a BRAFi/MEKi combination (Enco+Bini 450, Dabra+Tram or vemurafenib + cobimetinib) after discontinuing the study drug. Assuming a common class effect for the BRAFi/MEKi combinations, these patients were considered as crossover-like and their survival time was corrected accordingly using the rank-preserving structural failure time model. The adjustment for Enco+Bini 450 versus vemurafenib from COLUMBUS confirmed the trend of the base-case, with an HR (95% CI) of 0.57 (0.40; 0.77), using a Cox proportional hazard model (38).

The network of evidence is provided in Figure 15. Crossover-adjusted estimates based on the rank-preserving structural failure time model were available from COLUMBUS, COMBI-v, BRF113220 Part C, BRIM-3 and BREAK-3. Although COMBI-d did not allow crossover by protocol, the latest OS data cut used in our analysis (Long 2017 (50)) post-dated a protocol amendment whereby patients were allowed to crossover by patient/physician discretion; however, crossover adjusted results were not available from the publication. CoBRIM did not allow crossover. For both studies, data inputs used were equal to the base-case.

Figure 15: Evidence network for OS – sensitivity analysis, crossover adjustment



Abbreviations: Bin,binimetinib; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; Tram, trametinib; Vem, vemurafenib.
The most recent, mature data was used wherever available, as indicated by *.

The result of the sensitivity analyses for Enco+Bini 450 versus Dabra+Tram are presented in Table 25, showing that the analysis to account for crossover adjustment was consistent with the base-case analysis, favouring Enco+Bini 450 (HR<1; although the CrI crosses 1).

Table 25: NMA results for OS – sensitivity analyses

	Enco+Bini 450 vs Dabra+Tram	Dabra+Tram vs Enco+Bini 450
Sensitivity analysis (crossover adjustment)	HR (95% CrI): 0.90 (0.61, 1.34)	HR (95% CrI): 1.11 (0.75, 1.65)

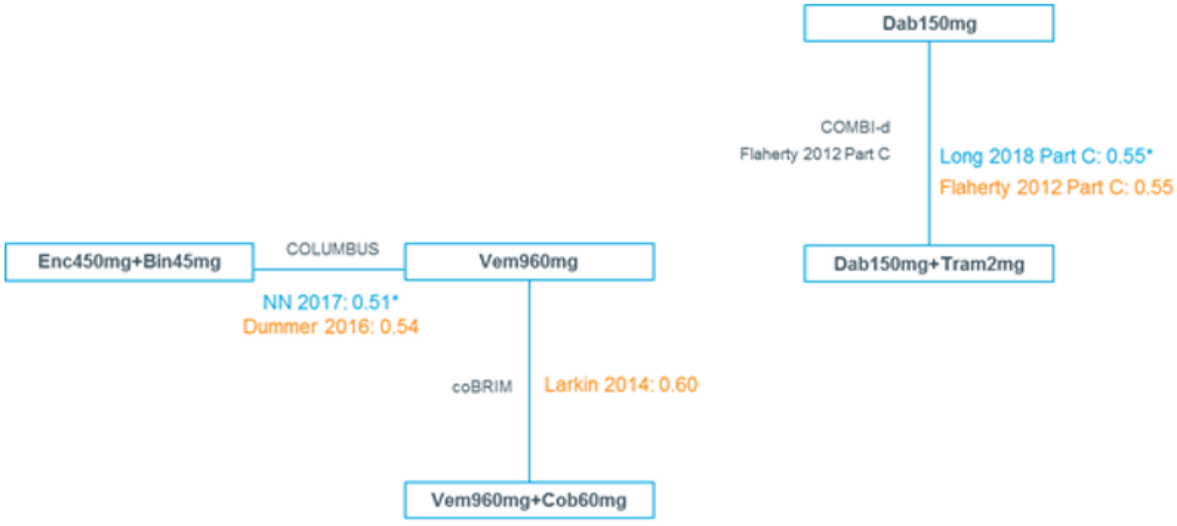
Abbreviations: CrI, credible interval; Dt, delta; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival.

B.2.9.3.2 Progression-free survival

B.2.9.3.2.1 PFS by BIRC

The primary outcome in COLUMBUS was PFS as assessed by BIRC (results described in Section B.2.6.1), as an approach to mitigate the risk of bias associated with the trial's open label design. Only a small number of studies eligible for evidence synthesis reported PFS data as assessed by BIRC and a comparison of Enco+Bini 450 with Dabra+Tram was not possible (Figure 16).

Figure 16: Evidence network for PFS – BIRC assessed



Abbreviations: Bin, Binimetinib; BIRC, Blinded Independent Review Committee; Cob, Cobimetinib; Dab, Dabrafenib; Enc, Encorafenib; PFS, progression-free survival; Tram, Trametinib; Vem, Vemurafenib.
The most recent, mature data was used wherever available, as indicated by *.

B.2.9.3.2.2 PFS post-hoc analyses

Sensitivity analyses were considered to evaluate the impact of using post-hoc data from COLUMBUS adjusting for stratification factors; controlling for imbalances in

terms of study design or patient characteristics may reduce between-study heterogeneity in the base-case network and thereby increase validity of results. Results from two post-hoc analyses were considered (38):

- PFS post-hoc analysis 1: Using a Cox proportional hazards (PH) model and adjusting for COLUMBUS stratification factors (AJCC cancer stage, ECOG PS) plus BRAF status, baseline LDH, and geographical region.
- PFS post-hoc analysis 2: Using a stratified log rank adjusting for BRAF status and baseline LDH covariates, using the Pike estimator to estimate the treatment HR for PFS together with a 95% CI.

Adjusting for stratification and other baseline factors was found to have a low impact on the results compared with the PFS investigator assessed base-case, yielding results that were consistent with the base-case analysis, when comparing Enco+Bini 450 versus Dabra+Tram.

Table 26: NMA results for PFS – sensitivity analyses

	HR (95% CrI)	
	Enco+Bini 450 vs Dabra+Tram	**Dabra+Tram vs Enco+Bini 450**
Sensitivity analysis (Cox PH model)	0.74 (0.54,1.00)	1.36 (1.00,1.84)
Sensitivity analysis (Log rank)	0.80 (0.59,1.09)	1.25 (0.92,1.69)

Abbreviations: CrI, credible interval; Dt, delta; HR, hazard ratio; PH, proportional hazards; NMA, network meta-analysis; OS, overall survival.

B.2.10 Adverse reactions

B.2.10.1 COLUMBUS

AE data were recorded in the COLUMBUS study. Data for the Safety Set, which included 192 patients treated with Enco+Bini 450, 192 patients treated with vemurafenib and 186 patients treated with Enco 300, who received at least one dose of study drug, is presented in this section.

The safety analysis represents the latest data presented to the EMA as part of the marketing authorisation application for Enco+Bini 450, based on a data cut-off of 9 November 2016 (32). This is an updated analysis from that presented in the CSR and the primary trial publication by Dummer et al, 2018 (Data cut-off 19 May 2016) (28, 29).

B.2.10.1.1 Duration of exposure

In the updated analysis of 9 November 2016, the median duration of study drug treatment in the Enco+Bini 450 arm [redacted] was longer than in both the Enco 300 [redacted] and vemurafenib [redacted] arms (Table 27). Within the Enco+Bini 450 arm, median duration of exposure to Enco 450 was the same as that of binimetinib [redacted] in the Enco+Bini 450 arm [redacted] received ≥48 weeks of study treatment while [redacted] in the Enco 300 and vemurafenib arms ([redacted] respectively) received ≥48 weeks of study treatment. Exposure versus planned dose (i.e. median dose intensity) was highest in the Enco+Bini 450 arm [redacted], compared with [redacted].

Exposure data as of the later efficacy data cut-off of 7 November 2017 is also presented in Table 28.

Table 27: Duration of exposure to study treatment – COLUMBUS, Safety Set, Part 1, data cut-off 9 November 2016

	Enco+Bini 450			Enco 300 N=192	Vemurafenib N=186
	Encorafenib N=192	Binimetinib N=192	Enco+Bini 450 N=192		
Duration of exposure (weeks)					
N	192	192	192	192	186
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure ≥48 weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity categories - n (%)					
<50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50 to <80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80 to <100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity (%)					
N	192	192	-	192	186
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Enco+Bini 450			Enco 300 N=192	Vemurafenib N=186
	Encorafenib N=192	Binimetinib N=192	Enco+Bini 450 N=192		
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.
Notes: A patient was counted in only one duration range, per treatment group. Exposure was defined as last dose date - first dose date + 1. Average daily dose = Cumulative dose / Number of dosing days. Actual dose intensity = Cumulative dose / Duration of exposure. Relative Dose Intensity (%) = 100 [(Cumulative dose / Duration of exposure) / Planned Dose Intensity]. The planned dose intensities were: encorafenib 450 mg QD + binimetinib 45 mg BID in Enco+Bini 450 arm, 300 mg QD in Enco 300 arm, 960 mg BID in vemurafenib arm.
Source: EMA MAA safety update (32) and associated end of text tables: 1.5.1.1-u; 1.5.1.3-u.

Table 28: Duration of exposure to study treatment – COLUMBUS, Safety Set, Part 1, data cut-off 7 November 2017

	Enco+Bini 450			Enco 300 N=192	Vemurafenib N=186
	Encorafenib N=192	Binimetinib N=192	Enco+Bini 450 N=192		
Duration of exposure (weeks)					
N	192	192	192	192	186
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	51.2	51.2	51.2	31.4	26.3
Min - Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity categories - n (%)					
<50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50 to <80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80 to <100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
=100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity (%)					
N	192	192	-	192	186
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	99.6	99.2	-	79.6	93.5
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BID, twice daily; Max, maximum; mg, milligram; Min, minimum; QD, once daily; SD, standard deviation.
Notes: A patient was counted in only one duration range, per treatment group. Exposure was defined as last dose date - first dose date + 1. Average daily dose = Cumulative dose / Number of dosing days. Actual dose intensity = Cumulative dose / Duration of exposure. Relative Dose Intensity (%) = 100 [(Cumulative dose / Duration of exposure) / Planned Dose Intensity]. The planned dose intensities were: encorafenib 450 mg QD + binimetinib 45 mg BID in Enco+Bini 450 arm, 300 mg QD in Enco 300 arm, 960 mg BID in vemurafenib arm.
Source: CSR OS addendum (33).

B.2.10.1.2 Adverse events

An overview of AE data is provided by treatment arm for the safety set (Table 29).

Table 29: Summary of deaths and AEs – COLUMBUS, Safety set, Part 1, data cut-off 9 November 2016

Category	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	Median duration of exposure: [redacted]		Median duration of exposure: [redacted]		Median duration of exposure: [redacted]	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
On-treatment deaths[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose interruption and/or adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; EOT, end of treatment; PT, preferred term.
Categories are not mutually exclusive. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
[a]Deaths occurring >30 days after end of treatment are not included: [b] Additional therapy includes all non-drug therapy and concomitant medications.
Source: EMA MAA safety update (32).

Table 30 presents a summary of AEs, regardless of relationship to study drug, by preferred term, treatment and severity (all grades and maximum Grade 3 or 4).

Table 30: AEs, regardless of relationship to study drug, by preferred term – overall (≥10% in any treatment arm) or Grade 3/4 (≥5% in any treatment arm); COLUMBUS, Safety set, Part 1, data cut-off 9 November 2016

Preferred term	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood CK increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GGT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkeratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle Spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palmoplantar keratoderma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPE syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Keratosis pilaris	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Photosensitivity reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Keratoacanthomas	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculopapular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritis generalised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunburn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CK, creatine phosphokinase; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysaesthesia.
Preferred terms are presented by descending order of frequency in the Enco+Bini 450 all grades column. A patient with multiple occurrences of an AE under a PT is counted only once for that PT. A patient with multiple AEs is counted only once in the total row. Where Grade 3/4 AEs were <5% in any arm these are not reported and are shown as a dash.
Source: EMA MAA safety update (32).

Table 31 presents a summary of SAEs, regardless of relationship to study drug, by preferred term, treatment and severity (all grades and maximum Grade 3 or 4), reported for ≥1.0% of patients in any treatment arm.

Table 31: SAEs, regardless of relationship to study drug, by preferred term – overall and Grades 3/4 (≥2% in any treatment arm); COLUMBUS, Safety set, Part 1, data cut-off 9 November 2016

Preferred Term	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; PT, preferred term; SAE, serious adverse event.
A patient is counted once within each preferred term and system organ class. Primary system organ classes are presented alphabetically; preferred terms are sorted within a primary system organ class in descending frequency of all grades, as reported in the Enco+Bini 450 column. Where Grade 3/4 AEs were <5% in any arm these are not reported and are shown as a dash.
Source: EMA MAA safety update (32).

B.2.10.2 Additional studies

Pooled safety data supporting the marketing authorisation application for Enco+Bini 450 has been derived from [redacted] patients with BRAF V600 mutation-positive metastatic melanoma across three clinical trials.

- [redacted] patients from COLUMBUS, Part 1 (as described in Section B.2.10.1)
- [redacted] patients from LOGIC-2, Part A
- [redacted] patients from Study CMEK162X2110, who were previously naïve to BRAFi (either as monotherapy or in combination with a MEKi).

An overview of the safety profile for Enco+Bini 450, based primarily on the COLUMBUS study, along with the pooled safety set is provided in Section B.2.10.3.

B.2.10.3 Safety overview

- In the COLUMBUS study (data cut-off November 2016):
  - Patients in the Enco+Bini 450 arm (n=192) had a median duration of exposure to study treatment (and resulting on-treatment follow-up) that was [redacted] than patients in the Enco 300 and vemurafenib arms, respectively. The dose intensity for encorafenib [redacted]. Despite this, a similar percentage of patients in all three treatment arms experienced at least one AE ([redacted]) and at least one serious AE (SAE) ([redacted]).

- These data suggest that 300 mg QD is the highest dose of encorafenib monotherapy that is tolerable, but that 450 mg QD is achievable with the addition of binimetinib. This is consistent with earlier data from the Phase I study CLGX818X2101 (NCT ID: NCT01436656, data not reported in this submission), which was a multicentre, open label, dose-escalation study of oral encorafenib in adult patients with locally advanced or metastatic BRAF mutant melanoma. [redacted] (75). The addition of binimetinib allows encorafenib to be dosed at 450 mg QD and results in numerically better tolerability and greater relative dose intensity relative to encorafenib alone.
- [redacted] in the Enco+Bini 450 arm, as compared with Enco 300 and vemurafenib arms, experienced at least one Grade 3 or 4 AE [redacted] AEs requiring dose interruption and/or adjustment [redacted] and AEs requiring additional therapy [redacted] The rates of AEs and Grade 3 or 4 AEs leading to treatment discontinuation [redacted].
- The incidence of on-treatment deaths (occurring during treatment or within 30 days of the last dose) [redacted]
- In the Enco+Bini 450 arm, the most frequently reported AEs (>20% of patients) by preferred term were [redacted]. The most frequently reported Grade 3 or 4 AEs (≥5% of patients) were [redacted]
- The most frequently reported SAEs (≥2.0% of patients) in the Enco+Bin 450 arm were [redacted] in the Enco 300 arm [redacted] in the vemurafenib arm [redacted] Grade 3 or 4 SAEs reported in

≥2.0% patients Enco+Bini 450 arm were [redacted] and [redacted]; in the Enco 300 arm were [redacted] and [redacted]; in the vemurafenib arm was [redacted]

- The pooled analysis of three clinical trials (COLUMBUS, LOGIC-2 and Study CMEK162X2110) which provide safety data for Enco+Bini 450 ([redacted]), showed similar findings to those of the COLUMBUS study alone.
- BRAFi/MEKi therapies are associated with characteristic AEs but each of the existing combinations (Dabra+Tram [comparator for this appraisal] and vemurafenib + cobimetinib [not approved by NICE]) have a distinct safety profile with unique toxicities that impact overall tolerability and may impact the ability to deliver optimal treatment.
  - For example: Pyrexia has been observed in 51–53% of patients treated with Dabra+Tram (20, 21), and photosensitivity observed in 48% of patients treated with vemurafenib + cobimetinib (58).
  - An analysis of class-based AEs of special interest, representing known effects of BRAFi and/or MEKi,[c] was conducted for the earlier data cut-off (19 May 2016; Gogas et al, ASCO 2018 (31)) and updated for the safety update (data cut-off 9 November 2016; (32)). This analysis showed that with Enco+Bini 450:
    - ◊ pyrexia[d] was relatively infrequent (18.2%), was generally of Grade 0–1 (23/35) and was mainly associated with disease progression or underlying infection (31); (November 9 2016 cut-off: [redacted] (32)).
    - ◊ photosensitivity[e] was relatively infrequent (4.7%), with only 1 event that was Grade 3 or higher (31); (November 9 2016 cut-off: [redacted] (32)).
    - ◊ serous retinopathy[f] occurred in 19.8% of patients but was mainly asymptomatic (Grade 1) or of low severity and reversible (31); (November 9 2016 cut-off: [redacted] (32)).

[c] Individual AEs describing similar clinical entities or pathophysiologic processes that represent known effects of available BRAFi and/or MEKi were grouped into AEs of special interest.
[d] Includes pyrexia, body temperature increased, hyperpyrexia, hyperthermia
[e] Includes photosensitivity reaction, solar dermatitis
[f] Includes retinal detachment, chorioretinitis, chorioretinopathy, cystoid macular oedema, macular retinal pigment epithelium detachment, retinal pigment epithelium detachment, macular detachment, macular oedema, metamorphopsia, retinal disorder, retinal exudates, retinal oedema, retinal pigment epitheliopathy, retinopathy, subretinal fluid.

- ◊ left ventricular dysfunction[g] occurred in 7.8% of patients, which was often managed by dose interruption and reduction but was generally reversible and did not require treatment discontinuation (31); (November 9 2016 cut-off: [redacted] (32)).

- Overall, the safety data demonstrate that Enco+Bini 450 is generally well tolerated with a differentiated safety profile in patients with BRAF V600-mutant melanoma
  - Based on the COLUMBUS study, Enco+Bini 450 has a tolerability profile that is favourable compared with either single-agent Enco 300 or vemurafenib, as demonstrated by the ability to deliver [redacted]
  - Common BRAFi/MEKi toxicities were generally manageable, reversible, and infrequently associated with treatment discontinuation with Enco+Bini 450, and no serious unexpected AEs of special interest were observed.
  - Based on outputs of the NMA, described in Section B.2.9., Enco+Bini 450 was associated with comparable rates of any Grade ≥3 AE (CrI for OR crossing 1), as compared with Dabra+Tram, which is already in clinical use and approved by NICE.

B.2.11 Ongoing studies

There are no additional data anticipated in the next 12 months from ongoing sponsor-funded Phase II or Phase III studies investigating the efficacy and/or safety of Enco+Bini 450 in adults with unresectable or metastatic BRAF V600 mutation-positive melanoma.

B.2.12 Innovation

Not applicable.

[g] Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction, and ejection fraction abnormal

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The clinical benefits of Enco+Bini 450 have been demonstrated in the pivotal, Phase 3, active-controlled, open-label RCT, COLUMBUS. The primary objective was met as Enco+Bini 450 significantly improved PFS, by blinded independent review, versus vemurafenib alone by doubling median PFS (14.9 months; 95% CI: 11.0, 18.5 vs. 7.3 months; 95% CI: 5.6, 8.2 months). Based on the pre-specified primary analysis, the HR for PFS in the Enco+Bini 450 arm relative to the vemurafenib arm was 0.54 (95% CI: 0.41, 0.71; one-sided stratified log rank p<0.0001; [November 2017 update: HR 0.51; 95% CI: 0.39, 0.67; one-sided stratified log rank p<0.0001]), equating to a 46% risk reduction.

Several secondary/sensitivity analyses of PFS were conducted and yielded similar HRs (95% CI) and median PFS values as the primary PFS analysis, reflecting the robustness of the PFS benefit. These include PFS by local investigator assessment (HR 0.49; 95% CI: 0.37, 0.64; nominal one-sided p<0.0001; [November 2017 update: [redacted]), per protocol analysis, unstratified testing, stratified testing based on alternate stratification factors (eCRF rather than randomisation strata) and variations in censoring rules.

In terms of OS data available at the November 2017 cut-off, a 39% reduction in the risk of death was observed in patients treated with Enco+Bini 450 compared with vemurafenib (HR: 0.61, 95% CI: 0.47, 0.79; nominal p<0.0001). The median OS was doubled in the Enco+Bini 450 arm versus the vemurafenib arm (33.6 months [95% CI: 24.4, 39.2] vs. 16.9 months [95% CI: 14.0, 24.5]). Sensitivity analyses of OS, including per protocol analysis, unstratified testing and stratified testing based on alternate stratification factors (eCRF rather than randomisation strata), yielded results consistent with the base-case results showing the OS benefit of Enco+Bini 450 to be robust.

A range of additional efficacy measures were also assessed, including durable reduction in tumour burden and HRQoL. Compared with vemurafenib, patients receiving Enco+Bini 450 treatment were more likely to achieve a clinically relevant reduction in tumour burden as defined by RECIST v1.1 (ORR by BIRC: 63.0% Enco+Bini 450 vs. 40.3% vemurafenib; [November 2017 update: 63.5% vs. 40.8%]).

Responses on Enco+Bini 450 treatment were durable, lasting a median of 16.6 months compared with a DOR of 12.3 months for vemurafenib treatment (By BIRC; [November 2017 update: 18.6 vs. 12.3 months]). The HRQoL findings were consistent with the observation of clinical benefit and improved tolerability of Enco+Bini 450 compared with single-agent vemurafenib and Enco 300; Enco+Bini 450 significantly delayed deterioration in HRQoL, as measured by median time to 10% deterioration on the FACT-M melanoma subscale and EORTC-QLQ-C30 global health status. Enco+Bini 450 treatment was also associated with clinically meaningful and statistically significant HRQoL gains over time, compared with both monotherapy treatments (vs. vemurafenib [FACT-M melanoma scale [redacted], [redacted]; QLQ-C30 global health status [redacted]]; vs. Enco 300 [FACT-M melanoma scale [redacted]; QLQ-C30 global health status [redacted]]).

The benefits of Enco+Bini 450 were also confirmed versus Enco 300 monotherapy in the COLUMBUS study. A marketing authorisation for Enco 300 monotherapy for treating adult patients with BRAF V600-mutant melanoma is not being sought and this arm was included in order to evaluate the contribution of binimetinib to the Enco+Bini 450. An estimated 25% risk reduction in disease progression (by BIRC) was observed for patients treated with Enco+Bini 450 compared with Enco 300 (HR: 0.75; 95% CI: 0.56, 1.00 [November 2017 update: HR 0.77; 95% CI: 0.59, 1.00]). Median PFS (by BIRC) estimates were 14.9 months (95% CI: 11.0, 18.5) and 9.6 months (95% CI: 7.5, 14.8) in the Enco+Bini 450 and Enco 300 arms, respectively. Although the PFS difference between the Enco+Bini 450 arm and the Enco 300 arm was on the verge of statistically significance (one-sided p=0.0256) by the stratified log-rank test based on data at the May 2016 data cut-off, the result was significant in the updated analysis (November 2017 data cut-off; p=0.0249). According to local investigator assessment of response, the PFS difference between the Enco+Bini 450 arm and the Enco 300 arm was consistent with that reported by the BIRC and was statistically significant (HR: 0.68; 95% CI: 0.52, 0.90; nominal one-sided p=0.003; [November 2017 update: [redacted].

In the absence of direct comparative data for Enco+Bini 450 versus Dabra+Tram, the current BRAFi/MEKi approved by NICE and the comparator for this decision problem, a NMA was conducted. The evidence networks comprised of a small number of studies (n=7) linking Enco+Bini 450 and Dabra+Tram via monotherapy

comparators. Results of the analysis favour Enco+Bini 450 for both PFS and OS, with HR<1 (Enco+Bini 450 vs. Dabra+Tram), although the credible intervals cross 1 (PFS: HR 0.77; 95% CrI: 0.57, 1.04; OS: HR 0.89; 95% CrI: 0.65, 1.23). Sensitivity analyses were consistent with base-case results, with results favouring Enco+Bini 450.

The median duration of exposure to study treatment in the Enco+Bini 450 arm ([redacted]) was [redacted] and [redacted] times longer than the median duration of exposure to study treatment in both the Enco 300 ([redacted]) and vemurafenib ([redacted]) arms, respectively. Despite this, Enco+Bini 450 demonstrated a tolerability profile that was favourable compared with either single-agent Enco 300 or vemurafenib, as demonstrated by the ability to deliver [redacted]. In addition, [redacted]. The incidence of on-treatment deaths (occurring during treatment or within 30 days of the last dose) [redacted]. The most frequently reported Grade 3 or 4 AEs (≥5% of patients) in COLUMBUS were [redacted].

Based on the NMA (Section B.2.9), Enco+Bini 450 was associated with a numerically higher rate of Grade ≥3 AEs and a numerically lower rate of SAEs versus Dabra+Tram, although the CrI crossed 1 in both cases. Naïve comparison of individual trials showed that pyrexia, an AE commonly seen with dabrafenib (4), occurred at a lower frequency with Enco+Bini 450 (Overall: 20% vs. 51–53% (20, 21)). Analysis of other AEs known to be associated with BRAFi and/or MEKi, including photosensitivity, serious retinopathy and left ventricular dysfunction showed these AEs to be generally manageable, reversible, and infrequently associated with treatment discontinuation with Enco+Bini 450. Furthermore, no serious unexpected AEs of special interest were observed. Overall, the safety data demonstrate that Enco+Bini 450 is generally well tolerated offering a differentiated safety profile in patients with BRAF V600-mutant melanoma.

The body of evidence demonstrates that the combination of Enco+Bini 450 can provide statistically significant and clinically meaningful improvements in PFS and OS (nominal p-value for OS) over the monotherapy, vemurafenib, as well as clinically meaningful improvements in PFS and OS over encorafenib monotherapy, while enabling encorafenib to be tolerated at a higher dose (450 mg) versus monotherapy (300 mg). Indirect evidence demonstrates that Enco+Bini 450 is at least as efficacious as combination therapy with Dabra+Tram, offering numerical improvements in PFS and OS.

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

B.2.13.2.1 Internal validity

Trial design

COLUMBUS was a large, multinational, active-controlled, well-conducted and methodologically robust study. An open-label design was chosen in the interests of patient safety, due to the characteristic MEKi toxicities, such as ocular side effects and raised blood creatine kinase, that would result in patients in the combination arm being functionally unblinded. In addition, treatment with vemurafenib is also associated with characteristic toxicities including photosensitivity (76) which again would result in unblinding of the study.

As described in EMA guidelines, the impracticality of employing a double-blind design due to differences in toxicity between study regimens is a frequent situation in oncology trials, and the choice of study endpoints, conduct of sensitivity analyses and independent review are recognised to limit potential bias related to the open-label nature of the trial (77).

Accordingly, the impact of a lack of blinding on the clinical response assessment in COLUMBUS was adequately controlled by using central blinded independent review committee assessment for the primary efficacy PFS analyses. During the independent review, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, as well as photographs, X-ray and whole-body bone imaging were evaluated and an assessment of tumour response (RECIST v1.1) and progression was provided to the Sponsor. The independent review provided the Sponsor with an overall time point response and integrated the available assessments from the radiology and oncology reviews for all applicable patients

enrolled in COLUMBUS. PFS and response outcomes were also assessed locally by the investigator. The open-label design is unlikely to yield biased results for OS, as OS is based on objective, all-cause mortality events (78).

Other precautions taken to minimise bias were the use of interactive response technology for randomisation and the sponsor personnel responsible for analysis and interpretation of the data remaining blinded to data that would systematically unblind patient treatment assignments until database lock for the primary analysis.

Statistical testing

Given the inclusion of multiple treatment arms and endpoints, a hierarchical testing procedure was adopted for statistical testing of the primary and key secondary efficacy endpoints in COLUMBUS, to control for Type-1 error (alpha). Accordingly, the Part 1 key secondary endpoint, PFS of Enco+Bini 450 versus Enco 300, was to be tested if the primary endpoint, PFS of Enco+Bini 450 versus vemurafenib, was statistically significant. OS was also to be tested as part of the hierarchical approach.

The primary endpoint was found to be statistically significant. However, the Part 1 secondary endpoint of PFS for Enco+Bini 450 versus Enco 300, although numerically superior, did not reach the pre-defined level for significance of $p<0.025$ (one-sided $p=0.0256$) at the planned data cut-off (145 PFS events for Enco+Bini 450 vs. vemurafenib and 191 PFS events for Enco+Bini 450 vs. Enco 300, May 2016).[h] This result may have reflected the improved efficacy observed with Enco 300 monotherapy compared with vemurafenib monotherapy (data not presented, nominal one-sided $p=0.004$ for PFS by BIRC).

As a result, OS analyses could not be formally tested, and nominal p-values were provided for descriptive purposes only.

Comparators

Vemurafenib monotherapy was selected as the active control for the primary efficacy analysis in COLUMBUS. Although this may not deemed to be the most suitable comparator based on the current preference for BRAFi/MEKi combination therapies over BRAFi monotherapies (11, 12, 19-21), at the time of study initiation, vemurafenib was the standard of care for the treatment of patients with BRAF V600

[h] Although the PFS difference between the Enco+Bini 450 arm and the Enco 300 arm was on the verge of statistically significance (one-sided p=0.0256) by the stratified log-rank test based on data at the May 2016 data cut-off, the result was significant in the updated analysis (November 2017 data cut-off; p=0.0249).

mutation-positive locally advanced unresectable or metastatic melanoma, while combination therapies were yet to be established. In conducting the NMA (see Section B.2.9) vemurafenib was found to be a common comparator across a number of studies assessing BRAFi targeted therapies.

Patient characteristics

There were some imbalances at baseline in patient characteristics. A higher percentage of patients in the Enco+Bini 450 arm compared with the Enco 300 and vemurafenib arms were ≥65 years old and were Caucasian (≥65 years: 31.3% vs. 20.6% vs. 26.7%; Caucasian: 94.3% vs. 89.7% vs. 86.9%). However, mean and median age were similar among the three treatment arms.

Stratified randomisation was used to balance treatment arms in terms of AJCC disease staging (7th Edition; IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG PS (0 vs. 1), which are known prognostic factors in this indication (63, 79). As such AJCC stage and ECOG PS were well-matched. Another established prognostic factor, elevated serum LDH (79, 80), was also similarly frequent across treatment arms (Enco+Bini 450, 28.6%; Enco 300, 24.2%; vemurafenib, 27.2%), as were the number of organs involved and the proportion with lung and liver involvement. However, of those patients with Stage IV M1C disease, more patients in the Enco+Bini 450 and Enco 300 arms had elevated LDH at study entry compared with the vemurafenib arm (25.0% and 25.3% vs. 18.8%, as percentage of patients in each arm). A higher percentage of patients presented with brain metastases at baseline in the Enco+Bini 450 and Enco 300 arms as compared with the vemurafenib arm (5.2% and 4.1% vs. 1.6%). Both factors may be anticipated to negatively impact on the overall effectiveness of treatment, and potentially lead to an underestimation of the relative effectiveness of Enco+Bini 450 versus vemurafenib.

Sub-group analyses showed PFS (BIRC) and OS results to be similar to analyses in the overall trial population, when assessed for age (<65/≥65 years) and race (Caucasian/non-Caucasian). PFS (BIRC) and OS analyses by CNS involvement (Baseline brain metastases, Yes/No) produced HRs versus vemurafenib that were greater than 1 in the presence of brain metastases. However, this subgroup consisted of only nine patients in the Enco+Bini 450 arm and three patients in the vemurafenib arm, and as such this result should be interpreted with caution. All other sub-group analyses were generally consistent with results from the overall population in terms of direction of effect (Enco+Bini 450 more efficacious than

vemurafenib and Enco 300 for PFS [BIRC] and OS). A small number of analyses generated non-significant results with the upper bound of the 95% CI for the HR crossing 1.

B.2.13.2.2 External validity

The evidence base for Enco+Bini 450 from the COLUMBUS trial reflects the anticipated licensed indication and the anticipated use of this treatment in clinical practice in the UK.

No major factors relating to the COLUMBUS trial have been identified which would likely impact on the applicability of the evidence to adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Trial populations compared with clinical practice

The COLUMBUS study was a multinational study, including 162 clinical sites across 28 countries in North America, Europe and the rest of the world. The majority of patients were randomised at centres across Europe (119 centres), including 8 in the UK

Patient demographics and characteristics at baseline are considered to be generally reflective of the patient population expected to receive Enco+Bini 450 in clinical practice.

COLUMBUS enrolled more males than females (approximately 58%:42%), with a mean age around 55 years (Range 20–89 years). The average age of diagnosis of melanoma in the UK is around 50 years (81) with 51% of cases in males (5). This data reflects melanoma diagnosed at any stage; it would be expected that patients progressing to later stages of the disease would be older, while diagnoses of late stage disease (stage III or IV) are more common amongst older patients and amongst males (5).

A comparison with a 2014 observational study of UK clinical practice show that patients in the COLUMBUS (see Section B.2.3.2) were generally well-matched to UK patients undergoing treatment for unresectable or metastatic melanoma in terms of age (mean 58 years), gender (56% male), ECOG PS (65% ECOG PS 0, 30% ECPG PS 1), metastatic staging (58% M1C, 27% M1B, 15% M1A) and baseline LDH levels (33% with elevated LDH) (82).

Patient characteristics, in terms of age, gender, ECOG PS, metastatic staging, and the proportion of patients with a V600E (versus V600K) mutation, are also broadly consistent with real-world studies of patients with unresectable or metastatic melanoma with BRAF-positive mutations treated with Dabra+Tram (83, 84).

Relevance of outcomes to clinical practice

The primary efficacy endpoint in COLUMBUS was PFS, and although OS is the most objective measure of meaningful clinical efficacy of investigational cancer therapies, the availability of life-extending immunotherapies and targeted therapies has made it more challenging to isolate the OS benefit of an investigational therapy, due to the potential effects on survival of both prior and subsequent treatments undergone by the patient. PFS is recognised as a legitimate surrogate for OS in melanoma, with studies suggesting that the correlation is stronger in melanoma than has been noted in other cancers (85, 86). PFS as a primary objective has been accepted in pivotal registration trials of treatments for metastatic melanoma on the basis of statistically significant, clinically meaningful improvements in PFS compared with standard chemotherapy (85). As such, a meaningful reduction in the risk of progression or death may be accepted to represent a legitimate measure of clinical benefit in patients with BRAF mutation-positive melanoma. As described previously, to prevent potential evaluation bias, the PFS assessment was based on centralised blinded independent review. By contrast, local investigator review of PFS was also included, and this could be viewed to provide results that were representative of real-life clinical practice.

Overall survival was assessed as a secondary endpoint, being the universally accepted direct measure of benefit that is easily and precisely measured by documenting the date of death, and of direct relevance to clinicians and patients when considering the use of life-extending therapies.

The impact of treatment on HRQoL was assessed using three recognised, reliable and validated tools – FACT-M, EORTC QLQ-C30 and EQ-5D-5L (87-89). As disease-specific tools, the FACT-M and EORTC QLQ C30 have been designed to capture the impact of melanoma (FACT-M) and more broadly cancer (EORTC QLQW-C30) on the patient's HRQoL. These capture the adverse symptoms that are most prevalent in metastatic melanoma patients, including fatigue, pain, sleep disturbances and appetite loss, as well as measures of role and social functioning and emotional functioning, which are highly impacted in these patients compared

with the general population. In contrast, the EQ-5D-5L is a standardised measure of health utility that provides a single index value for one's health status and is of most relevance to modelling the economic impact of Enco+Bini 450, in line with the NICE reference case.

Availability of comparative evidence

The absence of direct head-to-head trial data comparing Enco+Bini 450 with the current standard of care BRAFi/MEKi combination therapy Dabra+Tram, made it necessary to derive indirect estimates of relative treatment efficacy and safety by way of a Bayesian NMA. The NMA broadly considered BRAFi monotherapies and BRAFi/MEKi combination therapies, including the two therapies of relevance to this appraisal, Enco+Bini 450 and Dabra+Tram. Evidence networks were generally relatively weak, consisting mainly of single RCTs for the majority of links and at the most two RCTs.

Based on the COLUMBUS study, Enco+Bini 450 treatment resulted in an absolute median OS of 33.6 months in the Enco+Bini 450 arm of COLUMBUS, representing the longest OS reported of any BRAFi/ MEKi (Dabra+Tram median OS: COMBI-v = 26.1 months (49); COMB-d = 25.1 months (51)). Based on the NMA this translated into a numerical improvement in OS compared with Dabra+Tram, with a HR of 0.89 (95% CrI: 0.65, 1.23).

Importantly, a number of studies allowed crossover, either pre-planned or following an interim analysis of OS. When assessing OS by the intent-to-treat principle this would mean that any OS benefit observed following crossover would be attributed to the original treatment arm, potentially overestimating the benefit of this treatment. Use of corrected survival estimates (based on the rank-preserving structural failure time model) generated an OS estimate for Enco+Bini 450 versus Dabra+Tram which was consistent with the base-case analysis (HR 0.90; 95% CI: 0.61,1.34).

In the PFS base-case analysis, Enco+Bini 450 again demonstrated a numerical improvement compared with Dabra+Tram (HR 0.77; 95% CrI: 0.57, 1.04). This base-case analysis was based on locally assessed progression, which in open-label studies – five of seven studies in the evidence network were open-label – may be viewed as a potential source of bias. This can be controlled for by the use of blinded independent review, which was employed during the COLUMBUS study, as well as BRF113220 Part C. However, no other BRAFi studies within the evidence network reported on blinded independent assessment of PFS and therefore, a comparison of

PFS by BIRC for Enco+Bini 450 with Dabra+Tram was not possible (see Section B.2.9.3.2 for evidence network).

Although naïve comparison of results between trials should be interpreted with caution, PFS results from COMBI-v (open-label) and COMBI-d (double-blinded), which both assessed Dabra+Tram, demonstrated similar absolute median PFS results (11.4 months vs. 11 months (21, 51)). Similarly, PFS estimates from COLUMBUS for Enco+Bini 450 by investigator and by BIRC were seen to be similar. Overall, this suggests that any potential impact of blinding on the PFS outcome may be minimal.

Further analyses suggested comparability of Enco+Bini 450 and Dabra+Tram for EQ-5D index scores (differences less than the minimal clinically important difference of 0.08 points) and tolerability (based on credible interval for OR for incidence of any grade ≥3 AE and of any SAE crossing 1).

In general, the evidence networks were relatively sparse with single RCTs feeding each link of the evidence network in most cases, driving relatively high uncertainty and associated wide CrIs. Although Enco+Bini 450 showed numeric improvements in OS and PFS, all CrIs crossed one showing that NMA results should be interpreted with caution.

B.2.13.3 End of life

Based on data that shows that median OS with Dabra+Tram is in excess of 24 months in unresectable or metastatic BRAF V600 mutation-positive melanoma (COMBI-v = 26.1 months (49); COMB-d = 25.1 months (51)), Pierre Fabre do not believe that Enco+Bini 450 meets the end-of-life criteria.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify available economic evaluations, burden of illness and resource use studies in advanced or metastatic melanoma. Full details of the SLR methodology are presented in Appendix G. In total, nine full text publications were identified which reported cost-effectiveness analyses of BRAFi/ MEKi combination therapies or BRAFi monotherapies, all conducted from a US or European perspective; these studies are summarised in Appendix G, Section 1.3.

Separately, the NICE website was searched to identify TAs of relevance to the decision problem; technology appraisals of BRAFi monotherapies or BRAFi/ MEKi combination therapies were prioritised to guide the model structure, parameters and assumptions (15-18). NICE TAs for immunotherapies were also interrogated when specific assumptions related to these therapies was required. NICE TAs are referenced as required within specific subsections.

B.3.2 Economic analysis

None of the CEAs identified in the economic SLR (Appendix G) included Enco+Bini 450 as a comparator. Therefore, it was necessary to include a de novo economic model in this submission. Previous NICE TAs of treatments for unresectable or metastatic melanoma in the UK, along with published cost-effectiveness analyses identified in the economic SLR (all non-UK) were used to inform the model structure, assumptions and data sources.

The objective of the economic evaluation was to assess the cost-effectiveness of Enco+Bini 450 for the treatment of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma, versus Dabra+Tram.

The model perspective is the National Health Service (NHS) and Personal Social Services (PSS) in England. The cost-effectiveness analysis is based on individual patient data from the COLUMBUS trial (see Section B.2.3) and from an NMA conducted to estimate comparative efficacy and safety parameters (see Section B.2.9). The model is described in greater detail in the following sections.

B.3.2.1 Patient population

The economic evaluation includes patients with unresectable or metastatic BRAF V600 mutation-positive melanoma, as described in Table 1. This is consistent with the NICE scope, the population included in the COLUMBUS study and with the anticipated European marketing authorisation for Enco+Bini 450.

The base-case cohort characteristics reflect the average baseline patient characteristics in COLUMBUS (averages across all arms; Table 32).

Table 32: Base-case cohort characteristics at baseline

	All patients	Source
Age (sd)	55.3 (13.5)	Section B.2.3.2 (Table 6)
BSA (sd)	1.9 (0.24)	
Weight, Kg (sd)	80.4 (18.0)	
Percentage males	57.9%	

Abbreviations: BSA, body surface area; sd, standard deviation.

B.3.2.2 Model structure

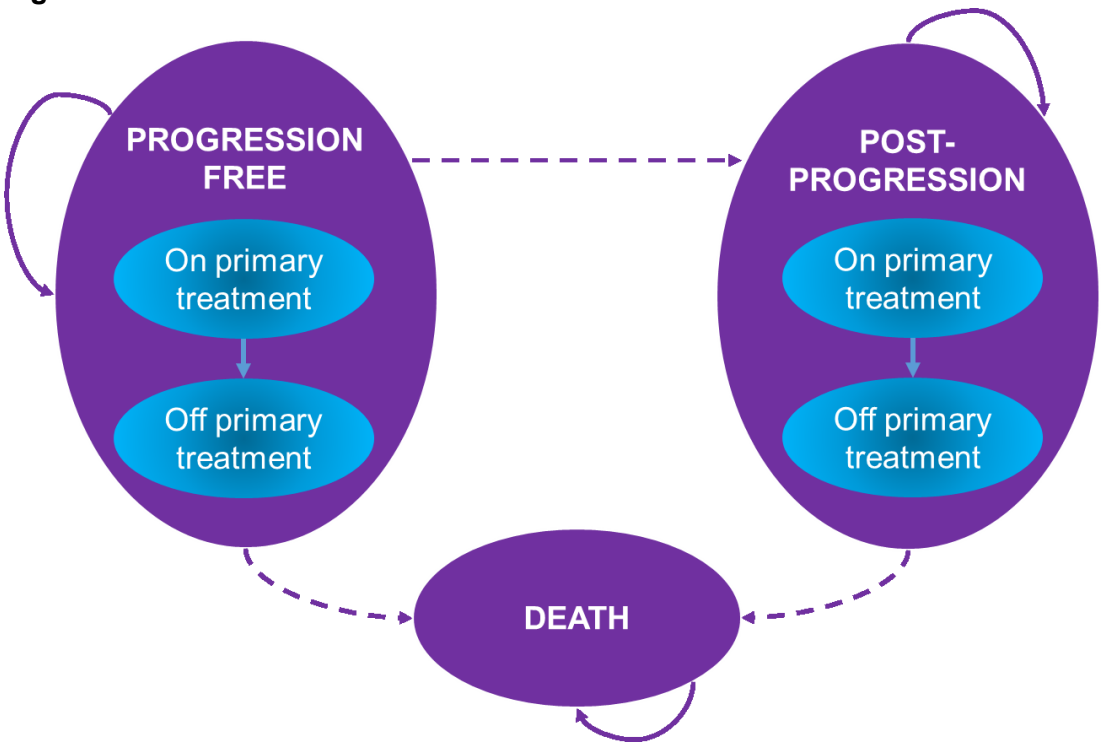
A partitioned survival analysis model (PartSA) with a lifetime horizon (30 years) was developed to determine the cost-effectiveness of Enco+Bini 450 versus Dabra+Tram in the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. The concept of the model is similar to that used in numerous prior economic evaluations of treatments for advanced or metastatic cancers, including the recent NICE appraisal of Dabra+Tram [NICE TA396] (17) in the treatment of unresectable or metastatic melanoma.

PartSA is the most commonly used modelling approach within NICE health technology assessments (HTAs) for interventions treating advanced or metastatic cancers (90). The advantages of such an approach in modelling this disease are as follows:

- Overall survival (OS) and progression-free survival PFS data from the clinical trial can be used directly in the model.
- Time dependencies and treatment effects are reflected within the survival curves (whereas a Markov model for example would require cumbersome tunnel states).
- HRs from network meta-analyses (NMAs) can be easily incorporated by applying these to the OS and PFS curves.

The current model was developed in MS Excel™ 2013 and it includes three mutually exclusive health states (Figure 17): progression-free (PF), post-progression (PP) and death.

Figure 17: Model structure



In the PartSA approach, state membership is determined from a set of non-mutually exclusive survival curves. The cohort enters the model in the PF health state and transitions to PP and death are defined by the PFS and OS curves. The proportion of the cohort remaining in the PF health state over time is derived directly from the PFS curve. State membership for the death state is calculated as 1 minus the OS curve and state membership for the PP health state is derived as the difference between the OS and the PFS curve (the proportion of patients who are alive but not progression-free).

In PartSA, the proportion of alive patients is "partitioned" between the PF and PP health states to allow differentiation in HRQoL and cost. This implies that, in the model, there is no explicit structural link between mortality and earlier progression events, and this is a limitation of PartSA models. To help address this point, extrapolation of OS was performed using OS observations from a relevant long-term registry and this was validated by a UK-based clinical expert to ensure clinical

plausibility (Section B.3.10). More detail on OS extrapolation is described in Section B.3.3.1.3.2.

Time to treatment discontinuation (TTD) was used to define the proportion of the cohort on primary treatment over time. Primary treatment refers to the treatment being assessed in each arm of the model (i.e. Enco+Bini 450 or Dabra+Tram).

The rationale for using TTD instead of PFS to define the proportion of the cohort on primary treatment, is that in clinical practice patients may either discontinue treatment pre-progression due to tolerability or toxicity issues or continue treatment post-progression if the clinician believes the primary treatment may still provide beneficial effects. Both such trends were observed in the COLUMBUS trial, with 26.0% of patients discontinuing treatment pre-progression in the Enco+Bini 450 arm for reasons including AEs (November 2017 data cut-off; See Appendix D, Section D.2.1.2) and 12% continuing treatment beyond both central and local progression (November 2017 data cut-off; COLUMBUS supplementary data table 14.1-1.5a). The TTD approach ensures that the proportion of patients assumed to be on primary treatment with Enco+Bini 450 at any given time is reflective of the treatment taken to achieve the clinical outcomes observed within the COLUMBUS trial and subsequently utilised within the model. This approach is also consistent with NICE TA396, in which the ERG considered that PFS was a poor proxy for time on treatment and thus treatment costs, and that time to treatment discontinuation would provide a more clinically plausible and accurate measure of time on treatment (17).

For the purpose of applying the appropriate costs in the model, the PF and PP health states were subdivided into ‘on primary treatment’ and ‘off primary treatment’. The sub-states are used ***only*** to derive the differential costs within the health state and therefore no differential treatment effect or HRQoL are applied in the sub-states. A summary of the membership and key definition of the three health states and associated sub-states is presented in Table 33.

Table 33: Summary description of health states and associated sub-states

Health state	Sub-state	Definition	Membership
PF		Alive and stable disease (Progression free)	PFS
	On primary tx	Alive, stable disease and receiving primary tx	Earliest data point (TTD, PFS)

Health state	Sub-state	Definition	Membership
	Off primary tx	Alive, stable disease and switched to subsequent antineoplastic tx	PFS minus PF on primary tx
PP		Alive and experienced worsening of the disease (post-progression)	OS minus PFS
	On primary tx	Alive, experienced worsening of the disease and continuing primary tx	TTD minus PF on primary tx
	Off primary tx	Alive, experienced worsening of the disease and receiving subsequent PPACT or BSC	PP minus PP on primary tx
Death		Dead	1 minus OS

Abbreviations: BSC, best supportive care; OS, overall survival; PF, progression free; PFS, progression free survival; PP, post-progression; PPACT, post progression anti-cancer therapy; tx, treatment.

B.3.2.2.1 Time horizon and cycle length

The base-case time horizon is 30 years, which is deemed sufficiently long to represent a life-time horizon and account for all incurred costs and effects. The model predicts that almost no patients (0.44% and 0.23% in the Enco+Bini 450 and Tram+Dabra arms respectively) remain alive at 30 years. The model has a cycle length of one month (365 days/12 months = 30.42 days per month), which corresponds to a sufficient length of time to account for changes in PFS, OS and TTD, and is not too short to impair computational efficiency. Since trial endpoints are included in the model based on observation of patients at the end of each month, half cycle correction was used. The need for half cycle correction decreases as cycles get smaller (e.g. one week), however one-month cycles still require this approach to adjust for the uncertainty about the timing of events.

B.3.2.2.2 Perspective and discounting

The base-case analysis takes the perspective of the NHS and PPS in England. Both costs and outcomes (LYs and QALYs) were discounted at 3.5%, in line with the NICE guide to the methods of technology appraisal 2013 (91). The impact of discounting at 0% and 6% was assessed in the sensitivity analysis.

B.3.2.2.3 Model outcomes

The results of the model are expressed in terms of incremental cost per life-year (LY) gained and incremental cost per quality adjusted life year (QALY) gained (incremental cost-effectiveness ratio [ICER]).

Table 34: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA396 (Dabra+Tram for unresectable/ metastatic melanoma) †	**Chosen values**	**Justification**
Time horizon	30 years	30 years	Sufficiently long to represent a life-time horizon and account for all incurred costs and effects
Treatment waning effect?	None	None	In the absence of data to suggest otherwise treatment effects are extrapolated beyond the trial period using established techniques
Source of clinical outcomes data	COMBI-d/COMBI-v pivotal trials for Dabra+Tram (direct comparative evidence versus comparators in scope)	- COLUMBUS study (Pre-planned [Section B.2.6] and post-hoc analyses (38)) - NMA (Section B.2.9)	COLUMBUS is the pivotal study for Enco+Bini 450 in the indication being assessed in this technology appraisal. Direct comparative data is not available versus Dabra+Tram, hence the use of an NMA to derive comparative data.
Source of utilities	EQ-5D data from COMBI-v and COMBI-d	- COLUMBUS study (Post-hoc analyses (37)) - NMA (Section B.2.9)	Utility values and efficacy data are taken from the same source for consistency. EQ-5D-5L was captured in the COLUMBUS study. An NMA was conducted to determine if treatment-specific differences were apparent.
Source of costs/ resource use	- BNF - NHS reference costs - The UK MELODY study (a study of resource utilisation in 220 people with melanoma) - Cost-of-illness study performed by INC Research	- NHS Reference costs (92) - Personal Social Services Research Unit (93) - British National Formulary (94) - Previous NICE TAs (95-97) - Previous published CE analyses (98) - Product SmPCs - UK-based costs/resource from the literature (99-101) - Expert opinion	All cost/resource were UK-specific where available. Review of previous NICE TAs and an SLR were used to identify relevant sources of costs and resource use.

Abbreviations: CE, cost-effectiveness; EQ-5D-5L, EuroQoL-5 dimensions 5 levels; NHS, National Health Service; NMA, network meta-analysis; TA, technology appraisal.
† TA396 is included in this table as is it the most relevant to the current appraisal.

B.3.2.3 Intervention technology and comparators

The intervention in the analysis is Enco+Bini 450, in line with the anticipated European marketing authorisation and the NICE scope. Similarly, the doses used are those assessed in part 1 of the COLUMBUS study and in line with the anticipated European marketing authorisation (Table 35). The comparator in the analysis is Dabra+Tram as defined in the NICE scope (see Section B.1.3.2 for further discussion); doses are consistent with the product SmPCs (Table 35).

Table 35: Characteristics of treatment regimens for comparators included in the model

BRAF targeted therapy	Drug(s)	Daily dose	Source
Enco+Bini 450	Encorafenib	Oral 450 mg QD	Draft SmPC (Appendix C)
	Binimetinib	Oral 45 mg BID	Draft SmPC (Appendix C)
Dabra+Tram	Dabrafenib	Oral 150mg BID	Product SmPC (4)
	Trametinib	Oral 2mg QD	Product SmPC (3)

Abbreviations: BID, twice daily; QD, once daily; SmPC, summary of product characteristics.

B.3.3 Clinical parameters and variables

B.3.3.1 PFS, OS and TTD

B.3.3.1.1 Summary

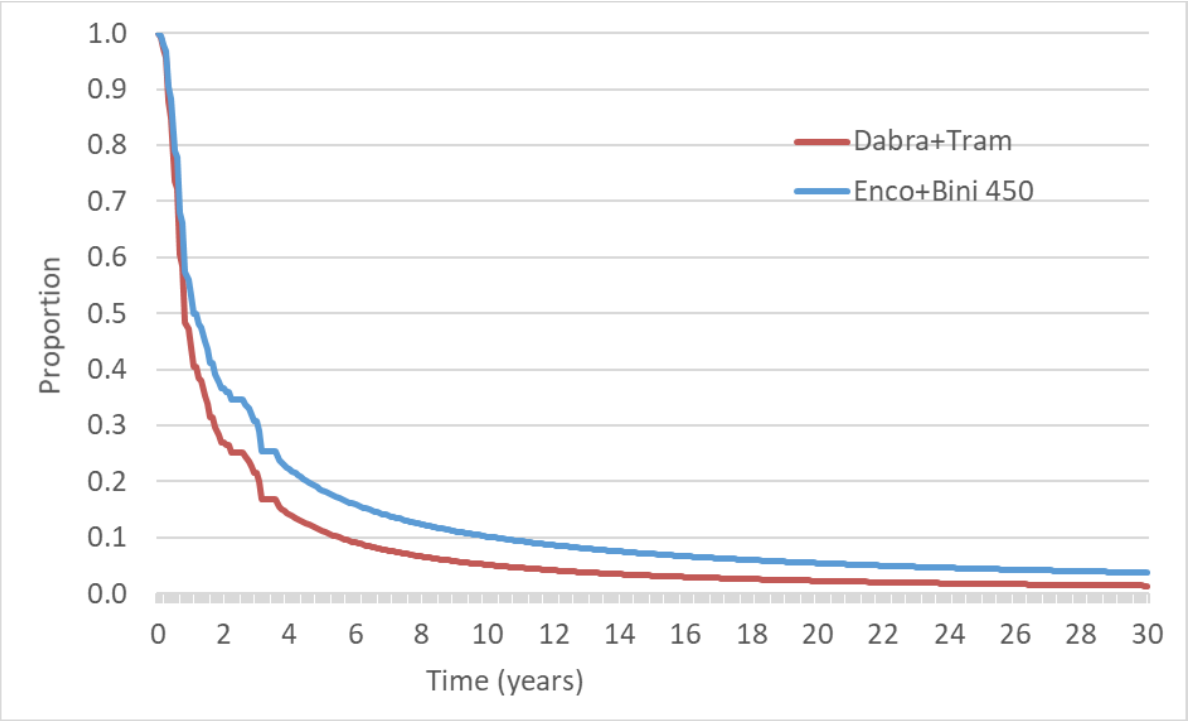
Key features of the approach used to derive PFS, OS and TTD long-term curves in the analysis are summarized below. Detailed description and justification of the approaches employed for each outcome are provided in Sections B.3.3.1.2 and B.3.3.1.3:

- **PFS**
  - As described in Section B.2.3, progression was assessed in the COLUMBUS trial by blinded independent review committee (BIRC) and locally by study investigators (local review). Local review of progression was used to inform the model, based on the relative availability of data for the NMA (See Section B.2.9.2.2 and B.2.9.3.2 for further details).
  - Enco+Bini 450: COLUMBUS Kaplan-Meier (K-M) PFS data by local review until a defined breakpoint (28 months) + Gamma parametric extrapolation.

- Dabra+Tram: numerical estimate of HR vs Enco+Bini 450 derived from the NMA (PFS by local review, FE model, no stratification) applied to the entire Enco+Bini 450 survival curve.

A graphical representation of the base-case PFS projections over the time horizon of the model for Enco+Bini 450 and Dabra+Tram is presented in Figure 18.

Figure 18: Base-case PFS projections for Enco+Bini 450 and Dabra+Tram

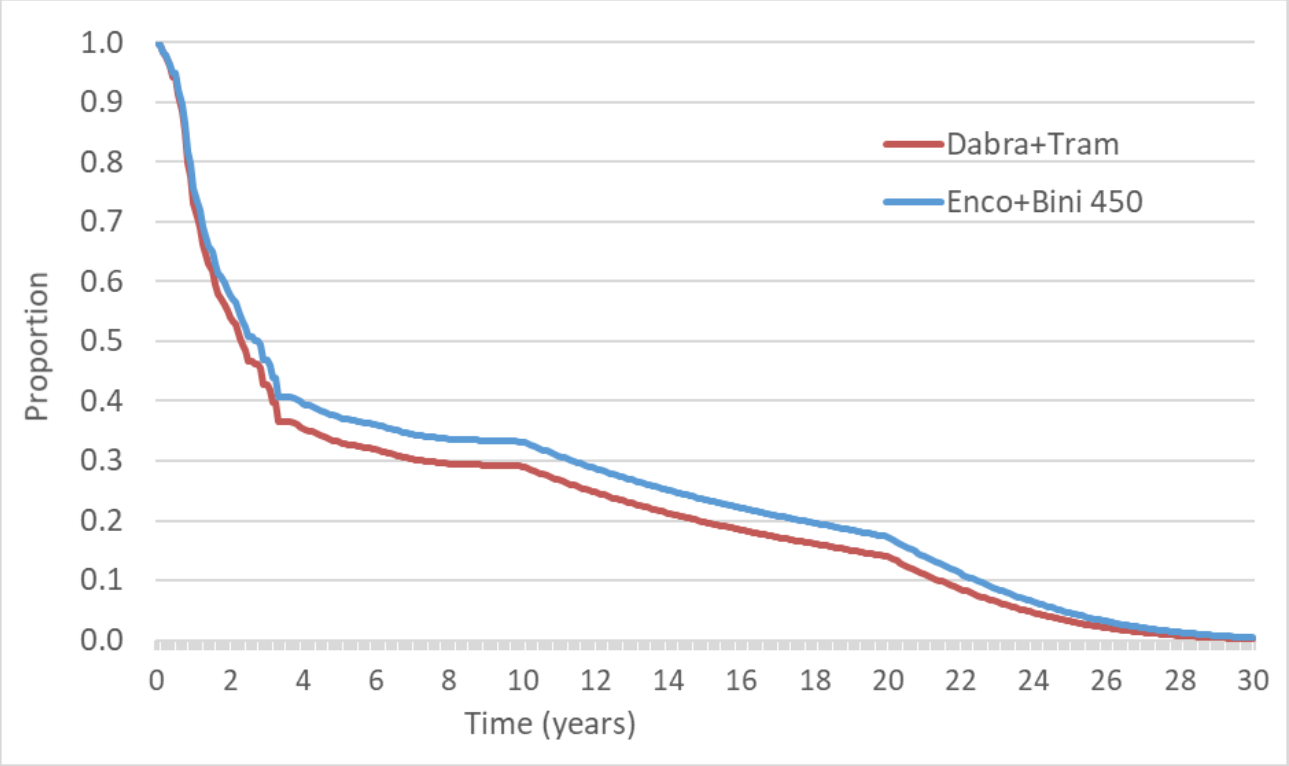


Abbreviations: PFS, progression-free survival.

- **OS**
  - Enco+Bini 450: COLUMBUS K-M OS data until available + American Joint Committee on Cancer (AJCC) data adjusted to account for the availability of newer treatments + general population mortality uplifted by increased risk of death in advanced melanoma patients.
  - Dabra+Tram: numerical estimate of HR vs Enco+Bini 450 derived from the NMA (FE model, no stratification) and applied to the entire Enco+Bini 450 survival curve.

A graphical representation of the base-case OS projections over the time horizon of the model for Enco+Bini 450 and Dabra+Tram is presented in Figure 19.

Figure 19: Base-case OS projections for Enco+Bini 450 and Dabra+Tram

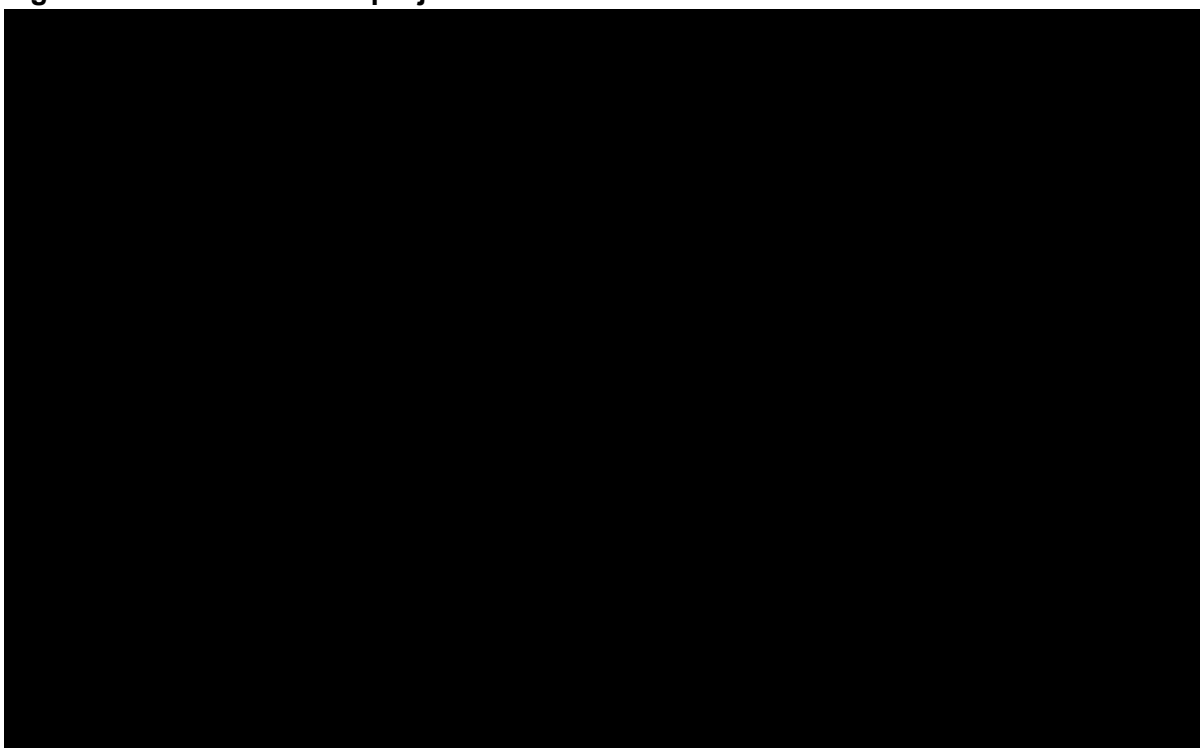


Abbreviations: OS, overall survival.

- **TTD**
  - Enco+Bini 450: COLUMBUS K-M TTD data until available (post-hoc analysis on TTD censoring death and “lost to follow up” [LFU]) + log-logistic parametric extrapolation.
  - Dabra+Tram: parity with Enco+Bini 450.

A graphical representation of the base-case TTD projections over 30 years for Enco+Bini 450 and Dabra+Tram is presented in Figure 20.

Figure 20: Base-case TTD projections for Enco+Bini 450 and Dabra+Tram



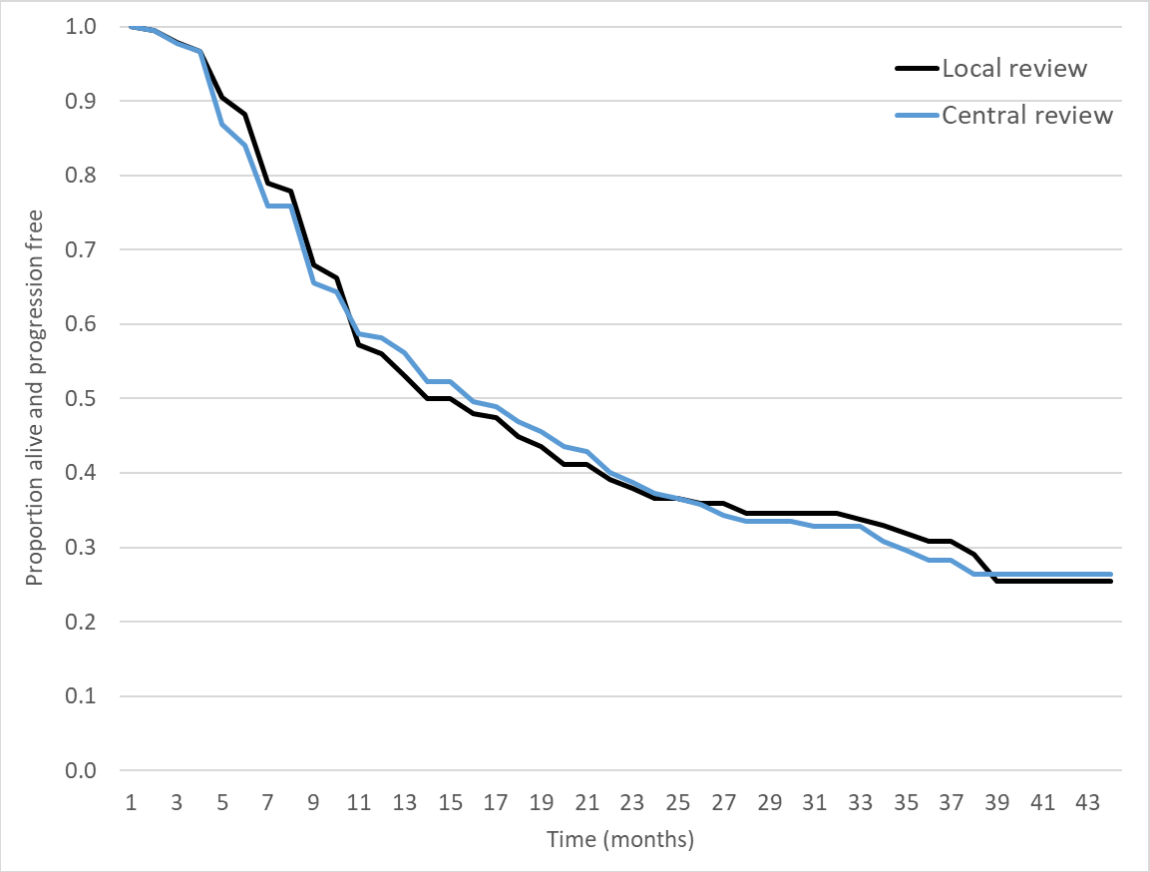
Abbreviations: TTD, time to treatment discontinuation.
Line for Dabra+Tram is the same as for Enco+Bini 450 assuming equivalence on TTD.

B.3.3.1.2 PFS, OS and TTD during trial period

B.3.3.1.2.1 PFS and OS

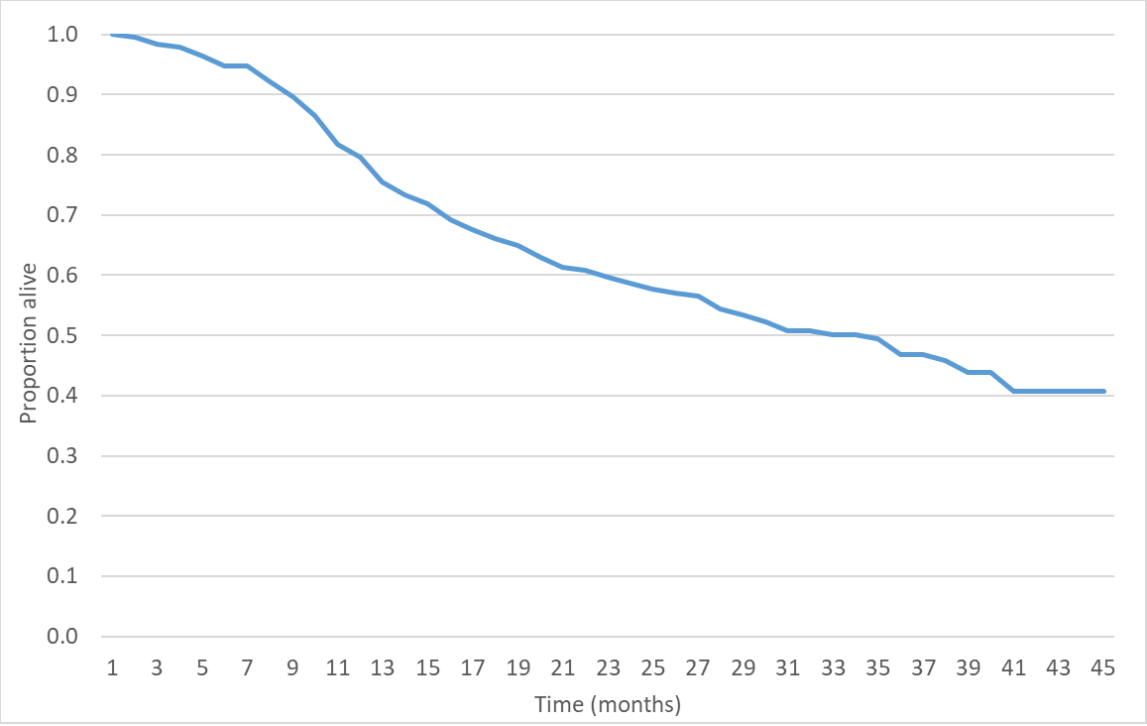
PFS and OS survival curves for Enco+Bini 450 were generated using patient level data from the latest data cut-off from the COLUMBUS trial (7 November 2017; See Section B.2.3.1 for further details) (Figure 21 and Figure 22). Since all other BRAFi targeted comparator therapies included in the NMA reported PFS from study investigator assessment, PFS failure times from the local review were used in the base-case analysis for comparative purposes. A PFS analysis comparing Enco+Bini 450 with Dabra+Tram via central independent review of progression was not feasible and hence was not considered further for inclusion in the model (See Section B.2.9.2.2 and B.2.9.3.2 for further details)

Figure 21: K-M curves for PFS by central and local review for Enco+Bini 450



Abbreviations: K-M, Kaplan-Meier; PFS, progression-free survival.

Figure 22: K-M curve for OS for Enco+Bini 450



Abbreviations: K-M, Kaplan-Meier; OS, overall survival.

B.3.3.1.2.2 TTD

Post-hoc analysis of COLUMBUS patient level data (38) was run to obtain TTD K-M data for Enco+Bini 450 (Figure 23). Two different definitions of discontinuation were used, namely:

- 1) discontinuation due to any reason and
- 2) discontinuation censoring on death and loss to follow up (LFU), which does not consider death and LFU as treatment discontinuation events.

Figure 23: K-M curves for TTD (by two definitions: any reason, censoring death and LFU) for Enco+Bini 450

Abbreviations: K-M, Kaplan-Meier; LFU, lost to follow up; TTD, time to treatment discontinuation.

TTD censoring death and LFU was used in the base-case to avoid double counting of deaths. As deaths are already captured as an event within PFS, they should not also be captured as discontinuation events. The TTD approach which censors on death and LFU also allows the model to capture the proportion of the cohort remaining on primary treatment, both pre-and post-progression. The impact of using TTD due to any reason was tested in a scenario analysis.

B.3.3.1.3 PFS, OS and TTD beyond trial period

K-M data are limited to the time of the trial for PFS, OS and TTD, and therefore to estimate the long-term effect associated with Enco+Bini 450, it was necessary to extrapolate beyond trial follow-up. Long-term extrapolations are highly sensitive to the parametric distributions applied and goodness of fit during the trial period may not always be informative with respect to the accuracy of curve projections beyond the follow-up period (102). To mitigate such concern, several extrapolation approaches were explored, and the extrapolated curves were validated by the clinical and health economic experts (See Section B.3.10). Two different approaches were explored:

1. Parametric extrapolation
2. Constant hazard

It should also be noted that K-M data are used where available and where the data is considered robust in order to fully utilise the data available from the trial. This approach is preferred over a fully parametric approach, for example, where the parametric distribution is used for the entirety of the model time horizon. In TA396 the ERG commented that “unless there are compelling reasons not to use all of the data available from a trial, it is preferable to incorporate the trial evidence as it is rather than extrapolate over the period for which data are available.”

1. Parametric extrapolation approach: The first approach involves fitting parametric survival models to the patient level data from COLUMBUS. Distributional parameters which created the closest possible survival curve to the observed K-M data were estimated for six different parametric distributions; Weibull, Exponential, Log-logistic, Log-normal, Gamma and Gompertz. Distributional parameters were used to inform the scale and shape of the extrapolated survival curves. The following formulas were used to derive parametric curves for PFS, OS and TTD. Each formula contains distributional parameters (constants) and a time variable (t):

- Weibull: =EXP(-λ*t ^ ρ)
- Exponential: =EXP(-λ*t)
- Log-logistic: =1/(1+ μ*t ^ σ)
- Log-Normal: =1-NORM.S.DIST((LN(t) - μ)/σ,TRUE)
- Gamma:
  - =GAMMA.DIST((1/ κ ^2)*(EXP(-β)*t)^(κ/σ),1/κ ^2,1,TRUE) if k<0
  - =1-GAMMA.DIST((1/ κ ^2)*(EXP(-β)*t)^(κ/σ),1/κ ^2,1,TRUE) if k>0

- Gompertz: =EXP(-(b/a)*(EXP(a*t)-1))

For each curve, the parametric model with best fit was assessed using Akaike's Information Criterion (AIC) and the Bayesian Information Criteria (BIC) where the best fitting distribution returns the lowest corresponding AIC and BIC. Visual inspection of the projected curve was also performed.

2. Constant hazard approach: An alternative approach to parametric models for long-term projection of survival data is the constant hazard approach. This method consists of identifying the point in time along the K-M curve beyond which a long-term linear trend in the hazard is observed. The hazard rate at the breakpoint is then applied as a constant for the remainder of the projection. The breakpoints were identified following visual inspection of the cumulative hazard plots from the K-M functions and by fitting a linear curve to the cumulative hazard plots and observing at which breakpoint the R^2 was maximum.

Both approaches were validated with the UK-based clinical expert in order to determine the most appropriate approach to be selected for the base-case.

The analyses are described in more detail in the following sections:

- PFS: Section B.3.3.1.3.1.
- TTD: Section B.3.3.1.3.3.
- OS: For OS, neither the constant hazard, nor the parametric extrapolation approach was used. Instead, in the base-case analysis, OS data from COLUMBUS was combined with AJCC mortality data and general population mortality to obtain a clinically plausible projection of survival in the long-run. This approach is described in greater detail in Section B.3.3.1.3.2 and the resulting curve was validated by the clinical expert for clinical plausibility (See Section B.3.10).

B.3.3.1.3.1 PFS

Both the parametric extrapolation approach and the constant hazard approach were explored for the long-term extrapolation of PFS. In the base-case, K-M data followed by the Gamma extrapolation was used.

When comparing the constant hazard approach and the parametric extrapolation approach, it was deemed that the parametric extrapolation approach provided the most clinically plausible outcome. The parametric extrapolation using Gamma

showed that the hazard rates continue to decrease over time and therefore the PFS data for Enco+Bini 450 remains positive in the long-run (i.e. around 10% of patients remain progression-free after 10 years). It could potentially be argued from a clinical point of view that this is overly optimistic, particularly as the baseline cohort have advanced disease status. However, expert opinion (See Section B.3.10) validated this approach, confirming that there would be a small proportion of patients who would remain progression free over the long-run, particularly with the availability of new treatments. Furthermore, application of the HR for PFS from the NMA for Dabra+Tram to this K-M + Gamma curve generates an estimate of PFS for Dabra+Tram at 10 years of around 5%. When comparing with a 5-year PFS of 13% from the BRF113220 study Part C (52), the longest trial-based data available, this would appear to be clinically plausible.

In contrast, the constant hazard approach assumes that the observed PFS benefit associated with treatment continues after the trial period (linear trend) and has been used previously as the extrapolation method in the NICE appraisal of Dabra+Tram for the treatment of unresectable or advanced BRAF positive mutations melanoma (17). However, this method generates 10-year estimates of PFS for Enco+Bini 450 that are approaching zero (~1%) and the clinical expert believed that the estimates from the constant hazard approach may be too pessimistic. As such, the option to use constant hazard (for both PFS and TTD) was explored in a scenario analysis (See Section B.3.8.3).

The parametric approach is described in full below, and the constant hazard approach is described in Appendix M.

Parametric extrapolation approach

The distributional parameters used to derive long-term projection of PFS (based on local review) are presented in Table 36. Table 37 shows the AIC and BIC values indicating that Gamma was the best-fitting for Enco+Bini 450 (i.e. lowest value for AIC and BIC). Visual inspection was also performed (Figure 24).

Table 36: Distributional parameters to inform the extrapolated parametric PFS curves for Enco+Bini 450

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
Parameter 1[1]	1.0405	1.0000	1.4456	1.1513	1.1714	-0.0208
Parameter 2[2]	0.0336	0.0381	0.0184	2.8049	-0.8755	0.0491

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
Parameter 3[3]	N/A	N/A	N/A	N/A	2.3719	N/A

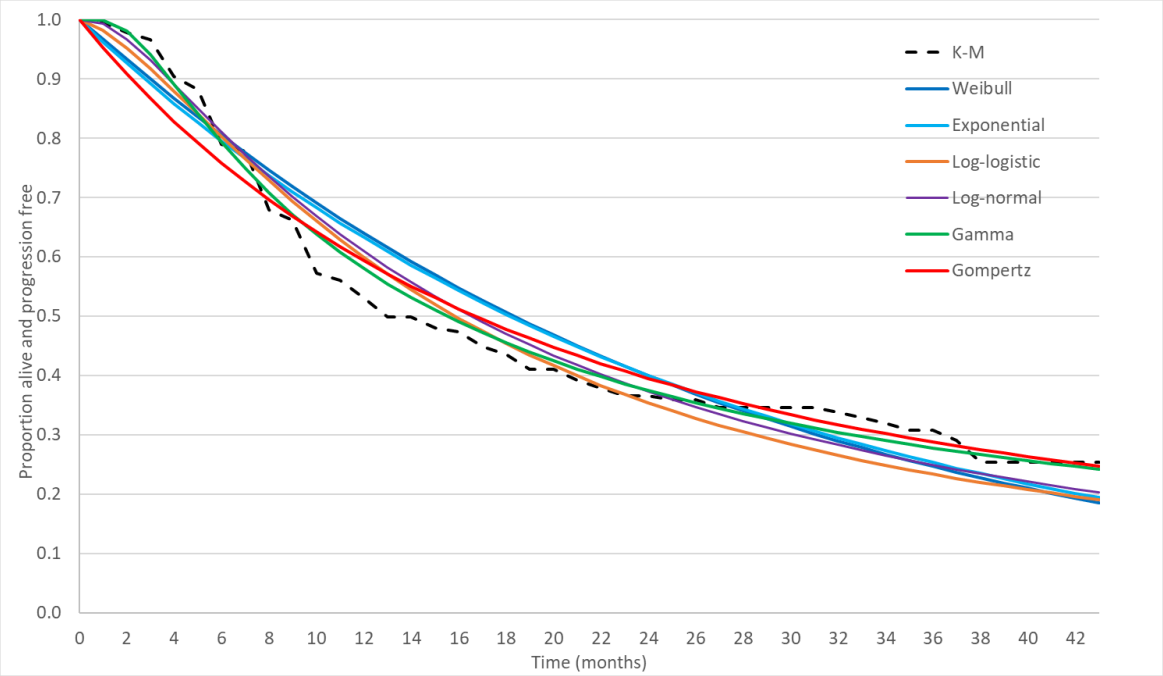
[1] ro (ρ) for Weibull and Exponential, sigma (σ) for Log-logistic, Log-normal and Gamma; [2] lambda(λ) for Weibull and Exponential, mu (μ) for Log-logistic, Log-normal, kappa (κ) for Gamma; [3] beta (β) for Gamma

Table 37: Measures of goodness of fit for PFS parametric models for Enco+Bini 450

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
AIC	1002.104	1000.370	982.863	977.272	**970.965**	997.524
BIC	1008.619	1003.628	989.378	983.787	**980.737**	1004.039

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
In bold: best-fitting parametric distribution

Figure 24: Visual inspection of parametric extrapolation of PFS by local review for Enco+Bini 450



Abbreviations: K-M, Kaplan-Meier; PFS, progression-free survival.

B.3.3.1.3.2 OS

When projecting long-term OS, there can be important limitations associated with the parametric or constant hazard approaches and these have been previously criticised by the ERGs reviewing NICE appraisals on advanced or metastatic melanoma (16-18). The main limitation in the context of the PartSA approach is that the OS extrapolation often reflects the within-trial trend in the rate of deaths, meaning that the increasing hazard of death continues throughout the extrapolation period but in

reality this may not be expected to occur over the long-run (90). Once all, or most patients have progressed, the hazard rate of death is expected to plateau. Therefore, the overestimation of the hazard of death in the extrapolation period may result in an underestimation of survival. The constant hazard method has similar limitations in that the constant hazard assumptions for long-term OS projections may also result in an implausible underestimation of OS. Furthermore, by applying a constant hazard independently to each arm, it is assumed that the impact of treatment on OS is maintained even when patients switch to other treatments post-progression. This may be considered a strong assumption given that new available treatments in unresectable or metastatic melanoma have shown to have important positive effects on mortality (64).

To address the extrapolation challenges highlighted above, an alternative three-part approach to modelling the base-case long-term OS was taken:

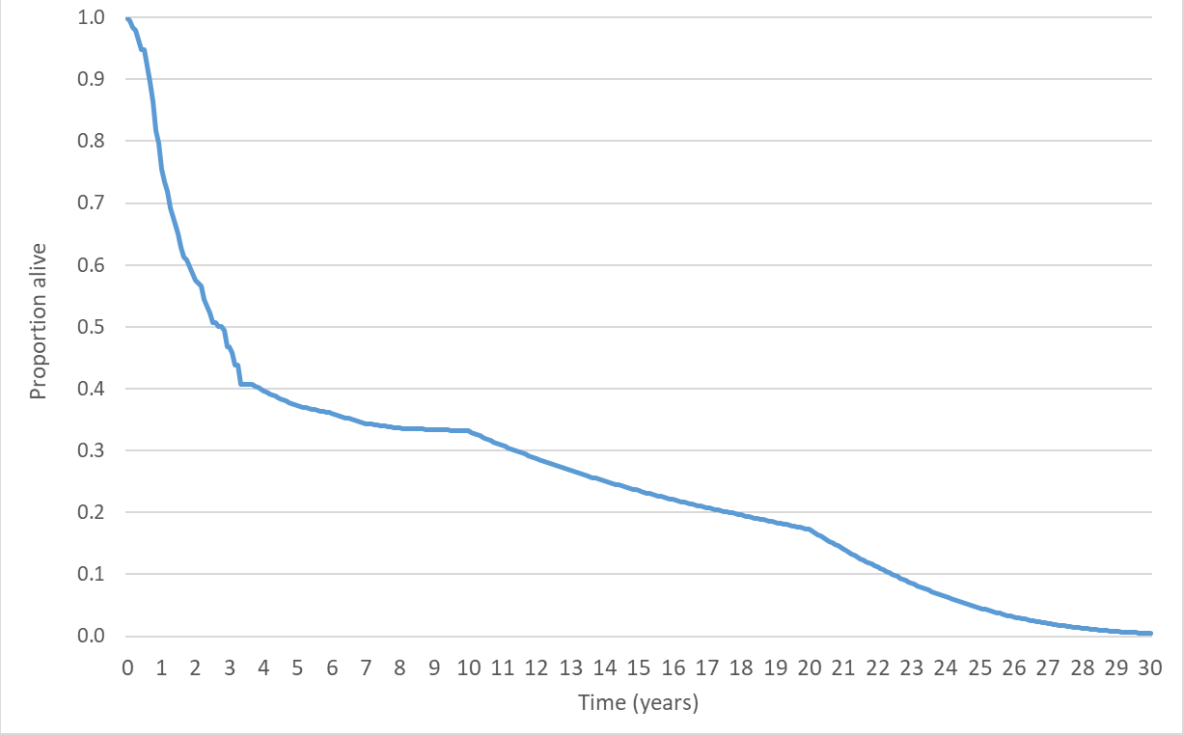
1. Trial period: Use of OS K-M data from COLUMBUS until available, with no extrapolation during this period (Figure 22).
2. End of trial period to Year 20:
    a. Use of mortality hazard rates from the AJCC melanoma registry data from the end of the trial follow-up period to year 20 (9). AJCC OS curves are published up to 20 years in advanced melanoma and for up to 10 years in metastatic melanoma (stage IV); therefore, OS curves for metastatic melanoma were extrapolated beyond 10 years based on a constant hazard assumption.
    b. Based on expert clinical opinion, a HR of 0.42 approximated from the Checkmate 066 study of nivolumab versus dacarbazine (103) was also applied to adjust for the availability of newer, more effective treatments since the AJCC registry reported (data collected through 2008).
    c. Further details are provided in Appendix N.
3. Year 20 to 30: Population mortality adjusted by a multiplier (HR=2.2) for patients with melanoma.
    a. Further details are provided in Appendix N.

This approach was recommended by the ERG to extrapolate long-term OS in NICE TA396 for Dabra+Tram (97), and further validated by clinical expert opinion.

Base-case OS projection

Figure 25 shows the resulting long-term survival projections for Enco+Bini 450 used in base-case analysis.

Figure 25: Base-case OS projections for Enco+Bini 450 over the model time horizon: K-M + case-mix adjusted AJCC mortality rate corrected for effect of new therapies + life-tables mortality uplifted by increased risk of death in melanoma



Abbreviations: AJCC, American Joint Committee on Cancer; K-M, Kaplan-Meier; OS, overall survival.

Details of the parametric extrapolation approach explored are described in Appendix O for information.

B.3.3.1.3.3 TTD

Similarly to PFS, two extrapolation methods were explored to project TTD over the time-horizon of the model. Long-term projection of TTD based on K-M data for Enco+Bini 450 from COLUMBUS and parametric extrapolation showed a plateau at very small proportions of patients (Figure 26 and Figure 27), whereas TTD curves extrapolated with the constant hazard approach decreased steadily to 0 (Appendix P). At 10 years, the percentage of patients estimated to remain on treatment is 5.17% and 1.62% using the parametric and the constant hazard approaches, respectively.

Following clinical expert opinion (See methods in Section B.3.10) it was deemed that the parametric approach (using KM + Log-logistic) was the most appropriate. In the

base-case PFS extrapolation (using KM + Gamma) it was predicted that approximately 10% of patients in the Enco+Bini 450 arm remain progression-free at 10 years. The clinical expert stated that it would be assumed that these patients would still be on primary treatment unless experiencing tolerability or toxicity issues and therefore the KM + Log-logistic approach (with 5.17% of patients remaining on treatment at 10 years) would be more clinically plausible than the constant hazard approach (where 1.62% of patients remain on treatment). In addition, using the parametric approach for TTD is in line with the approach used for PFS and is therefore consistent.

A scenario analysis was explored where the constant hazard approach was used for both PFS and TTD.

Parametric extrapolation approach

K-M data using TTD censoring death and LFU (as described in Section B.3.3.1.2.2), combined with the log-logistic extrapolation were used to project long-term TTD in the base-case analysis. The distributional parameters used to derive the long-term projection of TTD based on censoring death and LFU, are presented in Table 38. Table 39 shows the AIC and BIC values indicating that log-logistic was the best-fitting distribution t (i.e. lowest value for AIC and BIC). In addition, visual inspection was performed (Figure 26).

TTD projections based on discontinuation due to any reason are provided in Table 40, Table 41 and Figure 27 and is explored in scenario analysis.

Table 38: Distributional parameters to inform the extrapolated parametric TTD curves (based on censoring death and LFU)

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
Parameter 1[1]	1.00551	1	1.39665	1.27700	1.20197	-0.015897
Parameter 2[2]	0.04060	0.04131	0.02290	2.71680	0.26968	0.050761
Parameter 3[3]	N/A	N/A	N/A	N/A	2.85120	N/A

Abbreviations: LFU, lost to follow up; N/A, not applicable; TTD, time to treatment discontinuation.
[1] ro (ρ) for Weibull and Exponential, sigma (σ) for Log-logistic, Log-normal and Gamma; [2] lambda (λ) for Weibull and Exponential, mu (μ) for Log-logistic, Log-normal, kappa (κ) for Gamma; [3] beta (β) for Gamma

Table 39: Measure of goodness of fit for TTD parametric models (based on censoring death and LFU)

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
AIC	1176.275	1174.281	**1162.822**	1168.582	1169.135	1172.547

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
BIC	1182.790	1177.539	**1169.337**	1175.097	1178.908	1179.062

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; LFU, lost to follow up; N/A, not applicable; TTD, time to treatment discontinuation.
In bold: best-fitting parametric distribution.

Figure 26: Visual inspection of parametric extrapolation of TTD censoring death and LFU for Enco+Bini 450

Abbreviations: K-M, Kaplan-Meier; LFU, lost to follow up; TTD, time to treatment discontinuation.

Table 40: Distributional parameters to inform the extrapolated parametric TTD curves (discontinuation for any reason)

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
TTD any reason						
Parameter 1[1]	0.98982	1	1.39413	1.27598	1.21036	-0.0173
Parameter 2[2]	0.04540	0.04396	0.02550	2.64014	0.25571	0.0549
Parameter 3[3]	N/A	N/A	N/A	N/A	2.77160	N/A

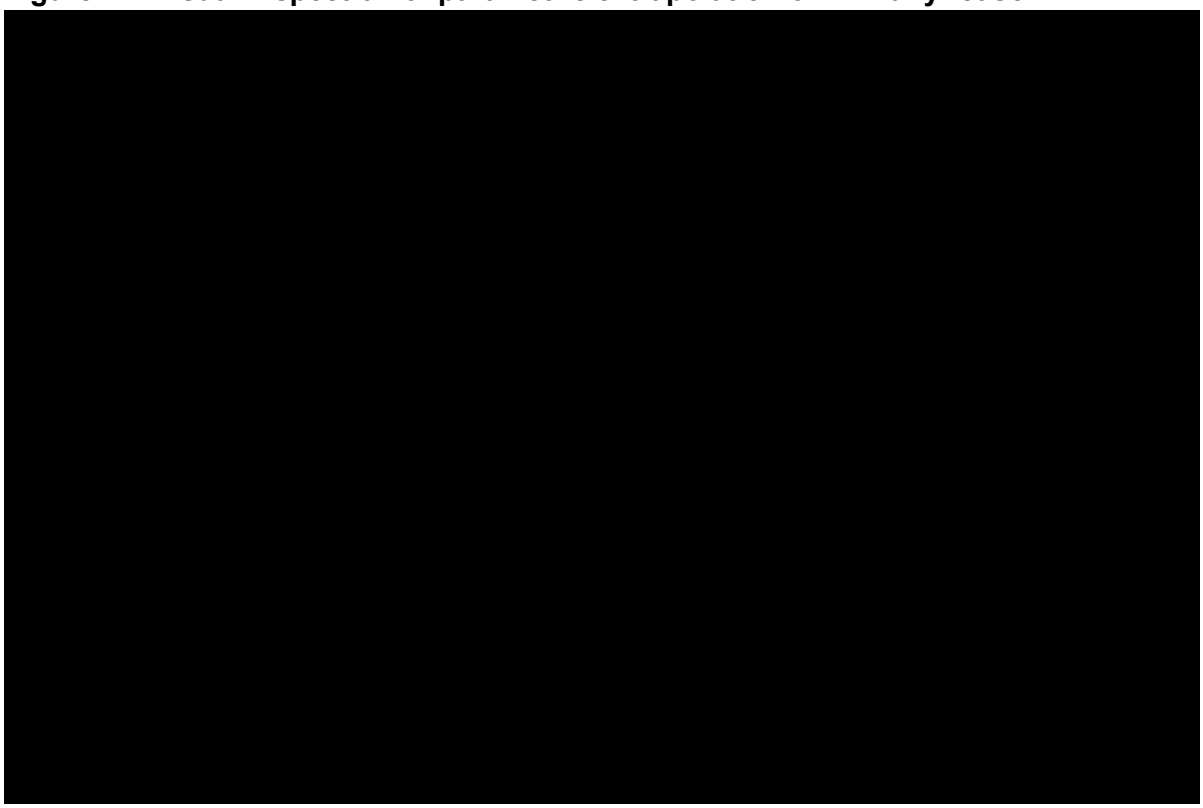
Abbreviations: N/A, not applicable; TTD, time to treatment discontinuation.
[1] ro (ρ) for Weibull and Exponential, sigma (σ) for Log-logistic, Log-normal and Gamma; [2] lambda (λ) for Weibull and Exponential, mu (μ) for Log-logistic, Log-normal, kappa (κ) for Gamma; [3] beta (β) for Gamma

Table 41: Measure of goodness of fit for TTD parametric models (discontinuation for any reason)

	Weibull	Exponential	Log-logistic	Log-normal	Gamma	Gompertz
AIC	1233.053	1231.076	**1218.738**	1224.519	1225.172	1228.420
BIC	1239.568	1234.333	**1225.253**	1231.034	1234.944	1234.935

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; N/A, not applicable; TTD, time to treatment discontinuation.
In bold: best-fitting parametric distribution

Figure 27: Visual inspection of parametric extrapolation of TTD any reason



Abbreviations: K-M, Kaplan-Meier; TTD, time to treatment discontinuation.

B.3.3.2 Adverse events

Adverse events (AEs) are applied in the model as one-off costs and do not belong to any health state. QoL decrements due to AEs are taken into account within utility values estimated for COLUMBUS patients (Section B.3.4) and therefore no additional AE disutilities are included in the model.

The model incorporates AEs likely to have a notable impact on costs, namely those of Grade 3 and 4 with an incidence of at least 5% in either the Enco+Bini 450 arm of COLUMBUS, or the Dabra+Tram arms of COMBI-v and COMBI-d. For Dabra+Tram, the weighted average of the incidence rates from COMBI-v and COMBI-d are used,

using data from the latest available data cut-offs. The adverse events included were hypertension, pyrexia, elevated blood creatinine kinase (CK), elevated gamma-glutamyltransferase (GGT) and elevated alanine aminotransferase (ALT) (Table 42).

Although there are limitations associated with modelling AE incidence rates from a naïve comparison of COLUMBUS, COMBI-v and COMBI-d, it allows for differences in specific AE rates to be captured. In contrast, if the OR from the NMA is used, a numerial benefit would be assumed for Dabra+Tram vs Enco+Bini 450 for all AEs included and this is not reflective of what is observed within the individual trials. In addition, the base case approach allows all relevant AEs from COMBI-d and COMBI-v to be included as well as those from COLUMBUS.

A scenario analysis was also included where AE rates were assumed to be equal for Enco+Bini 450 and Dabra+Tram (this scenario considered all effectiveness to be equal including OS, PFS and utilities, based on results of the NMA which generated results where the CrI always crossed the boundary of equivalence).

Table 42: Grade 3/4 AEs incidence from COLUMBUS, COMBI-v and COMBI-d (AEs ≥ 5% in either treatment)

Grade 3/4 AEs	Enco+Bini 450	Dabra+Tram		
	COLUMBUS Nov 2016 cut-off	COMBI-v March 2015 cut-off N=350†	COMBI -d 15 Feb 2016 cut-off N=209†	COMBI-d/ COMBI-v weighted average
	See Section B.2.10.1	NICE TA396 (96)	LONG 2017 Supp (50)	Calculated
Hypertension	[redacted]	15.4% (54)	5.7% (12)	11.8%
Pyrexia	[redacted]	4.6% (16)	6.7% (14)	5.4%
Blood CK increased	[redacted]	NR (set to 0%)	NR (set to 0%)	0.0%
GGT increased	[redacted]	5.4% (19)	NR (set to 0%)	3.4%
ALT increased	[redacted]	2.6% (9)	2.4% (5)	2.5%

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CK, creatine phosphokinase; GGT, gamma-glutamyl transferase.
† N numbers provided to enable calculation of weighted averages.

B.3.3.3 Incorporation of clinical data for Dabra+Tram

No direct comparative efficacy and safety data are available for Enco+Bini 450 versus Dabra+Tram and therefore an NMA was conducted to elicit estimates of relative treatment efficacy for PFS and OS (See Section B.2.9 for full details).

Since PFS and OS patient level data from the comparators' trials are not publicly available, it was not possible to derive K-M data points. Hence, a PH scale was used for PFS and OS outcomes, after testing that the PH assumption holds.

For base-case analyses, PFS and OS HRs versus Enco+Bini 450 were estimated via NMA networks based on PFS data by local review and OS unadjusted for crossover. A scenario was conducted based on OS adjusted for crossover, as described in Section B.2.9.

All analyses used numerical estimates of HRs even though CrIs crossed one (Table 43). Uncertainty was then considered in the probabilistic sensitivity analysis (PSA). Nevertheless, a scenario was also explored where equivalence was assumed (HR = 1).

Table 43: Estimates of comparative PFS and OS for Dabra+Tram vs Enco+Bini 450 utilised

Outcome	HR vs Enco+Bini 450	95% CrI
PFS	1.30	0.96, 1.77
OS, no crossover adjustment	1.12	0.81, 1.53
OS, crossover adjustment	1.11	0.75, 1.65

Abbreviations: CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

It was not possible to run an NMA on TTD, since none of the comparators' trials assessed for inclusion in the evidence network included TTD as a trial endpoint and the definition of exposure to treatment differed widely between trials.

In the absence of comparative data via an NMA, parity was assumed between Dabra+Tram and Enco+Bini 450. When comparing the median times of dose exposure within the COLUMBUS and COMBI-v/d trials, these were very similar between the two treatments (11.8 months for Enco+Bini 450 and 12.2 and 11.8 for Dabra+Tram in COMBI-v and COMBI-d, respectively (49, 50)).

Clinical expert opinion confirmed that it would be reasonable to assume that the time on treatment for Dabra+Tram and Enco+Bini 450 would be equivalent based on the median time of exposure results.

Further, this assumption is deemed to be plausible based on information available from the ERG review of TA396 (97) which suggests that the TTD curve lies above the PFS curve for Dabra+Tram (the ERG commented that a substantial proportion of

patients in the Dabra+Tram trials remained on primary treatment beyond progression). For Enco+Bini 450 however, it is shown in Figure 28 that the TTD curve is offset below the PFS curve. Figure 28 shows TTD and PFS curves assuming TTD is equivalent for Enco+Bini 450 and Dabra+Tram with the TTD curve lying below the Enco+Bini 450 PFS curve but above the Dabra+Tram PFS curve.

In TA396 the ERG reported that patients still on treatment in COMBI-v at 28 months was 29.1% and in COMBI-d at 29 months was 29.4% (97); at 28 months in COLUMBUS, 28.1% of patients were on treatment based on the TTD curve. This provides further support for assuming TTD is equivalent (HR = 1).

Scenario analyses are also presented for HRs of 0.9 and 1.1 (a variation of +/-10% from the base-case), where HR>1 represents a shorter time on treatment for Dabra+Tram versus Enco+Bini 450. A HR of 1.1 for TTD for Dabra+Tram versus Enco+Bini 450 was considered to be the upper limit of clinically plausibility following clinical expert input. When using a HR of 1.1, the difference in time on treatment predicted in the model between Enco+Bini 450 and Dabra+Tram is 4.47 months and it was felt that a difference longer than this was not likely to be clinically plausible.

Figure 28: TTD and PFS comparison

Abbreviations: PFS, progression-free survival; TTD, time to treatment discontinuation

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-5L was used to measure the QoL of patients in the COLUMBUS trial from which utility values can be derived:

- Data were collected using this questionnaire and then mapped to EQ-5D-3L within trial based on the UK valuation set, as described in Section B.2.4.3.3.
- This represents NICE's preference as per the NICE reference case.

A post-hoc analysis of COLUMBUS data (37) was conducted to derive utility scores pre-progression and ≥30 days post-progression, and a disutility at disease progression for inclusion in the economic model. The results were obtained from a generalized estimate equation (GEE) repeated measures model, including terms for the stratification factors (ECOG performance status, AJCC cancer stage), visit, progression status (pre-DP, on-DP, post-DP) and treatment (on vs. off any antineoplastic treatment).

B.3.4.2 Mapping

Not applicable. EQ-5D data used in modelling were derived from the COLUMBUS trial and were already mapped to the three-level valuation set (See Section B.2.4.3.3). Data for Dabra+Tram, derived from the COMBI-v trial and utilised in the NMA (See Section B.2.9), were collected using the three-level questionnaire and hence did not require mapping (65).

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify published evidence on the QoL of patients with unresectable or metastatic cutaneous melanoma. The main aim was to identify utility data from clinical trials of BRAFi (monotherapies or MEKi combinations), to facilitate an NMA comparison of Enco+Bini 450 with relevant comparators. The methodology of this SLR is described in Appendix H. Identified studies are described in Appendix D and were considered for inclusion in the NMA. Results from the NMA relating to utility data are described in Section B.2.9).

NMA analyses, conducted for pre-progression (difference in utility scores) and at Week 32 on treatment and at disease progression (differences in change from baseline) all elicited results for Enco+Bini 450 versus Dabra+Tram that numerically favoured Dabra+Tram, however the CrI for the delta crossed zero in all cases,

meaning that it crossed the line of equal effect. Furthermore the magnitude of the delta was less than the minimal clinically important difference for EQ-5D utility scores for all timepoints assessed (0.08 points (48)). The value of most relevance from a modelling perspective which could be applied to the pre-progression health state – the difference in pre-progression utility score – was 0.02 for Tram+Dabra (CrI -0.01 to 0.05).

Despite the limitations of the analysis (See Section B.2.9), it was deemed appropriate to include the difference in pre-progression utility scores between the two treatments in the base-case economic analysis, given that differences in clinical outcomes of OS and PFS derived from the NMA and in favour of Enco+Bini 450 were also numerical.

The incorporation of utilities into the model are described in Section B.3.4.5.

B.3.4.4 Adverse reactions

The utility values used in the model have been derived directly from data collected as part of COLUMBUS trial and, as such, they consider the negative QoL associated to any treatment related AEs. Hence, no further separate one-off disutility for AEs was included in the model.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The health-related quality of life (HRQoL) of the cohort over the time horizon of the model is considered by assigning a utility value to each health state and by applying a one-off decrement in HRQoL at progression and at end-of-life.

B.3.4.5.1 Utilities

Utility values pre-progression are assigned to the cohort in the PF health state and in the base-case are applied as treatment specific (Table 44) using the numerically different but not statistically different results from the NMA comparison described in Section B.2.9. A scenario is included where utilities in the PF health state for Enco+Bini 450 and Dabra+Tram are assumed to be equal.

The model also differentiates utility pre-progression between patients who are on or off any antineoplastic treatments. In the base-case, all patients receive subsequent treatment upon discontinuation and so this is only applicable in scenario analyses

where different options are explored for the way subsequent treatments are modelled (see section B.3.5.1.2).

Utility values for the PP health state, also obtained from the post-hoc analysis of COLUMBUS QoL data (37), are implemented as non-treatment specific (Table 44). The rationale behind this is that there is no evidence to justify a different subsequent treatment mix following progression and therefore it is expected that the QoL would also be equal. This approach is in line with the approach suggested by the ERG in the cost-effectiveness analysis of Dabra+Tram for TA396 (97); in addition, it maximizes the sample size for estimating a mean score, as per protocol, a limited number of patients completed EQ-5D ≥30 days post-progression.

Table 44: Health state utility values used in the model

	EQ5D	
	Average utility	**SE**
Progression free on antineoplastic tx		
Enco+Bini 450	0.78	0.02
Dabra+Tram*	0.80	N/A
Progression free off antineoplastic tx (scenario analysis only)		
All comparators	0.77	0.05
Post-progression		
All comparators	0.68	0.03

Abbreviations: EQ-5D, EuroQoL-5 dimensions; N/A, not applicable; sd, standard deviation; tx, treatment.
*Based on NMA (Section B.2.9.2.3).

B.3.4.5.2 Disutilities

A one-off disutility value was included in the model at progression to adjust for the QoL decrement typically associated with the worsening phase of the disease. This QoL decrement was derived from the post-hoc analysis of COLUMBUS data, by taking the difference between the average utility for progression-free patients and the average utility measured at progression (37). The disutility applied is -0.03.

Finally, QoL in the model was adjusted to reflect declining utility with age. A disutility for age was applied from the age of 65 years (-0.02) and a larger disutility (-0.05) from the age of 75 years (104) (Table 45). A scenario analysis is explored where the age-related utility decrement is excluded.

Table 45: Disutility associated with age

Age band	Disutility	Source
From year 65 to 74	-0.02	Kind 2009
From year 75 onwards	-0.05	Kind 2009

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The current analysis was developed with the aim of including costs that would closely represent the actual costs of treatment for the NHS and Personal Social Services in England.

In the current analysis, each health state is assigned relevant costs as follows:

- Progression free:
  - Cost of primary treatment (intervention and comparators in the model), including one-off treatment initiation cost, drug cost and dispensing and administration cost.
  - Cost of subsequent treatments for the cohort switching to new antineoplastic treatment pre-progression, including drug cost and dispensing and administration cost.
  - Routine management cost during antineoplastic treatment.

- Post-progression:
  - Cost of disease progression phase (one-off).
  - Cost of primary treatment, including drug cost and dispensing and administration cost, for the cohort who continues to receive primary treatment post-progression.
  - Cost of subsequent treatments.
  - Routine management cost during antineoplastic treatment for the cohort receiving any antineoplastic treatment post-progression.
  - Cost of BSC.

In addition to health state costs, the model considers the costs of adverse events associated with primary treatment and the cost of terminal care at the end of life.

Primary treatment costs are applied to the patients for as long as they are on treatment, which in the base-case is determined directly by the TTD curve (as described in Section B.3.3.1). This means that patients may be receiving primary treatment in both the progression free and progressed health states. In the base-case, all patients are assumed to receive subsequent treatment upon discontinuation from primary treatment and this is applied as a one-off cost at the time of discontinuation.

Cost and resource use data were identified by systematic means, as part of a broader systematic review of the economic literature. Methods are presented in Appendix G (combined searches for cost-effectiveness and cost/resource use literature), with a summary of relevant studies providing cost and resource use data provided in Appendix I. In total, 43 studies were identified which reported cost or resource use data relating to the management of advanced or metastatic melanoma, of which 8 were conducted in the UK and considered to be relevant to clinical practice in England. Cost sources from the SLR were assessed for possible inclusion in the model. Specific cost sources and justification are provided in the subsequent subsections.

Unless stated otherwise all costs were inflated to 2017/18 in a two-step process. Firstly, costs were inflated to the 2016/17 price level using the latest Hospital & Community Health Service Index (93). Secondly, the 2016/2017 cost was inflated by 1.243% to 2017/18, where 1.243% was the average (geometric mean) inflation of the index between 2013/14 and 2016/17.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Primary treatments

Enco+Bini 450 and Dabra+Tram are implemented in the model in line with the dosing recommendations of their respective (anticipated) marketing authorisations. Dabra+Tram is included based on list price from the British National Formulary (94). Enco+Bini 450 is included based on the PAS price approved by the Department of Health (Table 46). A scenario analysis is also included where the list prices for both Enco+Bini 450 and Dabra+Tram are used. In addition, a threshold analysis was performed to identify the discount for Dabra+Tram which would lead to an ICER of £20,000 versus the PAS price for Enco+Bini 450.

Table 46: Primary treatments prices and dosing schedule

Regimen	Drug	Tablets per pack	Pack price (£)	Cost per tablet (£)	Daily dose (mg)	Cost per day (£)
Enco+Bini 450	Encorafenib (75 mg tablet)	42	[redacted] (PAS)	[redacted]	450	[redacted]
	Binimetinib (15 mg tablet)	84	[redacted] (PAS)	[redacted]	90	[redacted]
Dabra+Tram	Dabrafenib (Tafinlar) 75 mg capsule)	28	1,400.00 (List)	50	300	200
	Trametinib (Mekinist) (2 mg tablet)	7	1,120.00 (List)	160	2	160

Abbreviations: mg, milligram; PAS, patient access scheme.

The model includes relative dose intensity (RDI) multipliers to account for the proportion of patients who remain on primary treatment but with a dose reduction (Table 47). RDI is an estimate of the ratio between the actual cumulative dose (in mg) and the planned cumulative doses. The impact of not considering RDIs in the calculation of primary treatment costs is tested in a scenario analysis.

Table 47: Estimated RDIs for primary treatment in the model

Regimen	Drug	Medication RDI	Source
Enco+Bini 450	Encorafenib	[redacted]	Mean RDI from COLUMBUS Nov 2017 data cut-off (Section B.2.10.1)
	Binimetinib	[redacted]	Mean RDI from COLUMBUS Nov 2017 data cut-off (Section B.2.10.1)
Dabra+Tram	Trametinib	0.96	NICE TA 396 company submission (96)
	Dabrafenib	0.92	NICE TA 396 company submission (96)

Abbreviations: CSR, clinical study report; RDI, relative dose intensity; TA, technology appraisal.

The total dose per drug cycle of 28 days was calculated by multiplying the total daily dose (corrected for RDI) by the number of days in the drug cycle and then rounding up to the nearest whole tablet. A dispending cost was assumed to be associated with each prescription administered for each drug cycle; each component of combination treatments was assumed to be prescribed at the same time incurring a single dispensing cost. The dispensing cost was based on 12 minutes of hospital pharmacist time, reported to be £13.60 (2015 cost-year) in the company submission for TA396 (96). This was inflated to £14.01 to reflect 2017/18 prices, as described in Section B.3.5.

Therapy costs adjusted to cost per model cycle (= 30.42 days) are displayed in Table 48.

Table 48: Primary treatment costs per model cycle*

Intervention	Total daily dose (mg)	Total daily dose based on RDI (mg)	Drug cost per model cycle based on RDI (£)	Total cost per model cycle including admin cost (£)
Encorafenib	450	[redacted]	[redacted]	[redacted]
Binimetinib	90	[redacted]	[redacted]	[redacted]
Enco+Bini 450			[redacted]	[redacted]
Dabrafenib	300	276.00	5,648.81	5,664.03
Trametinib	2	1.92	4,692.86	4,708.08
Dabra+Tram			**10,341.67**	**10,356.89**

Abbreviations: mg, milligram; RDI, relative dose intensity
*Model cycle = 30.42 days

A one-off cost of treatment initiation of £415.89 was applied once in the first cycle of the simulation. The initiation cost includes visits and examinations which are standard practice before a therapy is started and was inflated from the cost quoted in TA268 for ipilimumab (£365, cost year 2009/10; (95)) and subsequently used in TA396 for Dabra+Tram (96).

B.3.5.1.2 Subsequent treatments

B.3.5.1.2.1 Approach to modelling subsequent treatments

In the base-case, subsequent treatment costs are applied to all patients at discontinuation (based on the TTD curve) as a one-off cost. Applying the cost as a one-off rather than spreading the cost over time is a limitation of the analysis but there is insufficient data available to simulate how the cost would be spread. However, this is unlikely to have a large impact on the ICER since the median duration of subsequent treatment is less than a year (derived from Delea 2015 (98)). The base-case approach for modelling subsequent treatment costs was the preferred approach by the ERG in TA396 (97).

Two alternative approaches were also considered and explored in scenario analyses. These approaches are summarised in Table 49 and apply costs as a one-off; as such these alternate approaches are therefore subject to the same limitation described above.

Table 49: Options for modelling subsequent treatment

Approach	Timing	Applied to which patients	Assumptions
1. Base-case	At discontinuation	All patients	
2. Scenario	At discontinuation	- Pre-progression: the proportion of patients pre-progression who receive subsequent treatment† - Post-progression: A proportion of patients post-progression receive BSC only‡	Assumes that some patients will never receive subsequent treatment
3. Scenario	At discontinuation pre-progression or at progression	- Pre-progression: the proportion of patients pre-progression who receive subsequent treatment (as per approach 2)† - Post-progression: all patients apart from those who receive BSC only‡	Assumes that all patients eventually receive subsequent treatment (apart from those who receive BSC only)

†The percentage of patients switching to new antineoplastic treatment pre-progression was [redacted], based on a post-hoc analysis of COLUMBUS data at the 7 November 2017 data cut-off (38). Patients treated with Enco+Bini 450 and Dabra+Tram were assumed to be treated the same.
‡The percentage of patients not receiving any further antineoplastic treatment post-progression was [redacted], as derived from a post-hoc analysis of COLUMBUS data at the 7 November 2017 data cut-off (38), which is in line with the 40% suggested by the clinical expert.

B.3.5.1.2.2 Calculation of the costs of subsequent treatments

Subsequent treatment cost is implemented in the model based on the weighted average utilisation of subsequent treatments observed post-primary treatment. The same subsequent treatment distribution is applied at discontinuation pre- and post-progression. The distribution of subsequent antineoplastic treatment following discontinuation of primary treatment was obtained from a post-hoc analysis of COLUMBUS data (Table 50). In the base-case, the distribution in the Enco+Bini 450 arm of COLUMBUS was used to inform the percentages of patients receiving each subsequent treatment for both Enco+Bini 450 and Dabra+Tram. Assuming equivalence was a simplifying assumption, in the absence of clear data to show that subsequent treatments would be different between Enco+Bini 450 and Dabra+Tram and is consistent with the approach suggested by the ERG in NICE TA396 (97). In addition, a scenario analysis was run using the pooled results from the Enco+Bini 450 and vemurafenib monotherapy arms from COLUMBUS. In this scenario, we have taken account of the numerical differences observed in COLUMBUS between Enco+Bini 450 and vemurafenib.

Table 50: Subsequent treatments average utilisation derived from COLUMBUS†

	Enco+Bini 450 (utilised in base-case for Enco+Bini 450 and Dabra+Tram)	Vemurafenib	Enco+Bini 450 + vemurafenib (pooled; used in scenario analysis)
Ipilimumab	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]
Dabra+Tram	[redacted]	[redacted]	[redacted]
Ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]
Cobimetinib + vemurafenib	[redacted]	[redacted]	[redacted]
Immunotherapy + others	[redacted]	[redacted]	[redacted]
Bini+Enco 450	[redacted]	[redacted]	[redacted]
BRAFi + MEKi + others	[redacted]	[redacted]	[redacted]
Protein kinase inhibitors+ vemurafenib	[redacted]	[redacted]	[redacted]

Abbreviations: BRAFi, serine/threonine-protein kinase B-Raf; MEKi, mitogen-activated extracellular signal-regulated kinase.
Based on a post-hoc analysis of COLUMBUS assessing antineoplastic therapies received any time after last dose of study drug (37).

The expected cost of subsequent treatment was calculated by multiplying each estimated mean utilisation by the corresponding estimate of the cost of a single course of therapy and then taking the sum. The cost per course of therapy for each treatment included both the drug cost and the dispensing and administration cost (Table 51). Drug costs were obtained from the British National Formulary (94) and dosages are based on either published NICE appraisals, when available, or the respective SmPCs. Dacarbazine was used as representative for chemotherapies. For medications that are dosed based on weight or body surface area, these were obtained from the baseline characteristics of patients in COLUMBUS (See Section B.2.3.2). Due to insufficient data for all subsequent treatments included, RDIs for medication dose and administration were set to 100%.

In the base-case, the cost of wastage is considered, meaning that opened or partially used vials would not be shared and therefore the entire cost of the vial was included even if the dose administered was less than the entire vial. Exclusion of vial wastage was considered in a scenario analysis.

The cost of intravenous/subcutaneous administration was obtained from the latest published NHS Reference costs 2016-2017 (92) and corresponds to the tariff for 'Chemotherapy Outpatient (Procure Chemotherapy Drugs for Regimens in Band 1)' equal to £290 (92). As for primary treatment, a dispensing cost per cycle of £14.01 was applied for oral medications.

The expected cost per course of therapy for each subsequent treatment was calculated by combining estimates of mean duration (or max number of cycles) of treatment with the cost per month (Table 51). The mean duration of treatment for BRAFi targeted therapies (48.07 weeks) was based on mean PFS for vemurafenib in a previous cost-effectiveness study in BRAF-positive mutation unresectable melanoma (98). The same study was also used to obtain the mean duration of treatment of dacarbazine (23.55 weeks). For ipilimumab, duration was set to the maximum number of cycles defined in the SmPC (Every 3 weeks for 4 cycles (105)). For other immunotherapies mean duration was set to 28.86 weeks, corresponding to the mean value of PFS reported in the company submission for TA268 (ipilimumab in second line treatment of unresectable melanoma (95)) and used subsequently and accepted by the ERG in the company submission for TA396 for duration of subsequent treatment with immunotherapies (96, 97).

Table 51: Dosing schedules and costs for subsequent treatments

	Cost per mg (£)	Cost per unit* (£)	Total dose (mg) per day	Drug cost per day (£)	Frequency per drug cycle	Length of drug cycle (days)	Cost per mean duration including admin cost (£)
Encorafenib	[redacted]	[redacted]	450	[redacted]	28	28	[redacted]
Binimetinib	[redacted]	[redacted]	90	[redacted]	28	28	[redacted]
Vemurafenib	0.130	31.25	1,920	250.00	28	28	84,290.92
Dabrafenib	0.667	50.00	300	200.00	28	28	67,466.42
Trametinib	80.00	160.00	2	160.00	28	28	54,006.82
Cobimetinib	3.393	67.87	60	203.60	21	28	51,551.28
Protein kinase inhibitors (=trametinib)	80.00	160.00	2	160.00	28	28	54,006.82
Ipilimumab	75.00	3,750.00	241.29	18,750.00‡	1	21	76,160.00†
Nivolumab	10.975	439.00	241.29	3,073.00‡	1	14	48,528.09
Pembrolizumab	26.30	1,315.00	160.86	5,260.00‡	1	21	53,391.00
Dacarbazine	0.090	9.00	1,633.70	153.00‡	1	21	3,477.55
Nivolumab (when taken in combination with ipilimumab)							33,703.17**
Combination phase	10.975	439.00	80.43	1,317.00‡	1	21	5,268.00†,§
Monotherapy phase	As per nivolumab monotherapy						28,435.17§

Abbreviations: N/A, not applicable.
*Unit = tablet for orals or vial for infusions; †Cost based on max 4 cycles (105); ‡ wastage of leftover vial contents assumed (base-case); §Nivolumab, when taken in combination with ipilimumab, is taken in an initial combination phase every 3 weeks for 4 dosing cycles, followed by a monotherapy phase. For the monotherapy phase, drug cost per day is equivalent to nivolumab monotherapy, however it has been assumed that mean duration of treatment would be reduced by the length of the combination phase (i.e. 6.64 months [28.86 weeks] minus 2.75 months); **Total cost of nivolumab when taken with ipilimumab. Cost of ipilimumab when taken in this combination is the same as for ipilimumab monotherapy.

Since some of the subsequent treatments are combination therapies, the total costs per mean duration or maximum number of cycles were combined where relevant (Table 52). When the combination states 'other', the average of all mean treatments costs was used. The resulting weighted average cost of subsequent treatment, after primary treatment with Enco+Bini 450 or Dabra+Tram, for the base-case, was £65,353.99 (Table 52). In scenario analysis, where the pooled results from the Enco+Bini 450 and vemurafenib arms from COLUMBUS were used, the weighted average cost of subsequent treatment was £70,361.49.

Table 52: Subsequent treatments expected cost per course of therapy

	Total cost per mean duration (max number of cycles)	Weighted total subsequent tx cost (£)†
Ipilimumab	76,160.00	19,482.79
Pembrolizumab	53,391.00	11,588.74
Nivolumab	48,528.09	5,266.61
Chemotherapy	3,477.55	350.45
Dabrafenib	67,466.42	6,275.95
Dabra+Tram	121,473.24	5,649.92
Ipilimumab + nivolumab	109,863.17	5,109.91
Other	49,903.67	1,934.25
Vemurafenib	84,290.92	3,267.09
Cobimetinib + vemurafenib	135,842.20	4,212.16
Immunotherapy + others	95,292.83	2,216.11
Enco+Bini 450‡	[redacted]	0
BRAFi + MEKi + others‡	101,450.66	0
Protein kinase inhibitors + vemurafenib‡	138,297.74	0
Total weighted cost		**65,353.99**

Abbreviations: BRAFi, serine/threonine-protein kinase B-Raf; MEKi, mitogen-activated extracellular signal-regulated kinase; tx, treatment.
† Weighted by proportion of patients receiving each treatment, as per Table 50; ‡Used in scenario analysis only.

B.3.5.2 Health-state unit costs and resource use

Healthcare resource use in the management of melanoma (including medical consultations, home care, hospital visits, examinations, procedures and brain metastasis) was taken from a published study (99). Unit costs for each resource were obtained from official lists, such as NHS Reference Costs (92) and from published studies. Costs were inflated, where appropriate to 2017/18, as described in Section B.3.5. As per standard practice NHS Reference Costs were not inflated.

The resource use costs included in each health state of the model are presented in Table 53.

Table 53: Type of patient/disease management included per health state

Health state	Type of patient/disease management
Progression free	- Routine management during antineoplastic treatment
Post-progression	- Routine management during antineoplastic treatment - Management at progression - Routine management part of BSC

Abbreviations: BSC, best supportive care.

Resource use for routine management during antineoplastic treatment, disease management at progression and the routine management part of BSC was obtained from a study on healthcare resource use for melanoma conducted in Australia and 5 countries in Europe (including the UK) (McKendrick et al (99)) (Table 54); data were obtained through country-specific Delphi panels, comprising of healthcare professionals with experience in oncology. In addition, an extra medical oncologist consultation per month was added during antineoplastic treatment as suggested by the clinical expert involved in the validation of the model (See Section B.3.10).

Unit costs associated with each resource use are provided in Table 55.

Table 54: Resource use for management of disease during antineoplastic treatment, at progression and during BSC

	Routine management during antineoplastic treatment (per model cycle)	Management at progression (one-off)	Routine management part of BSC (per model cycle)
Medical consultations			
Medical oncologist consultation	1.00	1.00	0.67
Radiation oncologist consultation	0.03	0.10	0
Oncology nurse visit	0.60	0.00	0.20
GP consultation	0.33	0.00	0.53
Psychology specialist consultation	0.03	0.00	0.05
Surgeon consultation	0.02	0.05	0.20
Dermatologist consultation	0.00	0.00	0.02
BSC physician consultation	0.00	0.00	0.13

	Routine management during antineoplastic treatment (per model cycle)	Management at progression (one-off)	Routine management part of BSC (per model cycle)
Home care			
BSC physician/nurse visit	0.00	0.00	0.50
Home aid (non-medical specialist) visit	0.00	0.00	3.47
Hospital visits			
Inpatient stay (oncology/general ward)	0.25	0.20	0.33
Emergency department visit	0.03	0.00	0.05
Day hospital visit	0.25	0.00	0.13
Examinations			
Whole-body CT	0.33	0.00	0.00
Brain MRI	0.03	0.05	0.00
Brain CT-scan	0.00	0.05	0.00
Chest radiograph	0.03	0.05	0.00
PET-CT scan	0.02	0.00	0.00
Bone scan	0.02	0.00	0.00
Blood test (CBC, CMP)	1.00	0.00	0.00
Procedures			
Radiotherapy fraction	0.07	0.20	0.00
Surgical intervention	0.02	0.05	0.02
Limb perfusion	0.00	0.20	0.00
Limb infusion	0.00	0.00	0.00
Brain metastasis			
Whole-brain radiation	0.00	1.00	0.00
Stereotactic radiosurgery	0.00	0.20	0.00
Neurosurgery	0.00	0.10	0.00

Abbreviations: BSC, best supportive care; CBC, complete blood count; CMP, complete metabolic panel; CT, computed tomography; GP, general practitioner; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 55: Unit cost of resource use

	Unit cost (£)	Source
Medical consultations		
Medical oncologist consultation	176.24	NHS Reference costs 2016-2017, Outpatient Attendances Data (Medical Oncology, Consultant Led, unit cost)
Radiation oncologist consultation	136.43	NHS Reference costs 2016-2017, Outpatient Attendances Data (Clinical Oncology (Previously Radiotherapy), Consultant Led, unit cost)
Oncology nurse visit	82.00	NHS Reference costs 2016-2017, Community Health Services (Specialist Nursing, Cancer Related, Adult, Face to face)
GP consultation	36.00	PSSRU 2016 (Per patient contact lasting 9.22 minutes, including direct care staff costs, with qualification costs)
Psychology specialist consultation	168.65	NHS Reference costs 2016-2017, Outpatient Attendances Data (Clinical psychology, Total, Unit cost)
Surgeon consultation	141.19	NHS Reference costs 2016-2017, Outpatient Attendances Data (General surgery, Consultant-led, unit cost)
Dermatologist consultation	103.05	NHS Reference costs 2016-2017, Outpatient Attendances Data (Dermatology, Total, Unit cost)
BSC physician consultation	190.95	NHS Reference costs 2016-2017, Outpatient Attendances Data (Palliative medicine, Total, Unit cost)
Home care		
BSC physician/nurse visit	159.00	NHS Reference costs 2016-2017, Specialist Palliative Care (Medical Specialist Palliative Care Attendance, 19 years and over, Service description Outpatient - selected because of highest count)
Home aid (non-medical specialist) visit	70.00	NHS Reference costs 2016-2017, Specialist Palliative Care (Non-Medical Specialist Palliative Care Attendance, 19 years and over, Service description Other - selected because of highest count)
Hospital visits		
Inpatient stay (oncology/general ward)	552.59	Dabra+Tram for melanoma [TA396], Company Submission, ERG Report (96, 97). Updated to 2017 price level.
Emergency department visit	307.00	NHS Reference costs 2016-2017, Emergency Medicine (Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment, Type 01 admitted)
Day hospital visit	176.24	NHS Reference costs 2016-2017, Outpatient Attendances Data (Medical Oncology, Consultant Led, unit cost)

	Unit cost (£)	Source
Examinations		
Whole-body CT	143.00	NHS Reference costs 2016-2017, Diagnostic Imaging (Computerised Tomography Scan of more than three areas, Outpatient)
Brain MRI	159.00	NHS Reference costs 2016-2017, Diagnostic Imaging (Magnetic Resonance Imaging Scan of one area, with post contrast, 19 years and over, Outpatient)
Brain CT-scan	97.00	NHS Reference costs 2016-2017, Diagnostic Imaging (Computerised Tomography Scan of one area, with post contrast, 19 years and over, Outpatient)
Chest radiograph	30.00	NHS Reference costs 2016-2017, Directly Accessed Pathology Services (Direct Access Plain Film)
PET-CT scan	484.00	NHS Reference costs 2016-2017, Nuclear Medicine (Positron Emission Tomography with Computed Tomography (PET-CT) of more than three areas, 19 years and over, Outpatient)
Bone scan	292.00	NHS Reference costs 2016-2017, Nuclear Medicine (Nuclear Bone Scan of two or three phases, 19 years and over)
Blood test (CBC, CMP)	4.00	NHS Reference costs 2016-2017, Directly Accessed Pathology Services (Clinical Biochemistry and Hematology)
Procedures		
Radiotherapy fraction	681.00	NHS Reference costs 2016-2017, Radiotherapy (Preparation for Superficial Radiotherapy with Simple Calculation, with Technical Support, Outpatients and Deliver a Fraction of Adaptive Radiotherapy on a Megavoltage Machine, Outpatients)
Surgical intervention	772.00	NHS Reference costs 2016-2017, Non- elective short stay (Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over)
Limb perfusion	386.00	NHS Reference costs 2016-2017, Chemotherapy (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, Daycase and Reg Day/Night)
Limb infusion	260.00	NHS Reference costs 2016-2017, Chemotherapy (Deliver Simple Parenteral Chemotherapy at First Attendance, Daycase and Reg Day/Night)
Brain metastasis		
Whole-brain radiation	597.00	NHS Reference costs 2016-2017, Radiotherapy (Preparation for Simple Radiotherapy with Imaging and Simple Calculation, with Technical Support, Outpatient and Deliver a Fraction of Treatment on a Superficial or Orthovoltage Machine)
Stereotactic radiosurgery	2,167.00	NHS Reference costs 2016-2017, Non elective short stay (Average of Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 4+ and C Score 0-3)

	Unit cost (£)	Source
Neurosurgery	11,428.00	NHS Reference costs 2016-2017, Non elective long stay (Complex Intracranial Procedures, 19 years and over, with CC Score 4-7)

Abbreviations: BSC, best supportive care; CBC, complete blood count; CMP, complete metabolic panel; CT, computed tomography; GP, general practitioner; MRI, magnetic resonance imaging; PET, positron emission tomography.

The total costs per resource were obtained by multiplying the frequency of resource use by the respective unit cost (Table 56).

The model assumes that the entire cohort would eventually go through a period of BSC, which was assumed to last on average 4 months, as reported in the study by McKendrick (99). To avoid the use of tunnel states, the monthly BSC routine management cost was multiplied by 4 (average duration) and applied as a one-off cost at progression.

Table 56: Total cost per resource use during antineoplastic treatment, at progression and during BSC

	Routine management during antineoplastic tx (monthly cost £)	Management at progression (one-off cost £)	Routine management part of BSC (monthly cost £)
Medical consultations	**249.30**	**196.94**	**217.12**
Medical oncologist consultation	*176.24*	*176.24*	*118.08*
Radiation oncologist consultation	*4.09*	*13.64*	-
Oncology nurse visit	*49.20*	-	*16.40*
GP consultation	*11.88*	-	*19.08*
Psychology specialist consultation	*5.06*	-	*8.43*
Surgeon consultation	*2.82*	*7.06*	*28.24*
Dermatologist consultation	-	-	*2.06*
BSC physician consultation			*24.82*
Home care	**-**	**-**	**322.40**
BSC physician/nurse visit			79.50
Home aid (non-medical specialist) visit			*242.90*

	Routine management during antineoplastic tx (monthly cost £)	Management at progression (one-off cost £)	Routine management part of BSC (monthly cost £)
Hospital visits	**191.47**	**110.56**	**220.69**
Inpatient stay (oncology/general ward)	*138.15*	*110.52*	*182.35*
Emergency department visit	*9.21*	-	*15.35*
Day hospital visit	*44.06*	-	*22.91*
Examinations	**72.38**	**14.30**	**-**
Whole-body CT	*47.19*	-	-
Brain MRI	*4.77*	*7.95*	-
Brain CT-scan	-	*4.85*	-
Chest radiograph	*0.90*	*1.50*	-
PET-CT scan	*9.68*	-	-
Bone scan	*5.84*	-	-
Blood test (CBC, CMP)	*4.00*	-	-
Procedures	**63.11**	**174.80**	**15.44**
Radiotherapy fraction	*47.67*	*136.20*	
Surgical intervention	*15.44*	*38.60*	*15.44*
Limb perfusion	-	-	-
Limb infusion	-	-	-
Brain metastasis	**-**	**2,173.20**	**-**
Whole-brain radiation	-	*597.00*	-
Stereotactic radiosurgery	-	*433.40*	-
Neurosurgery	-	*1,142.80*	
Total costs	**576.20**	**2,669.76**	**775.57**

Abbreviations: BSC, best supportive care; CBC, complete blood count; CMP, complete metabolic panel; CT, computed tomography; GP, general practitioner; MRI, magnetic resonance imaging: PET, positron emission tomography.

Finally, a one-off cost of terminal care of £7,608.95 was applied to the proportion of new deaths at every cycle in the base-case (cost of £7,287 reported by Georghiou and Bardsley 2014 (101) and subsequently used in TA396 (96); inflated to the 2017/18 cost level). A scenario analysis where the cost of terminal care is excluded is also explored.

B.3.5.3 Adverse events unit costs and resource use

The approach for including AEs is described in Section B.3.3.2. For each AE except for blood CK increased, outpatient and inpatient costs were retrieved from the literature (100) and inflated to 2017/2018 costs.

Following the advice of the clinical expert (See Section B.3.10), the outpatient cost of blood CK increased was estimated based on 2 months of weekly blood tests (total 8 tests), at a cost of £4 per test (NHS Reference costs 2016-2017 (92)). The inpatient cost was assumed to comprise of the blood tests and a hospital stay which is required to ensure that the CK level is lowered (clinical expert opinion). The cost of the inpatient stay was obtained from NHS Reference costs 2016-2017 (£343; Non-elective short stay, Electrocardiogram Monitoring or Stress Testing (92)), generating a total inpatient cost of blood CK increased of £375.

The total cost per AE was obtained by calculating the weighted average cost of inpatient and outpatient costs (Table 58). Clinical expert opinion (see Section B.3.10) suggested that all grade 3 AEs were treated as outpatient, whereas all grade 4 AEs required an inpatient stay. Therefore, the percentage requiring inpatient stay was defined by the proportion of AEs which were grade 4 out of the total grade 3 and 4 AEs reported in COLUMBUS. A scenario analysis was included where it was assumed that all grade 3 and 4 AEs required hospitalisation.

Table 57: AEs outpatient and inpatient costs

	Outpatient one-off cost (£)	Inpatient one-off cost (£)	Source
Hypertension	262.19	4,022.19	Wehler et al 2017 (100)
Pyrexia	262.19	1,668.60	Wehler et al 2017 (100)
Blood CK increased	32.00	375.00	NHS reference costs 2016/17 (92)*
GGT increased	262.09	1,899.37	Wehler et al 2017 (100)
ALT increased	262.09	1,899.37	Wehler et al 2017 (100)

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CK, creatine phosphokinase; GGT, gamma-glutamyl transferase.
* Advised by clinical expert (See Section B.3.10).

Table 58: Percentage of the cohort requiring inpatient stay per AE

	Cohort requiring inpatient stay (%)	Source
Hypertension	[redacted]	Grade 4 AEs as proportion of Grade 3 and Grade 4 AEs (32)
Pyrexia	[redacted]	
Blood CK increased	[redacted]	
GGT increased	[redacted]	
ALT increased	[redacted]	

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CK, creatine phosphokinase; GGT, gamma-glutamyl transferase.

The total AE costs for Enco+Bini 450 and Dabra+Tram were calculated by multiplying each AE's weighted average cost by the respective total incidence rate (Table 42) and summing (Table 59).

Table 59: Total AEs cost for Enco+Bini 450 and Dabra+Tram

	Weighted average cost per AE (£)	AE costs Enco+Bini 450 (£)	AE costs Dabra+Tram (£)
Hypertension	262.09	13.63	30.93
Pyrexia	262.09	9.44	14.15
Blood CK increased	84.77	5.74	-
GGT increased	262.09	24.57	8.91
ALT increased	262.09	13.65	9.17
Total		**67.02**	**63.16**

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CK, creatine phosphokinase; GGT, gamma-glutamyl transferase.

It was assumed that AEs occurred within 1 year from the start of primary treatment (i.e. no discounting applies), based on the median time on treatment with Enco+Bini 450 in COLUMBUS being 11.8 months (See Section B.2.10.1); it was assumed for the purposes of applying AE costs that this was the same for Dabra+Tram.

B.3.5.4 Miscellaneous unit costs and resource use

Not applicable

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A table of variables and inputs used in the base-case analysis is provided in Appendix Q.

B.3.6.2 Assumptions

Table 60: Model assumptions

Model aspect	Base-case assumption	Justification	Cross reference to submission section
Time horizon	30 years	• Long enough to capture all relevant costs and effects • In line with previous appraisals	B.3.2.2.1
Discount rate	3.5% for costs and benefits	NICE recommendation	B.3.2.2.2
PFS extrapolation	K-M + Gamma	• Clinical plausibility based on clinical expert opinion • Best fitting parametric curve	B.3.3.1.3
PFS local or central review	Local	In order to compare in NMA	B.3.3.1.2.1
Time on treatment	Based on TTD with HR=1	• No detailed information on TTD available for use for Dabra+Tram arm (i.e. no K-M data) • KOL opinion • Most likely scenario based on limited available information in ERG critique of TA396 • Median time of dose exposure is similar for Enco+Bini 450 and Dabra+Tram	B.3.3.3
TTD extrapolation	K-M + log-logistic	• Clinical plausibility based on clinical expert opinion • In line with PFS approach • Best fitting parametric curve	B.3.3.1.3
TTD censoring	Censoring death and LFU	To avoid double counting	B.3.3.1.2.2
OS extrapolation	K-M + AJCC + lifetables	• Approach taken and recommended in TA396 • Representative of long-term mortality in metastatic melanoma patients • Clinical plausibility based on clinical expert opinion	B.3.3.1.3
OS HR applied to AJCC data	0.42	• This is applied in order to estimate the effect that new therapies may have on survival	B.3.3.1.3.2
OS adjustment	Not adjusted for crossover	Not in original COLUMBUS trial design	B.3.3.3
OS and PFS and utility from NMA	Use point values	• NICE's preference to model non-statistically significant differences in the base-case	B.3.3.3

Model aspect	Base-case assumption	Justification	Cross reference to submission section
Subsequent treatment cost	Applied as a one-off at discontinuation	• Most transparent • Preferred by ERG in TA396 • Insufficient data to be able to spread the cost	B.3.5.1.2.1
Subsequent treatment percentages	Assumed to be equal for Enco+Bini 450 and Dabra+Tram. %ages from the Enco+Bini 450 arm of post-hoc analysis are utilised	• In the absence of clear data to show that subsequent treatments would be different between Enco+Bini 450 and Dabra+Tram • Consistent with the approach suggested by the ERG in NICE TA396 • %ages from the Enco+Bini 450 arm are most relevant as Dabra+Tram and Enco+Bini 450 are both combination therapies	B.3.5.1.2.2
Relative dose intensity	Include	• To provide the most accurate estimation of actual cumulative dose	B.3.5.1.1
Utilities PF	Treatment specific, HR from NMA applied	Conservative assumption	B.3.4.5.1
Utilities PP	Equal for all treatments	• Patients would receive the same subsequent treatments and therefore utility would be equal	B.3.4.5.1
AEs	Grade 3/4 AEs with >5% incidence from COLUMBUS, COMBI-v or COMBI-d	All relevant AEs for both Enco+Bini 450 and Dabra+Tram are included	B.3.3.2
AE hospitalisations	Grade 4 hospitalised (in-patient), Grade 3 not	Clinical expert opinion	B.3.5.3
Utilities	EQ-5D	Required by NICE	B.3.4.1; B.3.4.5.1
Utility adjustment for age	Include	To reflect declining utility with age	B.3.4.5.2

Abbreviations: AE, adverse event; AJCC, American Joint Committee on Cancer; HR, hazard ratio; EQ-5D, EuroQoL-5 dimensions; ERG, evidence review group; HRQoL, health-related quality of life; K-M, Kaplan-Meier; KOL, key opinion leader; LFU, lost to follow up; NMA, network meta-analysis; OS, overall survival; PF, progression-free; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life-year; TA, technology appraisal; TTD, time to treatment discontinuation.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 61: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/ QALY)
Enco+Bini 450	[redacted]	5.884	4.223	[redacted]	0.613	0.453	Dominant
Dabra+Tram	353,603	5.271	3.770				

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

Clinical outcomes from the model and disaggregated results of the base-case cost-effectiveness analysis are provided in Appendix J.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) tests the impact of second order uncertainty by random, simultaneous variation of the input parameters on the model. Second order uncertainty does not include cohort characteristics, which are part of first order uncertainty. Therefore, age, percentage males, weight, BSA and distribution of the population per stage at study entry were not included in the PSA.

PSA analysis is performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions to estimate the cost effectiveness ratios. A Beta distribution was assigned to probabilities, proportions, utility and disutility data (once transformed into positive values) which take values between 0 and 1. A log-normal distribution was assigned to HRs and ORs. A Gamma distribution was assigned to costs, doses and resource use, which take positive values and are likely to be positively skewed. The Alpha and Beta values of the distribution were estimated based on the mean and standard deviation associated with each parameter. If the standard deviation was not available from the reporting study, then it was calculated based on the following assumption:

= (Upper range – lower range)/(2*NORMSINV(0.975))

The upper and lower ranges were based on CIs where reported and if not, they were based on a variation of +/- 20%.

A total of 10,000 Monte Carlo simulations were recorded. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated. The former shows the distribution of incremental cost and benefits under uncertainty and the latter the likelihood of being cost-effective at given acceptability thresholds.

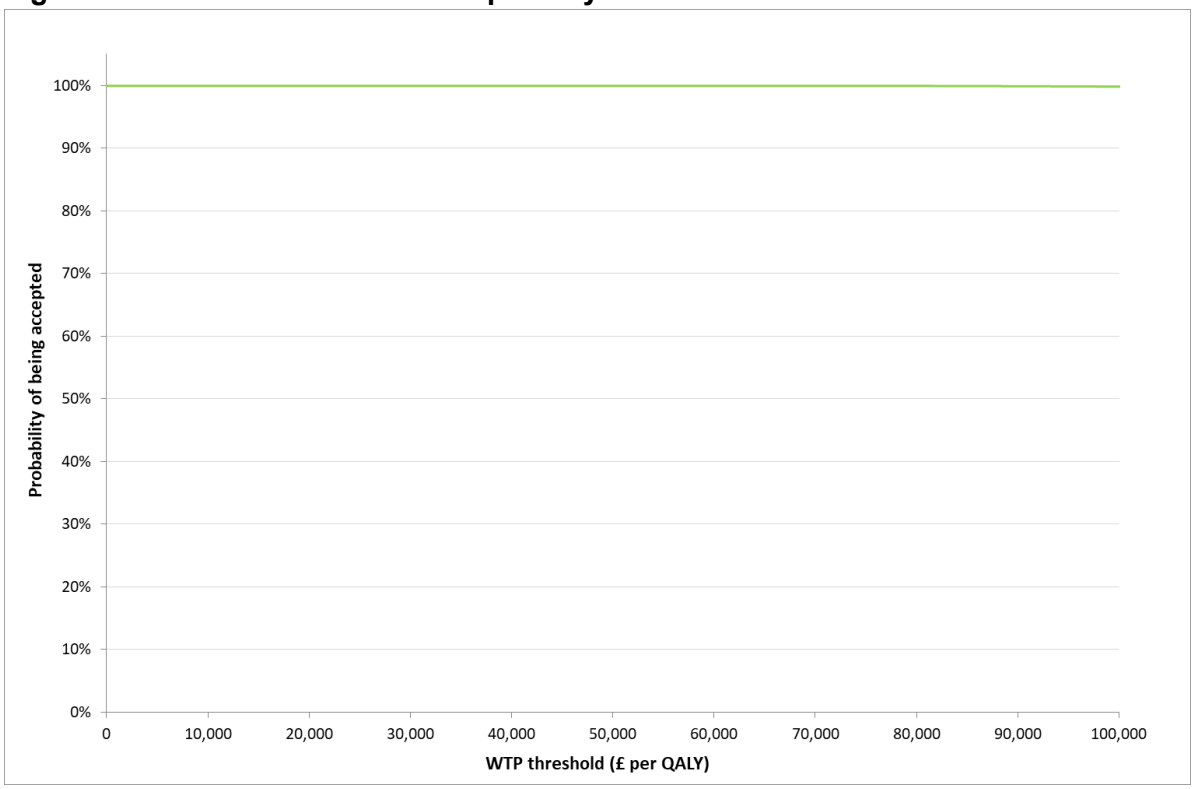
Variables, estimates of uncertainty, and distributional assumptions used in PSA are presented in Appendix Q.

Figure 29 and Figure 30 present the CEP and CEAC, respectively. The probability that Enco+Bini 450 was cost-effective at a threshold of £20,000 per QALY was 100%. Across 10,000 PSA simulations, Enco+Bini 450 was associated with mean cost-savings of [redacted](95% CI: [redacted], [redacted]) and mean incremental QALYs of 0.432 (95% CI: -0.870, 1.424) (95% CIs were calculated based on the 2.5 and 97.5 percentiles of these simulations). These results are considered to be consistent with deterministic cost-savings of [redacted]and a deterministic increase in QALYs 0.453.

Figure 29: Cost-effectiveness plane

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 30: Cost-effectiveness acceptability curve



Abbreviations: QALY, quality-adjusted life-years; WTP, willingness to pay.

B.3.8.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model variables were systematically and independently varied over a plausible range determined by either the 95% CI, or +/- 20% where no estimates of precision were available. Net monetary benefit was recorded at the upper and lower values to produce a tornado diagram, assuming a cost-effectiveness threshold of £20,000 per QALY.

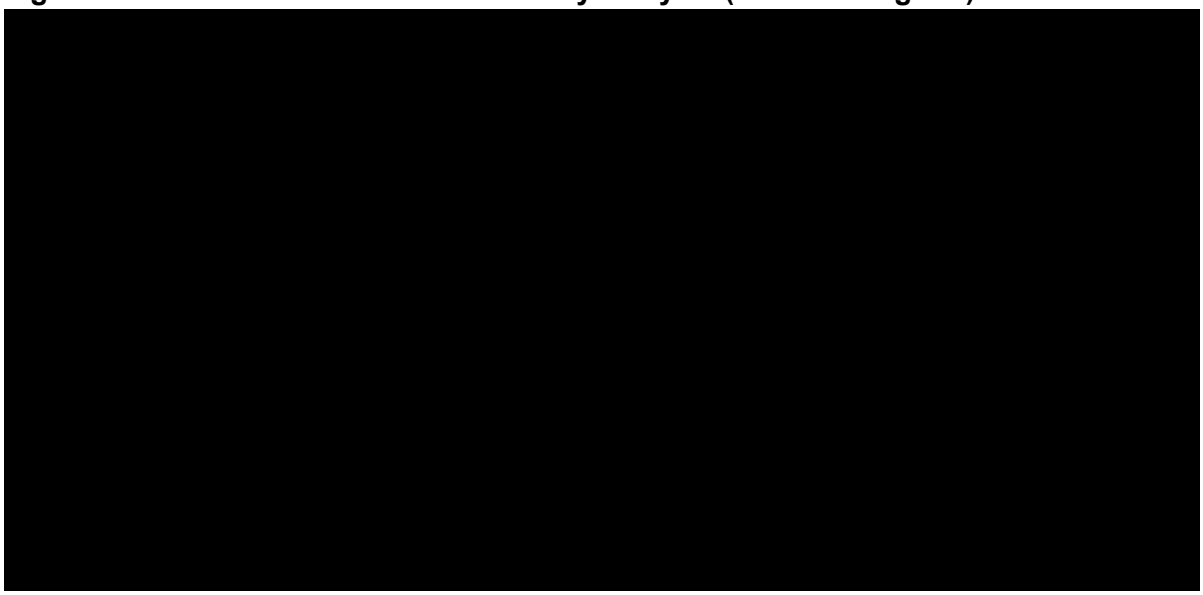
Upper and lower ranges of included parameters are presented in Appendix Q.

Figure 31 presents the results of the univariate sensitivity analysis in the form of a tornado diagram. The most influential parameter was found to be the HR for TTD for Dabra+Tram vs Enco+Bini 450. Other influential parameters were related to the dose of dabrafenib and trametinib (dose per administration and RDI).

Although the HR for TTD was varied by +/- 20% for the deterministic sensitivity analysis, this is not likely to be plausible in reality according to expert clinical opinion. As described in Section B.3.3.3, a HR of 1.1 would lead to a difference in time on

treatment of 4.47 months between Enco+Bini 450 and Dabra+Tram which was likely to represent the upper limit of clinical plausibility.

Figure 31: Results of univariate sensitivity analysis (tornado diagram)



Abbreviations: HR, hazard ratio; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; TTD, time to treatment discontinuation.

B.3.8.3 Scenario analysis

The results of scenario analysis are presented in Table 62. Most scenarios showed Enco+Bini 450 to be dominant versus Dabra+Tram. Exceptions to this included the following:

- When applying a [redacted] discount to the Dabra+Tram list price an ICER of [redacted] per QALY was estimated.
- When assuming equal effectiveness between Enco+Bini 450 and Dabra+Tram in terms of OS, PFS, PF utility and AE rates, Enco+Bini 450 was cost-saving (generating equal QALYs).

Table 62: Scenario analysis

Scenario	Enco+Bini 450		Dabra+Tram		Incremental				
	Total costs	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	ICER	NMB	% difference in NMB vs base case
Base-case	[redacted]	4.223	353,603	3.770	[redacted]	0.453	Dominant	[redacted]	-
Equal effectiveness for Dabra+Tram and Enco+Bini 450 (OS, PFS, PF utility, AE rates)	[redacted]	4.223	356,094	4.223	[redacted]	0.000	Less costly, equal effectiveness	[redacted]	-3.83%
PF utilities equal for Dabra+Tram and Enco+Bini 450	[redacted]	4.223	353,603	3.722	[redacted]	0.501	Dominant	[redacted]	0.55%
HR for TTD for Dabra+Tram vs Enco+Bini 450 = 0.9	[redacted]	4.223	395,773	3.770	[redacted]	0.453	Dominant	[redacted]	24.56%
HR for TTD for Dabra+Tram vs Enco+Bini 450 = 1.1	[redacted]	4.223	319,901	3.767	[redacted]	0.455	Dominant	[redacted]	-19.61%
Constant hazard approach for extrapolation of both TTD and PFS	[redacted]	4.112	314,959	3.693	[redacted]	0.418	Dominant	[redacted]	-13.08%
TTD any reason (not censored)	[redacted]	4.222	337,899	3.769	[redacted]	0.453	Dominant	[redacted]	-5.21%
HR adjustment for AJCC =1	[redacted]	3.396	346,588	3.030	[redacted]	0.366	Dominant	[redacted]	-2.63%
OS crossover adjustment applied	[redacted]	4.223	353,862	3.801	[redacted]	0.422	Dominant	[redacted]	-0.21%
RDIs all set to 1	[redacted]	4.223	370,804	3.770	[redacted]	0.453	Dominant	[redacted]	1.36%
Remove utility decrement for age	[redacted]	4.269	353,603	3.808	[redacted]	0.461	Dominant	[redacted]	0.10%
Subsequent treatment option 2 (see Table 49)	[redacted]	4.223	340,381	3.770	[redacted]	0.453	Dominant	[redacted]	2.34%

Scenario	Enco+Bini 450		Dabra+Tram		Incremental				
	Total costs	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	ICER	NMB	% difference in NMB vs base case
Subsequent treatment option 3 (see Table 49)	[redacted]	4.223	344,597	3.770	[redacted]	0.453	Dominant	[redacted]	0.24%
Vial wastage excluded	[redacted]	4.223	351,471	3.770	[redacted]	0.453	Dominant	[redacted]	0.09%
Exclude terminal care cost	[redacted]	4.223	347,235	3.770	[redacted]	0.453	Dominant	[redacted]	-0.10%
Both grade 3 and 4 AEs hospitalised	[redacted]	4.223	354,225	3.770	[redacted]	0.453	Dominant	[redacted]	0.07%
List price for both Enco+Bini 450 and Dabra+Tram	[redacted]	4.223	353,797	3.770	[redacted]	0.453	Dominant	[redacted]	-87.70%
PAS price for Enco+Bini 450 and [redacted] discount applied to Dabra+Tram (threshold analysis to reach ICER of [redacted])	[redacted]	4.223	[redacted]	3.770	[redacted]	0.453	[redacted]	[redacted]	[redacted]
Discount rates 0% for both costs and outcomes	[redacted]	5.436	402,531	4.772	[redacted]	0.664	Dominant	[redacted]	16.20%
Discount rates 6% for both costs and outcomes	[redacted]	3.644	329,091	3.286	[redacted]	0.358	Dominant	[redacted]	-8.00%

Abbreviations: AE, adverse event; AJCC, American Joint Committee on Cancer; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time to treatment discontinuation.

B.3.8.4 Summary of sensitivity analyses results

The results of PSA were found to be highly consistent with the deterministic base-case results and showed Enco+Bini 450 to be cost-effective versus Dabra+Tram in 100% of simulations, assuming a cost-effectiveness threshold of £20,000 per QALY.

The most influential parameters in deterministic sensitivity analysis were the HR for TTD for Dabra+Tram versus Enco+Bini 450 and the dose of dabrafenib and trametinib. The effects of other model parameters on the base-case NMB were found to be modest.

Most scenarios showed Enco+Bini 450 to be dominant versus Dabra+Tram. Exceptions to this included the following:

- When applying a [redacted] discount to the Dabra+Tram list price an ICER of [redacted] per QALY was estimated.
- When assuming equal effectiveness between Enco+Bini 450 and Dabra+Tram in terms of OS, PFS, PF utility and AE rates, Enco+Bini 450 was cost-saving (generating equal QALYs).

B.3.9 Subgroup analysis

Not applicable

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Quality assurance: A senior health economic modeller external to the model process performed quality assurance. The following quality assurance steps were performed:

- Review of modelling structural assumption and techniques chosen.
- Review of technical deployment (formulas, functionality).
- Review of data inputs and sources.
- Conduct extreme scenario analyses and validation of results.

Validation of model structure, assumptions and inputs: The final model structure, key assumptions and inputs were validated by both a clinical expert and a health economic expert in the UK with experience in the treatment of unresectable melanoma and with experience of oncology health economic modelling, respectively.

Both experts were provided with information on the model concept and proposed inputs and extrapolations.

- Further input from the clinical expert was sought via a face to face meeting, with the main objective being to ensure the clinical plausibility of the model structure and assumptions. Specific assumptions were checked as necessary with follow-up emails and phone calls.
- Input from the health economic was sought via videoconference, with the main objective of ensuring that the selected modelling approaches were methodologically sound and met the requirements of HTA bodies.

The clinical expert has participated in one further advisory board to support the collation of inputs. No further direct financial or non-financial conflicts are applicable.

Validation of model outcomes versus trial data: The internal validity of the electronic model was assessed by comparing model outcomes for Enco+Bini 450 and Dabra+Tram to those observed in COLUMBUS and in a pooled analysis of the COMBI-d/COMBI-v trials (106). Table 63 presents the results of this comparison, showing that the economic model was considered consistent with the pivotal trials for the two combination therapies.

For Enco+Bini 450, the results were very similar, as expected, because the model uses the trial data directly from COLUMBUS until the end of the trial. For Dabra+Tram the results are relatively consistent, however there are small differences due to the model using data from the NMA. The NMA evidence network was more extensive than the data provided by COMBI-d/COMBI-v, utilising data from three trials for Dabra+Tram and seven trials overall, and this is likely the reason for the discrepancy between the model and the COMBI-v/ COMBI-d trials.

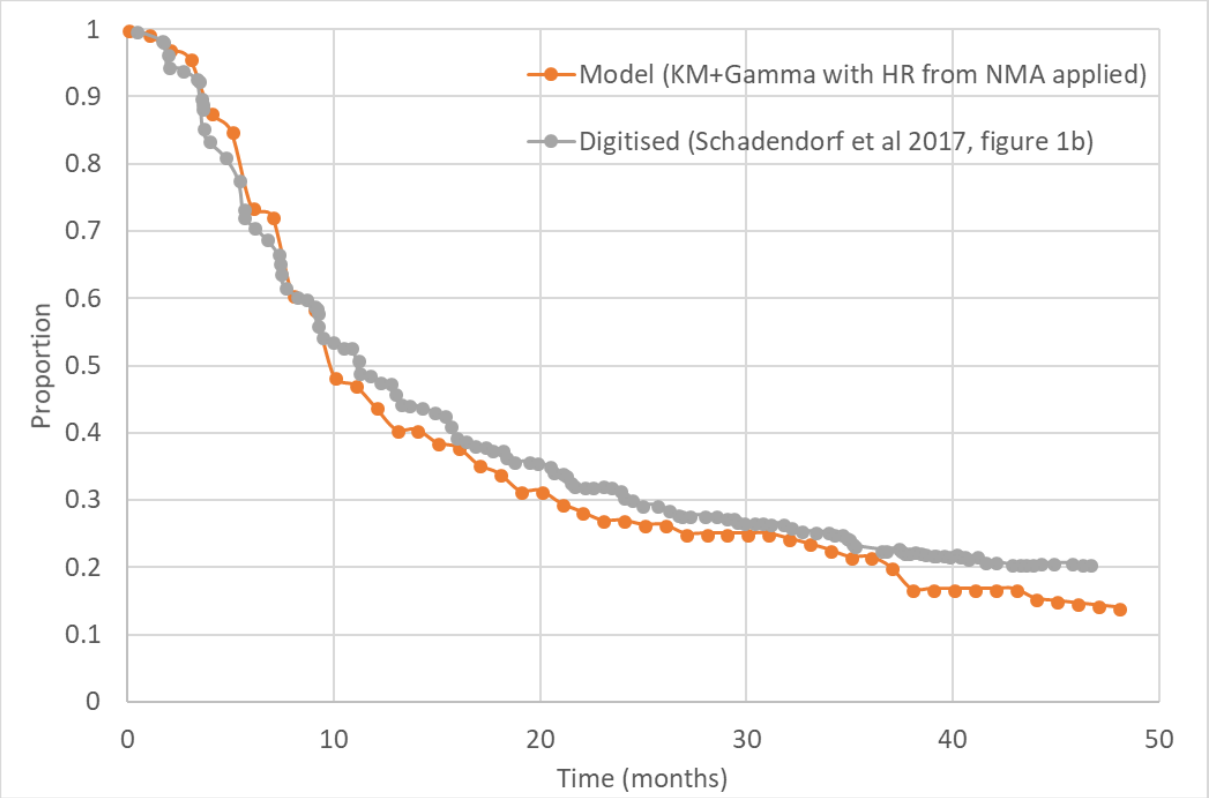
Table 63: Comparison of model outcomes and COLUMBUS/COMBI-d/COMBI-v

Outcome	Economic model base-case		Trial outcomes	
	Enco+Bini 450	Dabra+Tram	Enco+Bini 450 (COLUMBUS November 2017; Section B.2.6.2.1, B.2.6.5.1)	Dabra+Tram (COMBI-d/ COMBI-v) (106)
Median OS (months)	33.22	27.53	33.6	26.2
Median PFS (months)	12.98	9.84	13.0	11.1
Proportion surviving at month 12	0.755	0.730	0.755	0.74
Proportion surviving at month 24	0.576	0.539	0.576	0.53

Abbreviations: OS, overall survival; PFS, progression-free survival.

In order to compare visually against the trial results for Dabra+Tram, the PFS K-M curves from Schadendorf et al 2017 were digitised (106). This publication reported the pooled PFS results for COMBI-v and COMBI-d in Figure 1B in the publication. The digitised curve was plotted along with the predicted PFS for Dabra+Tram derived from the economic model (using K-M+Gamma with the HR from the NMA applied). Figure 32 shows that the curves are very similar, crossing at around 9 months and then following a similar trend up to 48 months (trial duration of COMBI-v and COMBI-d). This demonstrates that the combined modelling approach of using K-M+Gamma extrapolation for Enco+Bini 450 and applying HRs of comparative effectiveness from the NMA provided outcomes for Dabra+Tram which were broadly aligned with the pooled results of COMBI-v and COMBI-d.

Figure 32: PFS for Dabra+Tram using digitised COMBI-v/COMBI-d K-M data and economic model predicted values



Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier; NMA, network meta-analysis; PFS, progression-free survival.
Source of digitised data: Schadendorf et al 2017 (106).

B.3.11 Interpretation and conclusions of economic evidence

A systematic review of the economic literature did not identify any published economic evaluations for Enco+Bini 450 in unresectable or metastatic melanoma of relevance to the UK (see Section B.3.1), and so it was necessary to develop a de novo economic model. The model structure adopted is consistent with clinical practice and previous modelling approaches in melanoma, and oncology more broadly.

The core assumptions of the economic evaluation, including the modelling of key outcomes of OS, PFS and TTD were informed and validated by a UK-based clinical expert (see Section B.3.10.1 for validation methodology), and measurements of resource use and unit costs were taken from UK sources. The overall trial population of the pivotal Enco+Bini 450 trial, COLUMBUS is considered to be largely reflective of the population in UK clinical practice with unresectable or metastatic BRAF V600 mutation-positive melanoma (see Section B.2.13.2). The economic evaluation was

therefore considered highly relevant to the population of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma in England and Wales.

Key inputs of OS, PFS and TTD were all modelled using K-M data, followed by extrapolation beyond the trial period using established techniques. The base-case assumptions of K-M + extrapolation, and the choice of extrapolation technique were informed by a combination of clinical plausibility, statistical fit and a review of methods previously accepted or criticised by NICE or the ERGs on previous technology appraisals for melanoma interventions.

The main external data source used within the evaluation was an NMA to generate estimates of comparative efficacy between Enco+Bini 450 and Dabra+Tram. This is an obvious limitation of the evaluation but in the absence of a head-to-head trial comparing the two BRAFi/ MEKi combination therapies this reflects the best available evidence to date. The NMA showed numerical benefits of Enco+Bini 450 over Dabra+Tram in terms of OS and PFS, however credible intervals were relatively wide and crossed the boundary of no effect (CrI = 1). As such, comparing the economic value of Enco+Bini 450 with Dabra+Tram on the basis of clinical equivalence may be warranted.

The health economic analysis is driven predominantly by the primary treatment costs of Enco+Bini 450 and Dabra+Tram. The use of TTD to inform treatment costs, we believe, better reflects the true cost of treatment, as opposed to using PFS and was the preferred method of the ERG when NICE assessed Dabra+Tram in TA396. Although TTD curves were not available for Dabra+Tram and an NMA on TTD was not feasible, the equivalence assumption for the base-case analysis is based on the best available evidence for both combination treatments. Comparison of data from the key efficacy trials for Enco+Bini 450 and Dabra+Tram (COLUMBUS vs. COMBI-v/COMBI-d) demonstrated very similar dose exposure between the two treatments (11.8 months for Enco+Bini 450 and 12.2 and 11.8 for Dabra+Tram in COMBI-v and COMBI-d, respectively (49, 50)). Further, this assumption is deemed to be plausible based on information available from the ERG review of TA396 (97) which suggests that the TTD curve lies above the PFS curve for Dabra+Tram. For Enco+Bini 450 however, the TTD curve is offset below the PFS curve. In TA396 the ERG reported that patients still on treatment in COMBI-v at 28 months was 29.1% and in COMBI-d at 29 months was 29.4% (97); at 28 months in COLUMBUS, 28.1% of patients were

on treatment based on the TTD curve. This provides further support for assuming TTD is equivalent between the two treatments.

The base-case analysis, including Enco+Bini 450 at PAS price and Dabra+Tram at list price suggests that Enco+Bini 450 would lead to cost savings for the NHS compared with Dabra+Tram. Dabra+Tram list price would need to be discounted by [redacted] to generate an ICER of [redacted]. In the case where equivalence is assumed, the results show cost savings and equal QALYs. Within the limitations of the analysis outlined, we believe Enco+Bini 450 to be a cost-effective use of NHS resources for the treatment of patients with unresectable or metastatic BRAF V600 mutation-positive melanoma.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: COLUMBUS study, additional information

Appendix M: PFS extrapolation using constant hazard approach

Appendix N: OS extrapolation using AJCC data and life tables

Appendix O: OS extrapolation using parametric approach

Appendix P: TTD extrapolation using constant hazard approach

Appendix Q: Summary of variables applied in the economic model

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Single technology appraisal

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

Dear Andy,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 16 August 2018 from Pierre Fabre Ltd. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **24th September 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sana Khan, Technical Lead (Sana.Khan@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Zoe Charles
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for confidential information

Section A: Clarification on clinical effectiveness data

The COLUMBUS trial

A1. **Priority question**. Please confirm whether the analysis of the updated progression-free survival (PFS) data (November 2017 data cut-off) used the same statistical methodology and analysis population(s) as for the original PFS efficacy analysis (May 2016 data cut-off).

A2. **Priority question**. Please provide the median follow-up time for the updated PFS and interim overall survival (OS) analyses for all participants and by treatment group.

A3. **Priority question.** The ERG understands from the hierarchical testing approach employed in the COLUMBUS trial (Figure 2, page 27 of the company submission), that as test 3 (PFS of Enco+Bini 300 vs Enco 300) was not statistically significant, test 4a (interim analysis of OS for Enco+Bini 450+Bini vs vemurafenib) was not performed. Please confirm this is correct. Is it also correct that under the hierarchical testing approach, test 4b (final analysis of OS) for Enco+Bini 450 vs vemurafenib) will not be performed?

A4. The ERG notes that the percentage of patients who received prior immunotherapy at any disease stage is reported on page 25 of the company submission. Please provide the numbers of patients who received previous immunotherapy by treatment arm.

A5. It is stated on page 34 of the company submission (Section B 2.4.6, Sensitivity analyses and other supportive analyses) that a sensitivity analysis was performed:

"PFS by blinded independent review committee (BIRC) [Full Analysis Set] using stratification factors as provided in the electronic case report form (eCRF) as opposed to randomisation stratum (performed per the statistical analysis plan due to >5% discordance between randomisation strata and eCRF strata)."

Please explain why the discordance between randomisation strata and eCRF strata was >5%.

A6. A comparison of PFS events between BIRC and investigator assessment is provided in table 12, page 42 of the company submission. Please explain how a discordance between BIRC and investigator assessment for the PFS event of death has occurred for 23 participants across all treatment arms. It is also unclear how discordance between death (event) and a censored observation has occurred for one participant in the Enco+Bini 450 arm.

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A7. Please provide numerical results (hazard ratio [HR] and 95% confidence intervals) for the subgroup analyses presented graphically in Figure 18 (PFS), Figure 21 (OS) and Figure 22 (OS) of Appendix E.

Network meta-analysis

A8. **Priority question**. Please provide investigator-assessed PFS results (HR and 95% Credible Interval [CrI] of Enco+Bini 450 vs Dab+Tram) for the network restricted to the open label trials (COLUMBUS, COMBI-v, BRIM-3, BREAK-3 and BRF113220 Part C).

A9. In relation to population variations within the seven trials included in the NMA, it is stated on page 72 of the company submission that: "subgroup analyses were conducted to assess the impact of these potential effect modifiers'.

Please clarify if this statement relates to the subgroup analyses from the COLUMBUS trial (presented in Section 2.7 (page 61-62) and Appendix E of the company submission) or to the subgroup analyses from the NMA. If the latter, please provide further details and numerical results of these subgroup analyses.

A10. It is stated within Appendix D, Section D1.3.1 (assessment of NMA treatment effect scales) that: "to account for the findings from the assessment into the validity of the proportional hazards assumption, sensitivity analysis was considered for the OS and PFS base-case analyses, removing studies where the proportional hazards assumption was violated."

Please provide numerical results (HR and 95% CrI of Enco+Bini 450 vs Dab+Tram) for all outcomes in this sensitivity analysis.

A11. Please explain the statement made in Appendix D, Section D1.3.2 (Analysis assumptions) that: "The treatment node of dacarbazine or paclitaxel in the BRF113220 Part C trial is considered to interact in the same way as dacarbazine in other trials. This is an assumption that was previously used in another NMA and has been accepted in a previous NICE appraisal (27)."

Section B: Clarification on cost effectiveness data

B1. The outcome of 'time to treatment discontinuation' (TTD) is described on page 103 of the company submission as 'Enco+Bini 450: COLUMBUS K-M TTD data until available (post-hoc analysis on TTD censoring death and lost to follow-up + log-logistic parametric extrapolation '

The outcome of 'time to treatment failure' is pre-defined within the COLUMBUS trial protocol (Section 14.2.22, supplementary document Dummer et al 2018) as 'Time to treatment failure is the time from date of randomisation/start of treatment to the

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earliest date of death due to any cause, or date of discontinuation due to reasons other than ‘protocol violation ‘or administrative problem’. The time to treatment failure for patients who did not experience treatment failure will be censored at the last adequate tumour assessment’.

Please clarify whether TTD and time to treatment failure are different.

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Encl. checklist for confidential information

Section A: Clarification on clinical effectiveness data

The COLUMBUS trial

A1. **Priority question**. Please confirm whether the analysis of the updated progression-free survival (PFS) data (November 2017 data cut-off) used the same statistical methodology and analysis population(s) as for the original PFS efficacy analysis (May 2016 data cut-off).

Response:

The updated analysis of PFS at the November 2017 cut-off was performed using the same methodology and analysis population (FAS) as the original primary analysis (May 2016 cut-off) as defined in the statistical analysis plan (Version 5; please see Appendix 2 of reference (1), as supplied in the reference pack supporting the company submission).

A2. **Priority question**. Please provide the median follow-up time for the updated PFS and interim overall survival (OS) analyses for all participants and by treatment group.

Response:

Please see the requested information in Table 1 for PFS and interim OS (Data cut-off 7 November 2017).

Table 1: Follow-up times (months)

	Enco+Bini 450 N=192	Enco 300 N=194	Vemurafenib N=191	Total N=577
PFS, median (IQR)	32.3 (31.7–34.9)	32.0 (24.0–34.9)	22.2 (11.0–32.3)	32.1 (29.5–32.3)
OS, median (IQR)	37.2 (36.1–38.5)	36.3 (34.8–37.3)	35.9 (34.9–38.0)	36.8 (35.9–37.5)

Abbreviations: IQR, interquartile range; OS, overall survival; PFS, progression-free survival.
Median durations of follow-up for OS and PFS were estimated by reverse Kaplan-Meier analysis, for which median values are reported and reflect the potential follow-up in the absence of progressive disease or death.
Source: Dummer et al (2).

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A3. **Priority question.** The ERG understands from the hierarchical testing approach employed in the COLUMBUS trial (Figure 2, page 27 of the company submission), that as test 3 (PFS of Enco+Bini 300 vs Enco 300) was not statistically significant, test 4a (interim analysis of OS for Enco+Bini 450+Bini vs vemurafenib) was not performed. Please confirm this is correct. Is it also correct that under the hierarchical testing approach, test 4b (final analysis of OS) for Enco+Bini 450 vs vemurafenib) will not be performed?

Response:

Testing within the hierarchy was stopped when patients treated with Enco+Bini 450 showed a greater than 5-month improvement in median PFS compared with those treated with Enco 300, although the difference in PFS at the time of this initial analysis did not reach the pre-defined level for significance of $p<0.025$ ($p=0.0256$; data cut-off 19 May 2016).[a] This analysis represented pre-planned Test 2 in the hierarchy, as depicted in Figure 1 of the company submission Form B.

As a result, both pre-planned Test 3 (PFS, Enco+Bini 300 versus Enco 300) and Test 4a (OS, Enco+Bini 450 versus vemurafenib) could not be formally performed and descriptive statistics were provided (Figure 1). Nonetheless, the study sponsor remained masked to OS data until the OS analysis, and this analysis was performed when the prespecified number of events had occurred. The observed effect of Enco+Bini 450 on OS compared with vemurafenib was clinically meaningful (HR 0.61, 95% CI: 0.47, 0.79) and reached nominal significance (i.e., $p<0.0001$) (See Company submission Form B, Section 2.6.5.1.1, page 51). Furthermore, analysis of OS for Enco+Bini 450 versus Enco 300 was not powered but showed results that were consistent with PFS results (HR 0.81 [95% CI 0.61, 1.06]; See Company submission Form B, Section 2.6.5.1.1, page 51).

In line with the pre-planned testing hierarchy, Test 4b of OS Enco+Bini 450 versus vemurafenib will not formally be performed; however descriptive statistics will be available.

[a] Note that the PFS result for Enco+Bini 450 vs Enco 300 was statistically significant in the updated analysis (November 2017 data cut-off; p=0.0249).

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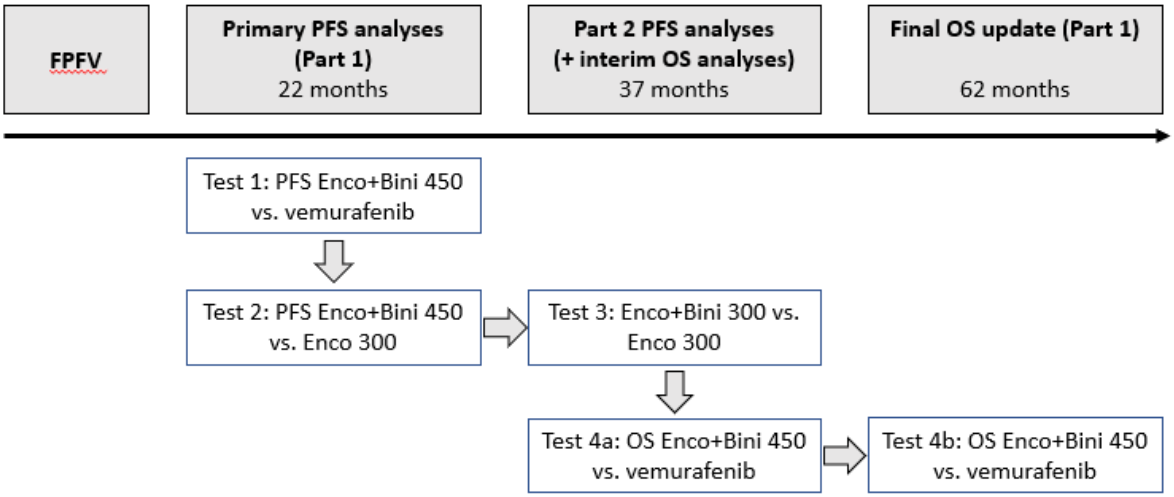
Figure 1: Timing of testing of primary and secondary endpoints



Abbreviations: Enco+Bini 300, encorafenib 300 mg QD in combination with binimetinib 45 mg BID; Enco+Bini 450, encorafenib 450 mg QD in combination with binimetinib 45 mg BID; FPFV, first patient first visit; Enco 300, encorafenib 300 mg QD; OS, overall survival; PFS, progression-free survival.

⇨ Hierarchical testing sequence

The timing of the analyses refers to the analysis cut-off date, i.e. when the expected number of events or time point was reached or is expected to be reached.

A4. The ERG notes that the percentage of patients who received prior immunotherapy at any disease stage is reported on page 25 of the company submission. Please provide the numbers of patients who received previous immunotherapy by treatment arm.

Response:

Table 2: Prior antineoplastic therapies – Ipilimumab, anti-PD1/PDL1 or interferons/ interleukins (FAS, Part 1)

	Enco+Bini 450 N=192 n (%)	Enco 300 N=194 n (%)	Vemurafenib N=191 n (%)
Any immunotherapy	57 (29.7)	58 (29.9)	57 (29.8)
Ipilimumab	7 (3.6)	10 (5.2)	7 (3.7)
Anti-PD1/PDL1	1 (0.5)	2 (1.0)	0
Interferons/interleukins	51 (26.6)	51 (26.3)	52 (27.2)
Ipilimumab – Setting[a,b]	n=7	n=10	n=7
Adjuvant	X (XXX)	X (XXX)	X (XXX)
Therapeutic-metastatic	X (XXX)	X (XXX)	X (XXX)

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	Enco+Bini 450 N=192 n (%)	Enco 300 N=194 n (%)	Vemurafenib N=191 n (%)
Anti-PD1/PDL1 - Setting[a,b]	n=1	n=2	n=0
Therapeutic-metastatic	X (XXX)	X (XXX)	X
Interferons/interleukins – Setting[a]	n=51	n=51	n=52
Adjuvant	XX (XXX)	XX (XXX)	XX (XXX)
Neoadjuvant	X	X (XXX)	X (XXX)
Therapeutic-metastatic	X (XXX)	X (XXX)	X (XXX)

Abbreviations: PD1, programmed death 1 (receptor); PDL1, programmed death (receptor) ligand 1.
[a]A patient may have multiple settings.
[b]A patient may have received ipilimumab or anti-PD1/PDL1 in combination.
Source: CSR Table 12 (3).

A5. It is stated on page 34 of the company submission (Section B 2.4.6, Sensitivity analyses and other supportive analyses) that a sensitivity analysis was performed:

"PFS by blinded independent review committee (BIRC) [Full Analysis Set] using stratification factors as provided in the electronic case report form (eCRF) as opposed to randomisation stratum (performed per the statistical analysis plan due to >5% discordance between randomisation strata and eCRF strata)."

Please explain why the discordance between randomisation strata and eCRF strata was >5%.

Response:

This study used an interactive response technology (IRT) to register and randomise patients. Patients were registered in the IRT once they signed the molecular pre-screening informed consent. Assessments being conducted were then registered in the screening IRT module. The screening assessments were performed within 3 weeks prior to randomisation. Randomisation was done on the same day as the start of study treatment. This means that there could be a time window of three weeks between registering assessments into the IRT and start of the electronic case report form (eCRF).

All analyses by strata were conducted based on information provided by the investigator in the IRT. A summary of stratification factors based on information entered into the IRT system versus information subsequently entered into the eCRF by treatment is provided in CSR Table 14.1-1.7.1a (prior to Protocol Amendment 2) and Table 14.1-1.7.2a (starting with Protocol Amendment 2), as provided in the reference pack supporting the company submission. In some cases, this information differed from data subsequently collected in the eCRF. Discordance rates of 11.1%, 6.6%, 2.3% and 0.3% were observed for the

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stratification factors of AJCC stage, prior immunotherapy for unresectable or metastatic disease (excluding adjuvant therapy), ECOG PS and BRAF mutation status.

The largest discordance rate was related to the AJCC stage (11.1%). The most likely explanation being a re-assessment of the AJCC staging by the investigator at randomisation (at treatment start).

The discordance in prior immunotherapy can also be explained, based on protocol amendment 2 which did not specify which immunotherapies would be considered. Therefore, patients with first-line use of interleukins or interferons (in a metastatic setting) could be included in the immunotherapy stratum. However, in the eCRF, interleukin or interferon use was not considered as prior immunotherapy in the first-line metastatic setting. This specific difference has no impact as the analyses conducted were (as per protocol) not stratified for prior immunotherapy given that only a small proportion of patients received prior immunotherapy.

As described in the company submission form B (page 44, Table 14) sensitivity analysis performed using the stratification factors as per the eCRF showed consistent results and no change in the PFS point estimate for the primary analysis (Enco+Bini 450 versus vemurafenib).

A6. A comparison of PFS events between BIRC and investigator assessment is provided in table 12, page 42 of the company submission. Please explain how a discordance between BIRC and investigator assessment for the PFS event of death has occurred for 23 participants across all treatment arms. It is also unclear how discordance between death (event) and a censored observation has occurred for one participant in the Enco+Bini 450 arm.

Response:

As per email correspondence with Thomas Feist (12th September), Pierre Fabre clarified that a discordance between BIRC and investigator assessment for the PFS event of death occurred for XX participants (not 23) across all treatment arms. This information is correctly shown in company submission Form B, Table 12, page 42. Details of these differences between BIRC and investigator assessment are provided below:

- For XXXX patients (XXXXX) patients in the Enco+Bini 450 arm and XXX patients in the Enco 300 arm), progression, as assessed by the investigators, was not confirmed by the BIRC following their central review. All XXXX patients subsequently died without having progression confirmed by BIRC. As such, for these XXXX patients:
  - for the PFS analysis, as assessed by the BIRC, the date of death was the date taken into account as that event occurred first according to BIRC.

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  - for the PFS analysis, as assessed by the investigator, the date of progression was the date taken into account as that event occurred first according to investigator.
- For XXXXX patients (XXX XXXXXXX in the Enco 300 arm and XXX XXXXXXX in the vemurafenib arm), progression had not been assessed by the investigator whereas this outcome was concluded by the BIRC following the central review. These XXXXX patients died within eight weeks after BIRC assessment. As such, for these XXXXX patients:
  - for the PFS analysis, as assessed by the BIRC, the date of progression was the date taken into account as that event occurred first according to BIRC
  - for the PFS analysis, as assessed by the investigator, the date of death was the date taken into account as that event occurred first according to investigator
- For one patient in the Enco+Bini 450 arm, the investigator considered that there were no adequate post-baseline tumour assessments for legibility reasons and was censored. The BIRC was able to perform the tumour assessment and did not conclude that disease progression had occurred. The patient died within eight weeks after this BIRC assessment.

A7. Please provide numerical results (hazard ratio [HR] and 95% confidence intervals) for the subgroup analyses presented graphically in Figure 18 (PFS), Figure 21 (OS) and Figure 22 (OS) of Appendix E.

Response:

Table 3: Subgroup analyses

Subgroup	HR (95% CI)		
	PFS based on BIRC for Enco+Bini 450 vs Enco 300[a]	OS for Enco+Bini 450 vs vemurafenib[b]	OS for Enco+Bini 450 vs Enco 300[c]
Sex			
Male	XXX (XXX, XXX)	0.70 (0.51, 0.98)	XXX (XXX, XXX)
Female	XXX (XXX, XXX)	0.57 (0.37, 0.87)	XXX (XXX, XXX)
Age (years)			
<65	XXX (XXX, XXX)	0.63 (0.46, 0.86)	XXX (XXX, XXX)
≥65	XXX (XXX, XXX)	0.71 (0.44, 1.15)	XXX (XXX, XXX)
Race			
Caucasian	XXX (XXX, XXX)	0.64 (0.49, 0.84)	XXX (XXX, XXX)
Non-Caucasian	XXX (XXX, XXX)	0.89 (0.38, 2.09)	XXX (XXX, XXX)
Region			
North America	XXX (XXX, XXX)	0.54 (0.22, 1.36)	XXX (XXX, XXX)
Europe	XXX (XXX, XXX)	0.65 (0.49, 0.86)	XXX (XXX, XXX)

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Subgroup	HR (95% CI)		
	PFS based on BIRC for Enco+Bini 450 vs Enco 300[a]	OS for Enco+Bini 450 vs vemurafenib[b]	OS for Enco+Bini 450 vs Enco 300[c]
Australia	XXX (XXX, XXX)	0.54 (0.10, 2.98)	XXX (XXX, XXX)
Other	XXX (XXX, XXX)	0.92 (0.37, 2.26)	XXX (XXX, XXX)
Japanese			
Yes	XXX (XXX, XXXX)	XXX (XXX, XXX)	XXX (XXX, XXX)
No	XXX (XXX, XXX)	XXX (XXX, XXX)	XXX (XXX, XXX)
LDH concentration			
<ULN	XXX (XXX, XXX)	0.51 (0.36, 0.71)	XXX (XXX, 1.02)
≥ULN	XXX (XXX, XXX)	0.95 (0.63, 1.43)	XXX (XXX, 1.45)
ECOG performance status			
0	XXX (XXX, XXX)	0.68 (0.50, 0.93)	XXX (XXX, 1.24)
1	XXX (XXX, XXX)	0.53 (0.34, 0.85)	XXX (XXX, 1.14)
BRAF mutation status			
V600E	XXX (XXX, XXX)	0.70 (0.53, 0.92)	XXX (XXX, XXX)
V600K	XXX (XXX, XXX)	0.31 (0.13, 0.74)	XXX (XXX, XXX)
Disease stage			
IIIB, IIIC, IVM1a, IVM1b	XXX (XXX, XXX)	0.70 (0.46, 1.07)	XXX (XXX, XXX)
IVM1c	XXX (XXX, XXX)	0.59 (0.43, 0.83)	XXX (XXX, XXX)
Primary site of cancer			
Skin melanoma	XXX (XXX, XXX)	XXX (XXX XXX)	XXX (XXX, XX)
Unknown	XXX (XXX, XX)	XX (XX, XX)	XXX (XXX, XX)
Number of organs involved at baseline			
1	XXX (XXX, XXX)	0.65 (0.35, 1.19)	XXX (XXX, XXX)
2	XXX (XXX, XXX)	0.63 (0.39, 1.03)	XXX (XXX, XXX)
3	XXX (XXX, XXX)	0.50 (0.29, 0.84)	XXX (XXX, XXX)
>3	XXX (XXX, XXX)	0.85 (0.52, 1.38)	XXX (XXX, XXX)
Baseline brain metastases			
Yes	XXX (XXX, XXX)	1.09 (0.22, 5.48)	XXX (XXX, XXX)
No	XXX (XXX, XXX)	0.63 (0.49, 0.82)	XXX (XXX, XXX)
Previous first-line immunotherapy			
Yes	XXX (XXX, XXX)	0.46 (0.13, 1.64)	XXX (XXX, XXX)
No	XXX (XXX, XXX)	0.65 (0.50, 0.85)	XXX (XXX, XXX)

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Subgroup	HR (95% CI)		
	PFS based on BIRC for Enco+Bini 450 vs Enco 300[a]	OS for Enco+Bini 450 vs vemurafenib[b]	OS for Enco+Bini 450 vs Enco 300[c]
Previous adjuvant therapy			
Yes	XXX (XXX, XXX)	0.83 (0.49, 1.41)	XXX (XXX, XXX)
No	XXX (XXX, XXX)	0.60 (0.44, 0.81)	XXX (XXX, XXX)

Abbreviations: AJCC, American Joint Committee on Cancer; BIRC, Blinded Independent Review Committee; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PS, performance status; ULN, upper limit of normal.
[a] Subgroup analyses: PFS based on BIRC for Enco+Bini 450 versus Enco 300 – FAS, Part 1, data cut-off 19 May 2016 (Supplement to Company submission Form B Appendices, Appendix E, Figure 18). Source: CSR end of text Figure 14.2-1.7.2a (3).
[b] Subgroup analyses: OS for Enco+Bini 450 vs. vemurafenib – FAS, Part 1, data cut-off 7 November 2017 (Supplement to Company submission Form B Appendices, Appendix E, Figure 21). Source: Dummer et al (2), CSR OS addendum Figure 14.2-2.2.1a (1).
[c] Subgroup analyses: OS for Enco+Bini 450 vs. Enco 300 – FAS, Part 1, data cut-off 7 November 2017 (Supplement to Company submission Form B Appendices, Appendix E, Figure 22). Source: CSR OS addendum Figure 14.2-2.2.2a (1).

Network meta-analysis

A8. **Priority question**. Please provide investigator-assessed PFS results (HR and 95% Credible Interval [CrI] of Enco+Bini 450 vs Dab+Tram) for the network restricted to the open label trials (COLUMBUS, COMBI-v, BRIM-3, BREAK-3 and BRF113220 Part C).

Response:

Results for the requested analysis are provided in Figure 2 and Table 4, and are consistent with the base case analysis, which also included the double-blinded RCTs, COMBI-d and coBRIM.

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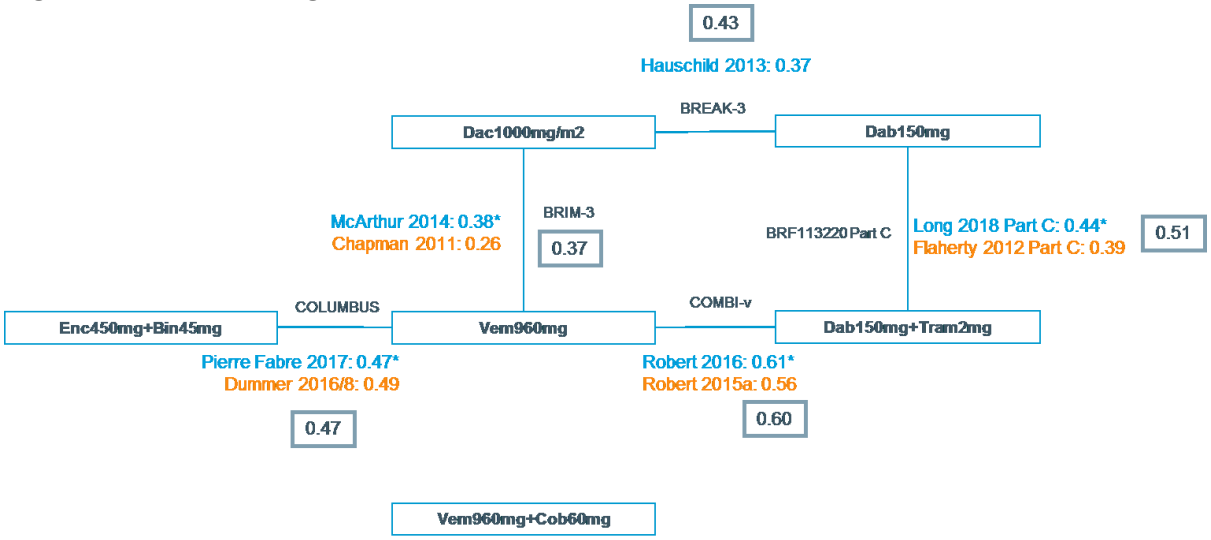
Figure 2: PFS (investigator) network of evidence (open-label studies)



Abbreviations: Bin, binimetinib; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; NMA, network meta-analysis; PFS, progression-free survival; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.
Estimates from studies highlighted in orange refer to the original publication, whereas those from studies highlighted in blue refer to updated results based on more mature data. The most recent, mature data was used wherever available, as indicated by *.

Table 4: NMA results for PFS (investigator, open-label studies, fixed effects model)

	Enco+Bini 450 vs Dabra+Tram	Dabra+Tram vs Enco+Bini 450
HR (95% CrI)	0.79 (0.58,1.07)	1.27 (0.93,1.72)
DIC	-1.28	
Total residual deviance	4.40 (1.52, 12.26)	

Abbreviations: CrI, credible interval; DIC, deviance information criterion; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

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A9. In relation to population variations within the seven trials included in the NMA, it is stated on page 72 of the company submission that: “subgroup analyses were conducted to assess the impact of these potential effect modifiers’.

Please clarify if this statement relates to the subgroup analyses from the COLUMBUS trial (presented in Section 2.7 (page 61-62) and Appendix E of the company submission) or to the subgroup analyses from the NMA. If the latter, please provide further details and numerical results of these subgroup analyses.

Response:

This sentence was originally added in reference to the sensitivity analyses rather than subgroup analyses and was left in the final submission in error. Please disregard. No sub-group analyses were conducted.

A10. It is stated within Appendix D, Section D1.3.1 (assessment of NMA treatment effect scales) that: “to account for the findings from the assessment into the validity of the proportional hazards assumption, sensitivity analysis was considered for the OS and PFS base-case analyses, removing studies where the proportional hazards assumption was violated.”

Please provide numerical results (HR and 95% CrI of Enco+Bini 450 vs Dab+Tram) for all outcomes in this sensitivity analysis.

Response:

Based on visual inspection of log cumulative hazard plots, studies that were deemed to violate the PH assumption were as follows:

- OS: BRF113220, BRIM-3, BREAK-3
- PFS: BRIM-3, BREAK-3

Results of sensitivity analyses excluding these studies are provided Figure 3 and Table 5 for OS, and Figure 4 and Table 6 for PFS. Results are consistent with the base case analyses.

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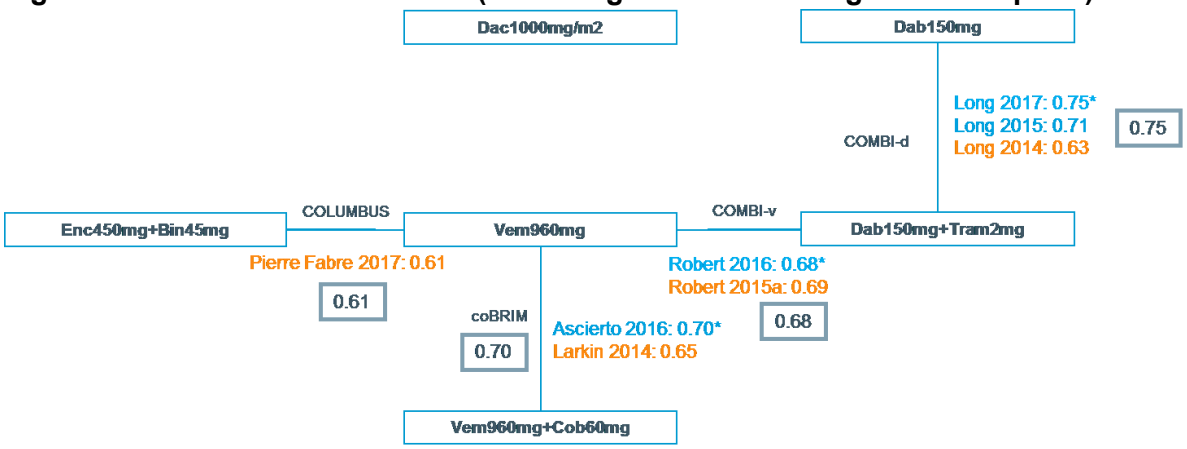
Figure 3: OS network of evidence (excluding studies violating PH assumption)



Abbreviations: Bin, binimetinib; BRAFi, serine/threonine-protein kinase B-Raf inhibitor; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; OS, overall survival; PH, proportional hazard; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.
Estimates from studies highlighted in orange refer to the original publication, whereas those from studies highlighted in blue refer to updated results based on more mature data. The most recent, mature data was used wherever available, as indicated by *.

Table 5: NMA results for OS (excluding studies violating PH assumption, fixed effects model)

	Enco+Bini 450 vs Dabra+Tram	Dabra+Tram vs Enco+Bini 450
HR (95% CrI)	0.90 (0.70, 1.17)	1.11 (0.86,1.43)
DIC	-2.40	
Total residual deviance	3.38 (0.49, 11.24)	

Abbreviations: CrI, credible Interval; DIC, deviance information criterion; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival.

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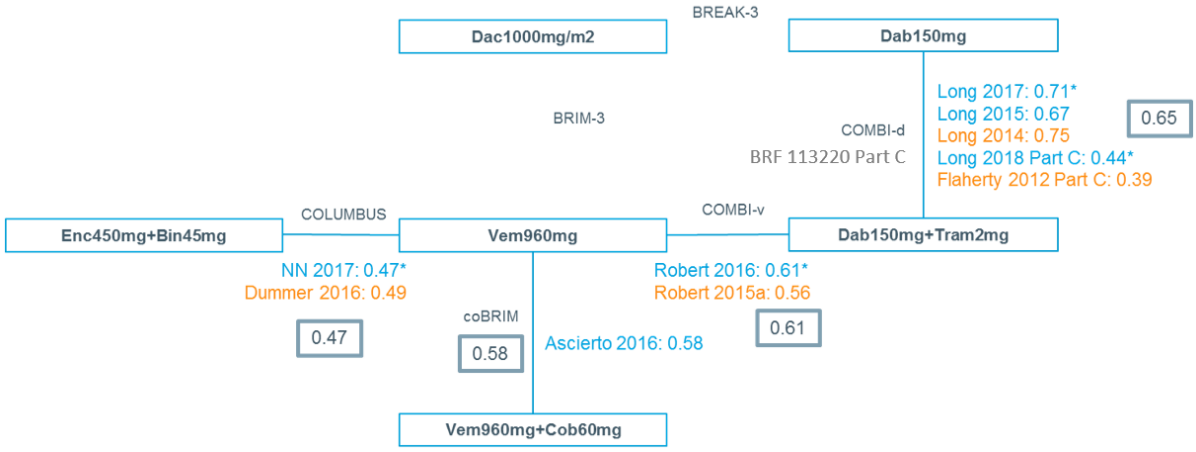
Figure 4: PFS network of evidence (excluding studies violating PH assumption)



Abbreviations: Bin, binimetinib; BRAFi, serine/threonine-protein kinase B-Raf inhibitor; Cob, cobimetinib; Dab, dabrafenib; Dac, dacarbazine; Enc, encorafenib; PFS, progression-free survival; PH, proportional hazard; Tram, trametinib; Vem, vemurafenib.
In networks of evidence showing data inputs for pairwise comparisons, these should be read from combination therapy to monotherapy or from BRAFi therapy to dacarbazine.
Estimates from studies highlighted in orange refer to the original publication, whereas those from studies highlighted in blue refer to updated results based on more mature data. The most recent, mature data was used wherever available, as indicated by *.

Table 6: NMA results for PFS (investigator, excluding studies violating PH assumption, fixed effects model)

	Enco+Bini 450 vs Dabra+Tram	Dabra+Tram vs Enco+Bini 450
HR (95% CrI)	0.77 (0.56,1.05)	1.30 (0.95, 1.77)
DIC	0.3388	
Total residual deviance	7.08 (4.19, 14.9)	

Abbreviations: CrI, credible Interval; DIC, deviance information criterion; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

A11. Please explain the statement made in Appendix D, Section D.1.3.2 (Analysis assumptions) that: "The treatment node of dacarbazine or paclitaxel in the BRF113220 Part C trial is considered to interact in the same way as dacarbazine in other trials. This is an assumption that was previously used in another NMA and has been accepted in a previous NICE appraisal (27)."

Response:

This statement was included incorrectly and does not apply to study BRF 113220 Part C, nor any of the studies included in the evidence network considered in the company submission.

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Section B: Clarification on cost effectiveness data

B1. The outcome of 'time to treatment discontinuation' (TTD) is described on page 103 of the company submission as 'Enco+Bini 450: COLUMBUS K-M TTD data until available (post-hoc analysis on TTD censoring death and lost to follow-up + log-logistic parametric extrapolation '

The outcome of 'time to treatment failure' is pre-defined within the COLUMBUS trial protocol (Section 14.2.22, supplementary document Dummer et al 2018) as 'Time to treatment failure is the time from date of randomisation/start of treatment to the earliest date of death due to any cause, or date of discontinuation due to reasons other than 'protocol violation 'or administrative problem'. The time to treatment failure for patients who did not experience treatment failure will be censored at the last adequate tumour assessment'.

Please clarify whether TTD and time to treatment failure are different.

Response:

"TTD any reason" and "time to treatment failure" as pre-defined in the COLUMBUS trial protocol are the same. When using "TTD censoring death and lost to follow up", as per the economic base case, the slight variation is that patients dying are considered as 'censored' (at the time of death, because at the time of death these patients leave the "On treatment" state of the partition model via the OS curve; thus the purpose of using "TTD censoring death and lost to follow up" was to avoid a "double-drop" of patients from survival curves in the economic model.

References

1. Array BioPharma Inc. Clinical Study Report Addendum: A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma. Clinical Study CMEK162B2301. Analysis of Overall Survival (OS) Study Part 1. 27 February 2018.
2. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018.
3. Array BioPharma Inc. Clinical Study Report: A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma. Clinical Study CMEK162B2301. 24 February 2017.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MELANOMA UK
3. Job title or position	PROJECT MANAGER MELANOMA UK DIGITAL PATIENT REGISTRY / APP
4a. Brief description of the organisation (including who funds it). How many members does it have?	Melanoma UK is a patient support and advocacy group, set up in 2007. The group was set up in memory of Jon Herron, a young man from Larne in Northern Ireland who sadly passed away in May 2008. Initially the aim was to fund raise and raise awareness of melanoma. The group started off as Factor 50 and became Melanoma UK in 2013. Our aim is to give patients and their families much needed support during the very difficult times faced upon diagnosis. We aim to get them access to the best care available and support them throughout the journey. Patients, families, carers and clinicians are at the heart of our work. We are passionate about our work and will work tirelessly to get results. Melanoma UK receives no government funding and relies on the support of its fundraisers & supporters to exist.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and	Melanoma UK not only provide face-to-face opportunities to meet and discuss how patients and carers deal with their condition, we now have a lot of our interaction taking place online, through blogs, internet forums and websites. Through the launch of the Melanoma UK Patient Registry we are now able to capture real time information on patient experience dealing with melanoma and the treatments available.

carers to include in your submission?	These various platforms provide patients and carers a safe space to post their hopes for the short-, medium- and long-term future and share their fears with others. Melanoma UK try to help people to understand their condition as we are a very hands on patient support group. For this submission we asked our patients via our various social media platforms and our registry database.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Personal (as a Carer)** As a carer I felt very overwhelmed because although I wasn't the patient, I was still 'living' with melanoma. I was the one who had to feed back to the family as my niece just didn't want to talk about her disease. I was uncertain every minute of the day however and realised that living with melanoma affects everyone differently. Knowing that my niece faced not just the physical affects, the emotional challenges faced as a carer bought on a wide range of feelings for me. I was in shock, I felt desperate and sometimes very isolated because I was uncertain of her future and couldn't really tell anyone. Trying to keep positive when deep down I knew this disease could kill her. **Feedback (patients)** Our patients have unanimously stated that the stress of living with melanoma can be seen physically, mentally and emotionally. Its not just the affects of the disease they are dealing with, its also stress, depression and anxiety. Maintaining a proper nutritional diet and all round a healthy lifestyle can take its toll.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients with *BRAF*-mutant melanoma still face significant challenges managing their disease and there remains a substantial need for well-tolerated treatments that delay disease progression and improve overall survival. This treatment could become a meaningful new therapy for patients with advanced *BRAF*-mutant melanoma.
8. Is there an unmet need for patients with this condition?	The princilple unmet need of patients dealing with metastaic melanoma is the lack of adequate treatments and limited options available
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Improve their overall condition and Hope
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	NO – melanoma is a disease that affects young, old, black, white……melanoma does not discriminate so neither should the treatment available

Other issues	
13. Are there any other issues that you would like the committee to consider?	MEL UK are so grateful to NICE for the approval of all the treatments that have come along since the days when we had nothing – the patient community recall the days when there was nothing in melanoma apart from dacarbazine and radiotherapy. We are keen to represent the patient voice today and the main unmet needs we hear from patients include uncertainty about their future, outcomes if melanoma were to spread, fears of melanoma returning The success of this treatment today could potentially improve/prolong a patient's life and although there is a commercial decision to be made, please don't let it all be about the numbers. Most patients do not know the significance of QALY, they are too busy fighting for their life.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • This treatment is vital for our patients. It gives them hope and confidence for their future • Patients and carers are at the center of everything we do and this treatment could potentially improve their life • There is more need for transformational drugs/treatments for melanoma sufferers	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Cambridge University Hospitals NHS Foundation Trust**

3. Job title or position	**Consultant and Associate Lecturer in Medical Oncology**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (I have not seen the company submission)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to control metastatic disease, prolong life expectancy and maintain good quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Median overall survival of metastatic melanoma untreated is around 8 months. In the last 5 years or so, outcomes from metastatic melanoma have radically improved with introduction of immunotherapy, and for the 45% or so of patients with BRAF mutant metastatic melanoma, the option also for BRAF targeted therapies. Since 2016, the BRAF+MEK inhibitor combination regimen, dabrafenib+trametinib, has been made available routinely (NICE TA 396) and the benefits to BRAF mutant metastatic melanoma patients achieved are extension of median overall survival to around 13 months. Some patients with lower disease volume can remain on treatment with disease controlled over several years. The 2 main limitations of dabrafenib+trametinib are 1) secondary resistance which limits duration of benefit for most patients, and 2) toxicity, with most patients experiencing immediate and chronic drug-related side effects that require treatment interrupting, dose modification and/or impact on quality of life. In this context, any equivalent BRAF+MEK inhibitor combination regimen that can match and/or extend efficacy beyond that seen with dabrafenib+trametinib with, in particular, a better side effect profile, will be of value to this subgroup of BRAF mutant melanoma patients
9. In your view, is there an unmet need for patients and	Yes – most patients with metastatic melanoma still die of their disease – median survival of those who manage to access optimal therapies with immunotherapy and BRAF targeted therapies is at best 3

healthcare professionals in this condition?	years. Survival and quality of life on treatment remain key factors that need improvement for these patients.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Most patients with BRAF mutant metastatic melanoma are eligible for both immune checkpoint inhibitors and BRAF targeted therapies. For patients being considered for BRAF targeted therapies, dabrafenib+trametinib is the only approved combination regimen and is available in the NHS, patients are registered via Bluteq. The combination of BRAF (dabrafenib) and MEK (trametinib) inhibitor has been shown to be superior to BRAF inhibitor (dabrafenib or vemurafenib) alone (see Combi-D and Combi-V clinical trial results) and, unusually, the combination od dabrafenib+trametinib has fewer skin-related side effects compared with BRAF inhibitor (dabrafenib or vemurafenib) alone. Patients are treated until disease progression.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance on dabrafenib+trametinib: TA 369 (June 2016) recommended access. TA 414 (Oct 2016) did not recommend vemurafenib+cobimetinib. This BRAF+MEKi combination has equivalent efficacy to dabrafenib+trametinib, but the manufacturer was not prepared to offer a PAS and the treatment was not consider to be cost-effective. The NICE melanoma management guidelines (NG14, 2015) predate routine access to BRAF targeted therapies and hence do not make reference to their use in clinical practice.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The order in which to access immunotherapy or BRAF targeted therapy for BRAF mutant metastatic melanoma is not clearly defined. However, for the purpose of this appraisal, sequencing of these 2 classes of treatments is not relevant, since this new combination regimen is being compared as an alternative to the only BRAF+MEK inhibitor combination regimen currently available on the NHS – dabrafenib+trametinib.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The new technology provides an alternative regimen choice to dabrafenib+trametinib.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	The new technology may potentially reduce healthcare resource requirements. Because dabrafenib+trametinib generates some cardiotoxicity, patients are required to undergo ECG and Echocardiograms prior to starting treatment and have these repeated intermittently on treatment. Encorafenib+Binimetinib does not appear to generate cardiac toxicities, so cardiac monitoring is not required. Other toxicities which are problematic with dabrafenib+trametinib are fevers, chills, flu-like symptoms and skin rash. These toxicities are all less frequent with encorafenib+binimetinib. The fevers and chills associated with dabrafenib+trametinib require close patient monitoring particularly in the first couple of months on treatment and can result in hospital admissions. This resource requirement is not apparent with encorafenib+binimetinib.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Seconday care, specialist melanoma oncology clinics only

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – the most conservative view would be equivalence to current care. The most optimistic would be an improvement in both quality and quantity of life compared with current care. From my own experience of treating 5 patients on encorafenib+binimetinib in the COLUMBUS trial, 4 patients remained on treatment for nearly 2 years, 3 patients to 3 years and 1 patient is completing a 4th year of treatment. Two patients remain on treatment in complete response. One patient stopped due to toxicity, but all other patients hae tolerated treatment with negligible side effects. This leads me to believe that the optimistic view described above may in fact be realistic.
• Do you expect the technology to increase length of life more than current care?	We do not have direct quality data to confirm this. However, indirect comparison suggests that encorafenib may be a more active BRAF inhibitor compared with dabrafenib. Our own albeit very small patient sample suggests that increase in length of life may be possible
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – there is good evidence that the side effect profile of encorafenib+binimetinib is superior to that of dabrafenib+trametinib and this is our own clinical experience.
13. Are there any groups of people for whom the technology would be more or	No. All patients with BRAF mutant metastatic melanoma should be able to access this treatment options, including, and in particular, those patients with brain metastases. Patients with brain metastases are often excluded from registration trials, but there is good evidence that these patients benefit from BRAF+MEK inhibitor therapy and should not be excluded from access.

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If anything, easier. Less patient monitoring is required. Also, trametinib is required to be refrigerated at all times. This is not the case with binimetinib. This makes it a much more manageable treatment for patients.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Patients will be monitored on treatment with imaging every 2-3 months. Progressive disease justifies stopping treatment.

Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Hopefully these will be captured
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – this regimen offers a better tolerated, easier to use regimen compared with standard dabrafenib+trametinib.
• Is the technology a 'step-change' in the	No, it's the same class of drug, but with benefits described as above

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Overall survival reported for encorafenib+binimetinib in the COLUMBUS trial is the longest reported for any BRAF+MEK inhibitor combination regimen in this patient population
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As already discussed, BRAF+MEK inhibitors do generate acute and chronic side-effects. Most are mild-moderate and manageable, but they do impact quality of life as well as tolerance and ability to deliver full doses of planned treatment. Compared with dabrafenib+trametinib, encorafenib+binimetinib appears to be better tolerated, recommended doses are maintained more easily and risk of hospital admissions are considerably lower.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – a limited number of sites in the UK took part in the Columbus trial.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important	Overall survival, progression free survival, response rate, adverse events

outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA396	No

22. How do data on real-world experience compare with the trial data?	We don't have any real world experience with encorafenib+binimetinib outside of the COLUMBUS trial. However, our experience with dabrafenib+trametinib both in and outside of trials suggests that we shouldn't expect significant differences.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Encorafenib+binimetinib is at least as effective as currently available dabrafenib+trametinib, with a better side effect profile
- Encorafenib+binimetinib offers benefits to the health service and to patients in requiring less safety monitoring, generating fewer treatment-related hospitalisations and not requiring refrigeration
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**University Hospital Southampton**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment for advanced (unresectable stage III and stage IV) melanoma is to reduce the burden of metastatic disease, minimise symptoms, and extend life while maintaining quality of life. With the increased survival seen in patients with advanced melanoma over the last 5-10 years, increasingly the aim is to allow patients to lead a relatively normal life while living with metastatic disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Responses within clinical trials of novel agents are clearly defined by RECIST and require a 30% reduction in the sum of diameters of metastatic lesions to confirm a positive response to treatment. In clinical practice however, even prolonged stabilisation of metastatic disease can be helpful if the treatment is well tolerated. Stabilising previously rapidly progressive metastases and allowing a patient to maintain good quality of life would in my view be deemed a successful outcome to treatment, although clearly significant shrinkage of metastases or even a complete response would be the ideal outcome.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Despite a number of new treatment options for patients with metastatic melanoma there remains a cohort of patients who struggle to tolerate the currently available agents. For those patients with a BRAF mutation currently approved options include combination BRAF/MEK inhibition with dabrafenib and trametinib, and for those who are intolerant of this approach the BRAF inhibitor monotherapy vemurafenib. For dabrafanib and trametinib a significant proportion of patients will experience significant toxicity with one study showing a treatment discontinuation rate of 13% due to side effects. Fever or chills is common with 54% of patients experiencing this at least once. This can be debilitating and of sufficient severity to warrant hospital admission. For a proportion of these patients this can be a recurrent event. Dose reductions can be offered as well as the concurrent use of steroids but

	despite this a proportion of patients will either be intolerant of these drugs, or have a significantly reduced quality of life as a consequence of toxicity. The current alternative in this situation would be to switch to vemurafenib however there is clear evidence that treatment with a BRAF inhibitor as a monotherapy is inferior to combination treatment with BRAF and MEK inhibitors. Equally many of the class effect toxicities of BRAF inhibitors, such as an increase in skin squamoproliferative lesions, are more frequent when a MEK inhibitor is not used. The significant photosensitivity associated with vemufarenib is also problematic with some patients experiencing blistering sunburn after very short periods of UV exposure, including through glass. As such there is a clear need for alternative agents with differing toxicity profiles to allow as many patients as possible to both benefit from disease control from these active anti-cancer drugs, but also to do so with miminal toxicity and therefore maximal quality of life.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE has issued guidance around the use of both dabrafenib and trametinib in combination, as well as vemurafenib monotherapy.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Patients with metastatic BRAF mutant melanoma have two main avenues of therapy in the form of BRAF directed agents, and immunotherapy. There is no robust evidence to support the order in which these approaches are used and in general both options are offered as first line treatment with a discussion with the patient as to the benefits of each. All patients with BRAF mutant melanoma should however be offered access to BRAF directed therapy at some stage in their treatment pathway.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Encorafenib and binimetinib in combination would not alter the current pathway of care but would provide an additional option for BRAF targeted therapy particularly in the cohort of patients who are intolerant of other drugs currently approved in this setting.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes this technology would be used in the same way as currently approved agents in NHS clinical practice.
• How does healthcare resource use differ between the technology and current care?	No difference.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist melanoma clinics in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment required.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	There is no directly comparable data between encorafenib and binimetinib vs dabrafenib and trametinib however looking at the relative comparison between the common comparator vemurafenib then the survival benefit for both agents appears similar.
• Do you expect the technology to increase health-related quality of life more than current care?	I would expect the current agent to improve quality of life for those patients who were intolerant of dabrafenib and trametinib due to fever and were subsequently switched to encorafenib and binimetinib and experienced less toxicity as a consequence.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are no currently recognised groups where this technology would be more or less effective or appropriate at initiation of treatment. This may however be more effective in patients unable to tolerate other BRAF inhibitors
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Unlikely to be any easier or more difficult to use than other agents.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with other agents in this class patients would require a BRAF mutation to be identified in their tumour prior to initiation of treatment. Treatment would then be given until unacceptable toxicity or lack of efficacy defined by radiological progression.
16. Do you consider that the use of the technology will result in any substantial health-	There is the potential for less clinically relevant toxicity compared to other agents in the class.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This is the same technology as other treatments already available so I wouldn't regard it as a step change, rather an alternative option for patients who don't do well on the alternatives.
• Does the use of the technology address any particular unmet need of the patient population?	Yes for those intolerant of existing agents.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Many of the side effects of this treatment are biochemical abnormalities which are unlikely to be noticed by the patient. Any clinically meaningful side effects have the potential to adversely affect quality of life as with all systemic cancer treatments.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The Columbus trial used vemurafenib as a comparator which is no longer the standard of care in the UK. The currently used agents dabrafenib and trametinib were however also studied in comparison to vemurafenib allowing the potential for indirect comparison.
• If not, how could the results be extrapolated to the UK setting?	Indirect comparison with the common comparator vemurafenib
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are survival and toxicity. Does this treatment extend life with manageable toxicity such that quality of life is preserved? The Columbus trial used PFS as primary endpoint with survival as a secondary endpoint. Recent publication of these results confirmed a survival advantage for encorafenib and binimetinib over vemurafenib . Toxicity data was also measured.
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Toxicity data has been reported in detail in the clinical trial of these agents.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA396	no
22. How do data on real-world experience compare with the trial data?	I am not aware of any real-word data on encorafenib and binimetinib.

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Encorafenib and binimetinib represent an alternative treatment option for patients with BRAF mutant advanced melanoma.
- Outcome data would suggest that encorafenib and binimetinib are at least as efficacious as the current standard of dabrafenib and trametinib
- The differing toxicity profile of encorafenib and binimetinib provide an additional treatment option for patients unable to tolerate the currently available agents in this class.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Melanoma UK and consequently I will not be submitting a personal statement.

Name: DIANE CANNON.....

Signed:

Date: 13.11.2018.....

……

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ID923 ERG REPORT

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

This report was commissioned by the NIHR HTA Programme as project number 17/109/14

Completed 18th October 2018

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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Declared competing interests of the authors: Professor Danson screened and enrolled patients for the COLUMBUS trial on behalf of the local principal investigator (Dr Lester) at Weston Park Hospital in Sheffield. The funding for the running of the trial was paid to the hospital. Within the last 3 years**,** Professor Plummer has been in receipt of consultancy fees from Pierre Fabre Ltd.

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervision of the collation of the final report
James Mahon	Critical appraisal of the economic evidence and critique of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the adverse event data
Eleanor Kotas	Cross checking of the submission search strategies
Joanne McEntee	Critical appraisal of the company submission
Sarah Danson	Clinical advice and critical appraisal of the clinical sections of the company submission

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LIST OF ABBREVIATIONS

AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
BID	twice daily
BIRC	blinded independent review committee
BOR	best overall response
BRAF	B-Raf proto-oncogene, serine/threonine-protein kinase
BRAFi	BRAF inhibitor
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CR	complete response
CrI	credible interval
CSR	clinical study report
Dab+Tram	dabrafenib in combination with trametinib
DCFB	difference in change from baseline
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
Enco 300	encorafenib 300 mg QD
Enco+Bini	encorafenib in combination with binimetinib
Enco+Bini 300	encorafenib 300 mg QD in combination with binimetinib 45 mg BID
Enco+Bini 450	encorafenib 450 mg QD in combination with binimetinib 45 mg BID
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-5L	EuroQoL-5 dimensions-5 levels
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FAS	full analysis set
FDA	Food and Drug Administration
FPFV	first patient first visit
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
ITT	intention-to-treat
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LY	life years
MEK	mitogen-activated extracellular signal-regulated kinase
MEKi	MEK inhibitor
MMRM	mixed-effect model for repeated measures
NE	not estimable
NMA	network meta-analysis
OR	odds ratio
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PH	proportional hazards
PP	post-progression
PPS	per-protocol set
PR	partial response

PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life year
QD	once daily
RAF	serine/threonine-protein kinase
RCT	randomised controlled trial
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SD	standard deviation
StD	stable disease
TTD	time to treatment discontinuation
TTR	time to objective response
ULN	upper limit of normal

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 (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

recommended for the adjuvant treatment of resected BRAF V600 mutation-positive melanoma by NICE in October 2018.The impact of adjuvant treatment with an immunotherapy on the treatment pathway in the metastatic setting is currently unknown.

Intervention

The intervention discussed in the CS is Enco+Bini 450 and this matches the intervention specified in the final scope issued by NICE. Encorafenib is available as 50mg and 75mg hard capsules. Binimetinib is available as 15mg film-coated tablets. The recommended dose of encorafenib, when used in combination with binimetinib, is 450mg (six 75mg capsules) once daily. The recommended dose of binimetinib, when used in combination with encorafenib, is 45mg (three 15mg tablets) twice daily.

Before receiving treatment with Enco+Bini 450, patients must have had confirmation of a BRAF V600 positive mutation using a validated test. Clinical advice to the ERG is that testing for BRAF V600 status in patients with melanoma is standard of care in the NHS.

Comparators

The comparator discussed in the CS and specified in the final scope issued by NICE is Dab+Tram.

Clinical advice to the ERG is that the first-line treatment given to many NHS patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma is an immunotherapy (pembrolizumab, nivolumab or the combination of nivolumab+ipilimumab). Only a minority of patients treated in the NHS, i.e., those with highly symptomatic disease or rapidly progressing disease, are treated with a targeted therapy as a first-line treatment, generally the combination of Dab+Tram; however, a BRAFi monotherapy treatment (vemurafenib or dabrafenib) may be used in patients who have contraindications to Dab+Tram.

Although not identified as comparators in the final scope issued by NICE, clinical advice to the ERG is that, if treated in the NHS, the patient cohort recruited to the COLUMBUS trial would be prescribed first-line treatment with an immunotherapy. However, there is no direct or indirect evidence to demonstrate whether Enco+Bini 450 is more effective than immunotherapy (pembrolizumab, nivolumab with or without ipilimumab, or ipilimumab) in this group of patients.

Outcomes

Data are available from the COLUMBUS trial for all five outcomes specified in the final scope issued by NICE: PFS, OS, response rate (reported as overall response rate [ORR] and

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 (BICR). 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 BICR. 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 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

efficacy (PFS and OS), safety and HRQoL. The company identified seven RCTs designed to investigate the efficacy of BRAFi therapies. Clinical efficacy and safety data were available from seven of these trials, whilst HRQoL data were collected as part of five of these trials.

Results from the NMAs showed no statistically significant differences between treatment with Enco+Bini 450 and treatment with Dab+Tram for the outcomes of investigator-assessed PFS and OS. Three different HRQoL NMA results were estimated: pre-progression, difference in change from baseline at Week 32 and at disease progression. The HRQoL results all favoured treatment with Enco+Bini 450 (Delta<0); however, the credible intervals (CrIs) cross 0 for all analyses. The ERG highlights that the numerical improvements in favour of Enco+Bini 450 were inferior to the minimal difference in EQ-5D-5L index score considered to be clinically important (0.08 points).

NMA results for the incidence of any Grade ≥3 AEs favoured treatment with Dab+Tram (odds ratio [OR>1]), while results for serious AEs favoured treatment with Enco+Bini 450 (OR<1). However, for both analyses, the CrIs crossed 1.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a broad systematic literature review to identify published evidence relevant to the clinical effectiveness of interventions for unresectable or metastatic melanoma. The ERG is satisfied with the company's search strategy and stated inclusion and exclusion criteria. The ERG is confident that the searching was carried out to an acceptable standard and is not aware of any additional studies that should have been included in the company's review.

The ERG considers that the COLUMBUS trial was of good quality and was well-conducted, with blinded independent review of PFS outcomes and collection of HRQoL data. The ERG notes that the patients recruited to the trial are largely representative of patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma who are treated in the NHS, with the caveat that very few patients in the COLUMBUS trial had brain metastases and none of the patients had a poor PS (i.e., PS ≥2).

The ERG notes that the clinical efficacy outcomes and the HRQoL outcomes of the COLUMBUS trial favour the use of Enco+Bini 450 and that treatment with Enco+Bini 450 appears to be well tolerated by patients. However, the ERG highlights that the results from the COLUMBUS trial do not provide evidence for the clinical effectiveness of Enco+Bini 450 versus Dab+Tram, the comparator specified in the final scope issued by NICE.

The results of the company's NMAs comparing Enco+Bini 450 with Dab+Tram showed no statistically significant difference between these two treatments for investigator-assessed PFS, OS, AEs and HRQoL. For all base case and sensitivity analyses, credible intervals (CrIs) were wide and crossed 1.

The ERG considers that the results of the NMAs should be viewed with caution due to numerous methodological limitations. The limitations include the sparsity of evidence in the networks (particularly the HRQoL network), the variability in the lengths of trial follow-up (2 years to 6 years), the differences between trials in median follow-up for OS (11 months to 33.3 months), the inclusion of dacarbazine within the networks, and that only an NMA of PFS by local investigator review (rather than BIRC) was feasible. Five of the seven trials included within the NMA were of an open-label design and investigator assessment of PFS in open-label trials may be subject to bias.

The ERG highlights that PFS results from the COLUMBUS trial showed that Enco+Bini 450 is more effective than vemurafenib, the PFS results from the COMBI-v trial showed that the Dab+Tram is more effective than vemurafenib and that PFS results from both trials for patients treated with vemurafenib are comparable. In addition, clinical advice to the ERG is that Enco+Bini 450 and Dab+Tram are likely to be similar in terms of clinical effectiveness outcomes.

NICE currently recommends the use of several immunotherapies for the treatment of advanced (unresectable or metastatic) melanoma (i.e., ipilimumab monotherapy, nivolumab monotherapy, nivolumab in combination with ipilimumab or pembrolizumab). The immunotherapies can be used in all patients, regardless of BRAF status. The ERG notes from NICE's comments on the draft scope for this appraisal that NICE did not consider immunotherapies to be appropriate comparators to Enco+Bini 450. NICE further commented that immunotherapies were not included in any previous scopes in this disease area. The ERG notes that ipilimumab (the only immunotherapy recommended by NICE at that time) was not included as a comparator in the final scope for the appraisal of Dab+Tram in TA396. 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; the rationale for not including immunotherapies as comparators in the final scope issued by NICE is unclear.

The ERG considers that as many NHS patients will be treated with an immunotherapy, results from the company's NMAs are only relevant to patients in the NHS with highly symptomatic or rapidly deteriorating disease. However, their relevance may be limited as only patients with a

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 tunnel 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 tunnel state, utility values differed by primary treatment but in all other states (including other tunnel 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 to [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 that the two populations experience different incidences of Grade 3 and 4 AEs. 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.
- On the basis that patients treated with Enco+Bini 450 and Dab+Tram experience different incidences of Grade 3 and 4 AEs, 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

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B1.3 of the company submission (CS). The Evidence Review Group (ERG) considers that the company's description presents an adequate summary of the underlying health problem. Key points made by the company and considered by the ERG to be particularly relevant to the current appraisal are presented in Box 1.

Box 1 Key points from the company's description of underlying health problem

Description of the disease

- Melanoma originates from skin cells called melanocytes and, in its earliest form, will present as benign lesions[1] which can then progress through various stages of malignancy. In its earliest stages, melanoma is often asymptomatic and the 10-year survival for patients with Stage 1A (confined to the skin) melanoma is 93%.[2] However, as the disease spreads, or metastasises to nearby lymph nodes (regional metastases, Stage III), or to more distant parts of the body (distant metastases, Stage IV),[2] survival rates deteriorate. The survival rate at 5 years for patients with Stage IIIB disease is 59%, whilst the 1-year survival rate is as low as 33% for patients with Stage IV disease (depending on the site of metastasis).[2]
- Around 9% of patients with melanoma will be diagnosed with advanced stages of disease (Stage III or Stage IV).[3] In addition, patients may progress from early stage disease to advanced disease, despite treatment; an estimated 20% of primary melanomas progress to metastatic disease.[4]
- Around 50% of melanomas express a mutated form of the B-Raf proto-oncogene kinase (BRAF) and over 90% of these are BRAF V600 mutations.[5]

Epidemiology

- Melanoma, an aggressive form of skin cancer, is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases.[3] In 2016 there were 13,748 new diagnoses of melanoma registered in England[6] and 1,937 deaths.[7] Melanoma incidence increases from around age 20–24, with significantly more females affected in younger age groups, while more males are affected in older age groups.[3] Melanoma incidence rates in the UK have increased by 128% since the early 1990s and the rate is predicted to increase by a further 7% by 2035.[3]

Source: adapted from CS, Section B1.3

The ERG notes that patients with metastatic melanoma may experience pain, excessive tiredness or weight loss.[8] Patients may also experience a range of other symptoms according to where in the body the disease has metastasised.[8] Melanoma commonly metastasises to the lymph nodes, lungs, liver, bones, abdomen and the brain.[8]

2.2 Company's overview of current service provision

The company's overview of current service provision is presented in Section B1.3 of the CS. The ERG considers that the company's overview presents an accurate summary of current service provision and highlights the key points made by the company in Box 2. For clarity, the treatment options recommended by the National Institute for Health and Care Excellence (NICE), and discussed by the company in Box 2, are listed in Table 1.

Box 2 Key points from the company's overview of current service provision

Treatment options

- Treatment options for patients with unresectable or metastatic melanoma are guided by the presence of BRAF mutations, prior treatment history and patient and disease characteristics.[2,4,9]
- NICE clinical guideline NG14,[10] published in 2015, recommends that for patients with unresectable Stage III melanoma or with metastatic (Stage IV) melanoma, systemic cancer treatment with either targeted treatments or immunotherapy should be considered.
- At the time of the publication of NG14,[10] targeted therapies recommended by NICE were the BRAF inhibitor (BRAFi) monotherapies, vemurafenib[11] and dabrafenib.[12] Subsequently, NICE has recommended combination therapy with the MEK inhibitor (MEKi) trametinib and BRAFi dabrafenib,[13] with the expectation that this combination would replace the monotherapy options of vemurafenib and dabrafenib. BRAFi with MEKi combination treatments are now considered as standard of care for BRAF mutant melanoma. ESMO guidelines recommend trametinib plus dabrafenib as a first-line option in patients with BRAF mutation-positive disease.[9]
- Immunotherapies currently recommended by NICE for treating advanced melanoma (irrespective of BRAF mutation status) include nivolumab in combination with ipilimumab,[14] nivolumab monotherapy,[15] pembrolizumab monotherapy[16,17] and ipilimumab monotherapy.[18,19]
- NICE clinical guideline NG14[10] and ESMO guidelines[9] do not state a preference for either targeted BRAFi+MEKi or immunotherapy for the first line treatment of BRAF V600 mutation-positive metastatic melanoma. However, it is recognised that these treatments may offer differing efficacy profiles which make them suitable for different sub-populations of patients. The BRAFi+MEKi combination therapies offer high response rates and rapid response induction associated with symptom control, whilst nivolumab and pembrolizumab, offer lower response rates, but responses may be more durable. Responses associated with ipilimumab are lower than those associated with nivolumab and pembrolizumab.[2]
- Cytotoxic chemotherapy with dacarbazine should be considered only if targeted therapy or immunotherapy are not suitable.[2,4,9,20]

BRAFi=BRAF inhibitor; ESMO=European Society for Medical Oncology; MEK=mitogen-activated extracellular signal-regulated kinase MEKi=MEK inhibitor
Source: adapted from CS, Section B1.3

Clinical advice to the ERG is that dabrafenib and vemurafenib monotherapies are used in the NHS to treat selected patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma, for example patients with a history of cardiac complications.

Table 1 Treatment options recommended by NICE for advanced (unresectable or metastatic) melanoma

Targeted therapy	NICE Guidance	Treatment type	NICE recommendation
Trametinib+Dabrafenib	TA396[13] (2016)	BRAFi+MEKi combination	For treating unresectable or metastatic melanoma with a BRAF V600 mutation
Dabrafenib	TA321[12] (2014)	BRAFi	For treating unresectable or metastatic BRAF V600 mutation‑positive melanoma
Vemurafenib	TA269[11] (2012)	BRAFi	For treating BRAF V600 mutation‑positive unresectable or metastatic melanoma
Immunotherapy			
Nivolumab	TA384[15] (2016)	PD-1 antibody	For treating advanced (unresectable or metastatic) melanoma in adults
Nivolumab with ipilimumab	TA400[14] (2016)	PD-1+CTLA4 antibody combination	For treating advanced (unresectable or metastatic) melanoma
Pembrolizumab	TA366[17] (2015, updated 2017)	PD-1 antibody	For treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab
Pembrolizumab	TA357[16] (2015, updated 2017)	PD-1 antibody	For treating advanced (unresectable or metastatic) melanoma after the disease has progressed with ipilimumab and, for BRAF V600 mutation‑positive disease, a BRAFi or MEKi
Ipilimumab	TA319[19] (2014)	CTLA-4 antibody	For previously untreated advanced (unresectable or metastatic) melanoma
Ipilimumab	TA268[18] (2012)	CTLA-4 antibody	For previously treated advanced (unresectable or metastatic) melanoma
Cytotoxic chemotherapy			
Dacarbazine	NG14[10](2015)	Cytotoxic chemotherapy	Consider dacarbazine for people with Stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable (NICE cautions that dacarbazine is not licensed for the treatment of melanoma)

BRAFi=BRAF inhibitor; CTLA-4=cytotoxic lymphocyte-associated protein 4; PD-1=programmed cell death protein 1

The company has discussed the role of BRAF inhibitors, BRAFi+MEKi combinations and immunotherapies in the treatment of advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The company states that NICE guidelines[10] and the European Society of Medical Oncology (ESMO) clinical guidelines[9] do not specify the treatment sequence of BRAFi+MEKi combinations and immunotherapies. The company also states that it is recognised that these treatments may offer differing efficacy profiles which make them suitable for different sub-populations of patients. The BRAFi+MEKi combination therapies offer high response rates and rapid response associated with symptom control, whilst nivolumab and pembrolizumab, offer lower response rates (response rates associated with ipilimumab are lower than those for nivolumab or pembrolizumab), but responses may be more durable.[9]

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 not included in the CS. 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.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope[22] issued by NICE and that addressed within the CS is presented in Table 2. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 2 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 PAS addendum. 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

The company presents clinical evidence for this appraisal from the COLUMBUS trial, an open-label, phase III, RCT. Patients recruited to the COLUMBUS trial were randomised to receive either Enco+Bini 450, encorafenib 300mg monotherapy (Enco 300), or vemurafenib monotherapy. To enable comparisons to be made between the effectiveness of treatment with Enco+Bini 450 and Dab+Tram, the company has conducted network meta-analyses (NMAs). The outcomes from the NMAs are used by the company to populate their economic model.

3.1 Population

The patient population described in the final scope[22] issued by NICE and discussed in the CS is adults with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. This matches the patient population in the marketing authorisation for Enco+Bini 450 that was issued by the European Medicines Agency (EMA) in September 2018.[23]

No treatment line is specified in either the final scope[22] issued by NICE, the CS, or the marketing authorisation.[23] The COLUMBUS trial inclusion criteria allowed the recruitment of patients who were treatment-naïve or who had progressed on, or after, first-line treatment with an immunotherapy in the metastatic setting. However, the company states that only 6% of patients recruited to the COLUMBUS trial had received prior treatment with an immunotherapy in the metastatic setting. This means that the evidence presented in the CS can be considered to be for the clinical effectiveness of Enco+Bini 450 as a first-line treatment option.

Patients with untreated central nervous system (CNS) lesions were excluded from the COLUMBUS trial. This means that there is no clinical evidence to support the use of Enco+Bini 450 in patients with advanced (unresectable or metastatic) BRAF 600 mutation-positive melanoma who have untreated brain metastases. As only 3.5% of the patients recruited to the COLUMBUS trial had pre-treated brain metastases, this means that there is only limited clinical effectiveness evidence to support the use of Enco+Bini 450 in this subgroup. Clinical advice to the ERG is that, in the NHS, patients with brain metastases represent an important patient subgroup.

Only patients with an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 or 1 were recruited to the COLUMBUS trial. This means that there is no clinical effectiveness evidence for the use of Enco+Bini 450 in patients with ECOG PS ≥2.

The ERG is aware that there is a move towards treating patients with melanoma in the earlier, adjuvant setting. The combination treatment of Dab+Tram was recommended for use in the treatment of resected BRAF V600 mutation-positive melanoma by NICE in October 2018.[24] Two other appraisals of adjuvant treatments, pembrolizumab[25] and nivolumab,[26] are currently

under consideration by NICE. The impact of using an adjuvant treatment with either a combination BRAF+MEK inhibitor, or an immunotherapy on the treatment pathway in the metastatic setting is currently unknown.

3.2 Intervention

The intervention discussed in the CS is Enco+Bini 450 and matches the intervention specified in the final scope[22] issued by NICE.

Encorafenib is a rapidly accelerated fibrosarcoma (RAF) kinase inhibitor that suppresses the pathway in melanoma tumour cells that express BRAF mutations (CS, p9). Binimetinib inhibits the kinase activity of mitogen-activated extracellular signal-regulated kinase (MEK) 1 and MEK 2, resulting in the inhibition of BRAF V600 mutant cell lines (CS, p9). The combination of encorafenib and binimetinib inhibits the RAF and MEK kinases in melanoma tumour cells to augment inhibition of intracellular signalling and greater anti-tumour activity (CS, p9).

Encorafenib is available as 50mg and 75mg hard capsules. The recommended dose of encorafenib, when used in combination with binimetinib, is 450mg (six 75mg capsules) once daily. Binimetinib is available as 15mg film-coated tablets. The recommended dose of binimetinib, when used in combination with encorafenib, is 45mg (three 15mg tablets) twice daily (CS, Table 2). Treatment with Enco+Bini 450 should continue until the patient no longer derives benefit or develops unacceptable toxicity (CS, Table 2). Clinical advice to the ERG is that for some patients, the daily treatment regimen of 12 tablets associated with Enco+Bini 450 might be problematic.

Before receiving treatment with Enco+Bini 450, patients must have confirmation of a BRAF V600 positive mutation obtained using a validated test. The company states (CS, p10) that, as BRAF testing is a requirement for the use of Dab+Tram (NHS standard of care), the introduction of Enco+Bini 450 will not require a change in clinical practice. Clinical advice to the ERG is that testing for BRAF V600 status in patients with melanoma is standard of care in the NHS.

3.3 Comparators

The comparator discussed in the CS is Dab+Tram. This matches the comparator specified in the final scope[22] issued by NICE. In the absence of any head-to-head trials comparing treatment with Enco+Bini 450 versus Dab+Tram, the company has conducted NMAs.

As discussed in Section 2.2 of this ERG report, clinical advice to the ERG is that the first-line treatment given to many NHS patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma is an immunotherapy (pembrolizumab, nivolumab or the

combination of nivolumab+ipilimumab). Only a minority of patients treated in the NHS, i.e., those with highly symptomatic or rapidly progressing disease are treated with a targeted therapy as a first-line treatment, generally the BRAFi+MEKi combination of Dab+Tram; however, a monotherapy (vemurafenib or dabrafenib) may be used in patients who have contraindications to Dab+Tram.

Clinical advice to the ERG is that, if treated in the NHS, the patient cohort recruited to the COLUMBUS trial would be prescribed first-line treatment with an immunotherapy. It is not known whether Enco+Bini 450 is more effective than immunotherapy (pembrolizumab, nivolumab with or without ipilimumab or ipilimumab monotherapy) in this group of patients. The company has carried out NMAs to assess the relative efficacy of Enco+Bini 450 versus Dab+Tram; however, results from this assessment are only relevant to patients in the NHS with highly symptomatic or rapidly deteriorating disease (as these are the only patients who are likely to be treated with Dab+Tram in the first-line setting). In addition, the ERG notes that only patients with an ECOG PS of 0 or 1 were recruited to the trials included in the company NMAs and so are likely to be fitter than patients with highly symptomatic or rapidly deteriorating disease treated in the NHS. The ERG notes that the results of the COLUMBUS trial (Enco+Bini 450 is more effective than vemurafenib) are consistent with the results of the COMBI-v trial (Dab+Tram is more effective than vemurafenib).

NICE currently recommends the use of several immunotherapies for the treatment of advanced (unresectable or metastatic) melanoma, ipilimumab monotherapy, nivolumab monotherapy, nivolumab in combination with ipilimumab or pembrolizumab (Table 1). The immunotherapies can be used in all patients, regardless of BRAF status. The ERG notes from NICE's comments on the draft scope[27] for this appraisal that NICE did not consider immunotherapies to be appropriate comparators to Enco+Bini 450. NICE further commented that immunotherapies were not included in any previous scopes in this disease area. The ERG notes that ipilimumab (the only immunotherapy recommended by NICE at that time) was not included as a comparator in the final scope for the appraisal of Dab+Tram in TA396.[13] The ERG acknowledges that immunotherapies were not identified as comparators in the final scope[22] issued by NICE; however, the rationale for that decision is unclear as immunotherapies are currently recommended by NICE for this group of patients.

3.4 Outcomes

Clinical evidence for the efficacy of Enco+Bini 450 versus vemurafenib and versus Enco 300 is presented in the CS. Data are available from the COLUMBUS trial for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), OS, response rate (reported as overall response rate [ORR] and duration of response [DOR]), AEs of

treatment and health-related quality of life (HRQoL). The company has also reported the outcomes of analyses of time to objective response (TTR) and time to treatment response.

The company explains (CS, p50) that due to the hierarchical testing procedure used in the COLUMBUS trial, the results presented in the CS for the key secondary outcome of OS are descriptive only. Please see Section 4.5.1 of this ERG report for discussion of the company's statistical testing procedure.

The outcomes for the clinical effectiveness of Enco+Bini 450 versus Dab+Tram are available from the company's NMAs. The outcomes presented in the CS are PFS, OS, HRQoL and AEs. Please see Section 4.9 of this ERG report for discussion of the NMAs.

3.5 Economic analysis

As specified in the final scope[22] issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 30-year time horizon (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

In the final scope[22] 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 progressed on or after first-line immunotherapy. The company reports (CS, p8) that only 6% of patients in the COLUMBUS trial had received prior immunotherapy in the metastatic setting and that, given the small number of patients, it was not possible to conduct any subgroup analyses based on prior treatment (CS, p8).

3.7 Other considerations

The company did not identify any equality issues (CS, p12). The ERG is aware that the company has agreed a Patient Access Scheme (PAS) price for Enco+Bini 450 with the Department of Health (DH). The PAS prices of Enco+Bini 450 and the list prices of Dab+Tram are used in all the cost effectiveness analyses presented in the CS. Dabrafenib and trametinib are provided to the NHS under a PAS; the discounted prices for these two drugs are confidential and, therefore, not known to the company. The ERG has, however, re-run the company's base case analysis using the discounted prices of all drugs included in the company model and the results are provided in a confidential appendix.

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

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D of the CS. The ERG assessed whether the review was conducted in accordance with the key features listed in Table 3. Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence are appropriate. The ERG has run its own searches and is confident that no relevant clinical publications have been missed.

Table 3 ERG appraisal of systematic review methods used by the company

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 applied by two or more reviewers independently?	Yes
Were data extracted by two or more reviewers independently?	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not reported
Were appropriate methods used for data synthesis?	Yes

Source: LRiG Checklist 2017

4.1.1 Data extraction

It is unclear whether data were extracted by one reviewer, or independently by two reviewers.

4.1.2 Quality assessment methods

The company has (appropriately) applied the criteria in the NICE Guide to the Methods of Technology Appraisal[28] that are recommended for use when assessing the quality of RCTs. It is unclear whether the quality assessment was completed by one reviewer, or independently by two reviewers.

4.1.3 Data synthesis

The company identified only one trial, the COLUMBUS trial, that reported clinical effectiveness outcomes for Enco+Bini 450 in patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. In the absence of any head-to-head trials comparing the clinical effectiveness of treatment with Enco+Bini 450 versus Dab+Tram, the comparator stipulated in the final scope[22] issued by NICE, the company has conducted NMAs.

4.2 Identified trials

4.2.1 Studies of Enco+Bini 450

The COLUMBUS trial is the only identified RCT that provides evidence for the use of Enco+Bini 450 in patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. Neither of the comparators in the COLUMBUS trial (i.e., Enco 300 or vemurafenib) match the comparators specified in the final scope[22] issued by NICE. All information relevant to the COLUMBUS trial presented in this ERG report is taken directly from the CS, unless otherwise stated.

The company identified an ongoing, phase II, single-arm study[29] of Enco+Bini 450 in patients with locally advanced or metastatic BRAF V600 mutation-positive melanoma. The company reports (CS, p14) that data from the LOGIC-2 study[29] were presented as supportive evidence in the company's regulatory submission to the EMA.[23] As the LOGIC-2 study[29] does not provide comparative data and the results from the trial do not inform the economic model, the company has not discussed the LOGIC-2[29] study in the CS (CS, p14).

4.2.2 Studies of comparator treatments

In the absence of any head-to-head comparisons of the clinical effectiveness of Enco+Bini 450 versus Dab+Tram, the company has conducted a series of NMAs. The six trials included in the company's NMAs (in addition to the COLUMBUS trial) are briefly described in Table 4. Please see Section 4.9 of this ERG report for discussion and critique of the company's NMAs.

Table 4 Trials included in the company's network meta-analyses

Trial	Intervention	Comparator(s)
COLUMBUS[30-32]	Enco+Bini 450	Encorafenib 300mg Vemurafenib
COMBI-v[33,34]	Dab+Tram (300mg Dab+2mg Tram daily)	Vemurafenib
COMBI-d[35-37]	Dab+Tram (300mg Dab+2mg Tram daily)	Dabrafenib
BRF113220 Part C[38-42]	Dab+Tram (300mg Dab+1mg Tram daily)	Dab+Tram (300mg Dab+2mg Tram daily) Dabrafenib
CoBRIM[43-45]	Vemurafenib+Cobimetinib	Vemurafenib
BREAK-3[46-48]	Dabrafenib	Dacarbazine
BRIM-3[49-52]	Vemurafenib	Dacarbazine

4.3 Characteristics of the COLUMBUS trial

4.3.1 Trial characteristics

The COLUMBUS trial is a two-part, phase III, open-label RCT. In Part 1 of the trial, 577 patients were randomised to receive treatment with either Enco+Bini 450, Enco 300 monotherapy or vemurafenib. The trial is being conducted internationally, in 28 countries, with

eight centres (14 patients) in the UK. Patients were recruited to the trial between December 2013 and April 2015.[30]

Part 2 of the COLUMBUS trial is ongoing, with 344 patients randomised, in a 3:1 ratio, to receive either encorafenib (300mg) monotherapy or encorafenib 300mg+binimetinib. The company states (CS, p15) that Part 2 was added to the COLUMBUS trial in response to a requirement from the US Food and Drug Administration (FDA) for the company to determine the clinical effectiveness of Enco+Bini 450 compared with Enco+Bini 300 and to assess the contribution of binimetinib to the treatment combination. The company states (CS, p16) that only the results of Part 1 of the COLUMBUS trial are relevant to the present appraisal as patients in Part 1 have received the dosing regimen stipulated in the marketing authorisation, Enco+Bini 450. The company also states (CS, p37) that encorafenib 300 will not be licensed for use in patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.

All information presented in the CS, and in this ERG report, are from Part 1 of the COLUMBUS trial.

Patients were randomised in a 1.1.1 ratio to receive daily oral treatment with Enco+Bini 450, encorafenib monotherapy (300mg), or vemurafenib. Stratification factors were disease stage, ECOG PS (0 versus 1) or prior first-line immunotherapy (yes or no).

Clinical advice to the ERG is that the trial eligibility criteria are reasonable, and that the participating treatment centres are representative of treatment centres in the UK. The ERG is satisfied that the COLUMBUS trial was well designed and well-conducted.

4.3.2 Baseline characteristics of patients recruited to the COLUMBUS trial

The baseline characteristics of the patients randomised in the COLUMBUS trial are summarised by the company (CS, Table 6, p23). The ERG agrees with the company that the patient characteristics (age, gender, race, weight, ECOG status, BRAF mutation status, disease stage, time from diagnosis to metastatic disease, number of organs involved at baseline and lactate dehydrogenase [LDH] levels) are similar across the three arms of the trial. The ERG also agrees with the company that, in the group of patients with Stage IV M1C disease at baseline, there was an imbalance of patients with elevated LDH levels across the Enco+Bini 450, Enco 300 and vemurafenib arms (25%, 25.3% and 18.8% respectively). The ERG notes that high levels of LDH are a marker of poor prognosis. The ERG notes that the patients recruited to the COLUMBUS trial appear to be similar to the patients recruited to the

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 (70%) in the COLUMBUS trial were of ECOG PS 0 and the remainder (30%) 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] (Table 5).

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 5 Assessment of risk of bias for the COLUMBUS trial

Study question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree. Patients were randomised via an automated interactive voice response system
Was the concealment of treatment allocation adequate?	Yes	Agree. The use of the automated interactive voice response system ensures that clinicians and patients were unable to predict or manipulate the treatment arm to which any given patient was randomised
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	NA	Disagree. There was no blinding of patients, caregivers or investigators in the COLUMBUS trial. The open-label nature of the trial provides an opportunity for subjective results and investigator-assessed outcomes to be biased. However, the PFS and response to treatment outcomes were subject to BIRC
Were there any unexpected imbalances in drop-outs between groups?	Not clear (patients in the vemurafenib arm were able to cross-over)	Disagree. The ERG does not consider patient cross-over to constitute dropping out. There appears to be no imbalance in dropout rates between the trial arms
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree, the company made available the clinical study report, protocol and statistical analysis plan alongside its submission
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	Agree
Were appropriate methods used to account for missing data	Yes	Agree

BIRC= Blinded Independent Review Committee
Source: CS, Table 9 and ERG comment

4.5 Statistical approach adopted for the COLUMBUS trial

In this section, the ERG describes and critiques the statistical approaches used to analyse data collected during the COLUMBUS trial that relate to the outcomes stipulated in the final scope[22] issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the CS, the original trial protocol (which was available as a supplementary document to the COLUMBUS trial publication)[30] and the clinical study reports (CSRs) of the two data cut-off times with trial statistical analysis plans (TSAPs) included as appendices to the CSRs.[54,55]

4.5.1 Efficacy outcomes and statistical analysis approach

Primary efficacy outcome

The primary efficacy endpoint for Part 1 of the COLUMBUS trial was PFS for Enco+Bini 450 versus vemurafenib.

PFS was defined as the time from the date of randomisation to the date of the first documented progression or death due to any cause, whichever occurred first. PFS was primarily determined according to BIRC of tumour data and survival information, and local investigator assessments were used as supportive analyses. Definitions of progression, scoring methods and timing of assessments (baseline and post-screening) are provided by the company (CS, Table 5). For patients without a PFS event, or who started any new antineoplastic therapy, PFS was censored at the date of the last adequate tumour assessment. Censoring rules for the PFS endpoint are available (CS, Table 8).

PFS was analysed in the full analysis set (FAS) according to the treatment arm, and stratified by cancer stage and ECOG PS. Differences in PFS between treatment with Enco+Bini 450 and vemurafenib arms was tested using a stratified log-rank test at a one-sided 2.5% cumulative level of significance. Kaplan-Meier (K-M) methodology was used to obtain estimates of medians (in months), 95% confidence intervals (CIs), 25th and 75th percentiles. K-M PFS probabilities at 4-month intervals from 4 months to 24 months, and 95% CIs were also estimated. The hazard ratio (HR) of PFS was estimated via Cox proportional hazards (PH) regression, stratified by cancer stage and ECOG PS at baseline, and the 95% CI of the HR was based on the Wald test.

Key secondary efficacy outcomes

A key secondary endpoint of Part 1 of the COLUMBUS trial was PFS for Enco+Bini 450 versus Enco 300. The same statistical approach was taken for this secondary PFS endpoint as for the primary PFS endpoint (TSAP version 5,[55] Section 7.5.1, p48).

The other key secondary endpoint for Part 1 of the COLUMBUS trial of relevance to this appraisal was OS, defined as the time from the date of randomisation to the date of death due to any cause. If a death was not observed by the date of analysis cut-off, OS was censored on the date of last contact, and for patients with no post-baseline survival information, OS was censored on the date of randomisation. OS was described using K-M methodology (as described for primary outcome, PFS) and the HR of OS was estimated via Cox PH regression, stratified by cancer stage and ECOG PS at baseline, and the 95% CI of the HR was calculated using the Wald test.

The ERG is satisfied that the definitions and statistical approaches for the primary and key secondary efficacy outcomes were pre-specified (TSAP version 5,[55] Section 7.5.1 and 7.5.2) and that the outcome definitions and statistical approaches were appropriate.

Other efficacy outcomes

Other secondary efficacy outcomes were best overall response, ORR, DCR, TTR, and DOR. These secondary outcomes are not used in the company's economic model and, therefore, are not described in detail in this ERG report. A summary of the definitions, statistical approaches and results of these outcomes is provided in Appendix 1, Section 8.1.1 of this ERG report

Subgroup analyses, sensitivity analyses and other supportive analyses

Subgroup analyses were performed for PFS and OS based on gender, age, race, region, Japanese patients, LDH level at baseline, ECOG PS, BRAF mutation status, AJCC stage, primary site of cancer, number of organs involved at baseline, baseline brain metastases, prior immunotherapy and prior adjuvant therapy. The analyses included K-M event probability summaries and HRs with 95% CI from un-stratified Cox PH models.

Multivariate Cox regression was also performed to examine the effect of potential prognostic factors provided at least 10 patients were available in the considered subgroup: tumour tissue mutation status (V600E versus V600K); gender (male versus female); age (continuous); baseline brain metastases (yes versus no); LDH baseline level (continuous); geographical region (North America versus Europe [including Russia] versus Australia versus others).

Several additional sensitivity, and other supportive, analyses were conducted for the primary PFS analysis and key secondary efficacy analyses at the data cut-off dates of 19th May 2016 and 7th November 2017, providing nominal p-values for descriptive purposes. All additional analyses were pre-specified (TSAP version 5,[55] Section 7.5.1 and 7.5.2) and are described in Section B 2.4.6 (p34) of the CS. Results of primary analyses, sensitivity analysis and supportive analyses are summarised in Section 4.6.2 of this ERG report.

Sample size and hierarchical testing approach

A hierarchical approach was taken for the statistical testing of primary efficacy (PFS) and secondary efficacy (PFS and OS) outcomes, as shown in Figure 1 and was pre-specified within the TSAP version 5,[55] (Section 3.1, p14 to 17).

Evidence from Part 1 of the COLUMBUS trial is presented from three cut-off dates in the CS:

- Data cut-off 19th May 2016: All trial outcomes, except for OS: Part 1 primary PFS analysis (Test 1: Enco+Bini 450 versus vemurafenib and Test 2: Enco+Bini 450 versus Enco 300, see Figure 1) and response data (ORR, DCR, TTR and DOR).

- Data cut-off 9th November 2016: Updated safety outcomes (for EMA marketing authorisation application)
- Data cut-off 7th November 2017: Part 1 interim OS analysis (Test 4a: Enco+Bini 450 versus vemurafenib, see Figure 1), updated PFS (Enco+Bini 450 versus vemurafenib and Enco+Bini 450 versus Enco 300) and updated response data (ORR, DCR, TTR and DOR).

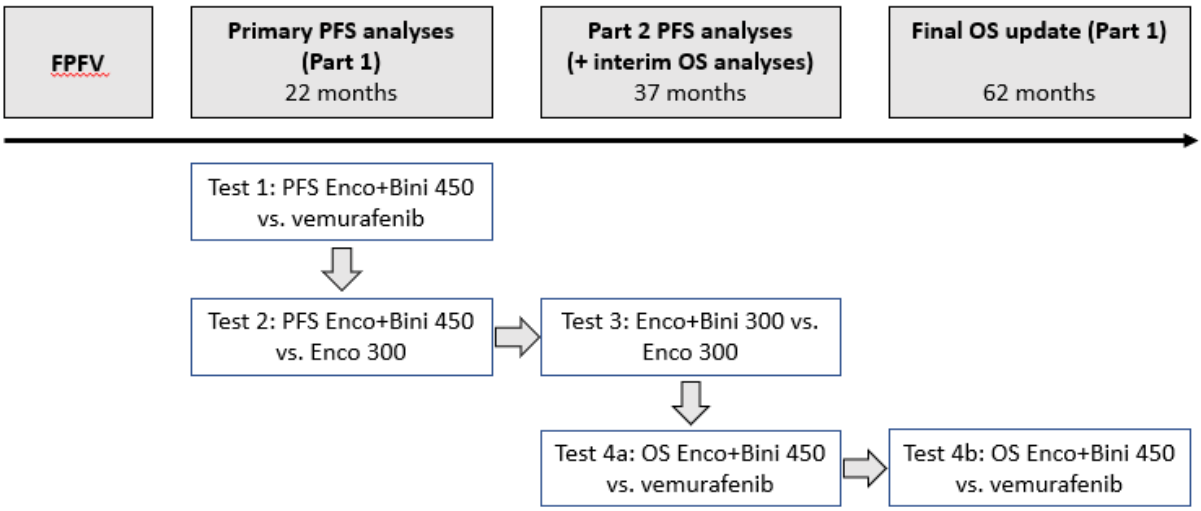

Figure 1 Timing of testing of primary efficacy (PFS) and secondary efficacy (PFS and OS) outcomes

BID=twice per day; Enco+Bini 300=encorafenib 300mg QD in combination with binimetinib 45mg BID; Enco+Bini 450= encorafenib 450mg QD in combination with binimetinib 45mg BID; FPFV=first patient first visit; OS=overall survival; PFS=progression-free survival; QD=once per day; vs=versus
Source: CS, Figure 2

As confirmed by information contained within the TSAPs (within the CSRs) at the two data cut-off times,[54,55] the updated analyses of PFS and response were performed according to the same methodological approach as for the primary analysis (data cut-off 19th May 2016).

The primary PFS analyses of Part 1 data had two objectives: to test both Enco+Bini 450 versus vemurafenib (primary efficacy comparison) and Enco+Bini 450 versus Enco 300 (key secondary efficacy comparison). Therefore, the key secondary comparison, PFS of Enco+Bini 450 versus Enco 300, was the sample size driver. It should also be noted that Enco 300 and vemurafenib are both comparators to Enco+Bini 450 in the COLUMBUS trial and, therefore, the ERG suggests that no direct comparison between Enco 300 and vemurafenib should be made.

Accounting for an anticipated 15% loss to follow-up for PFS, for the key secondary efficacy comparison of Enco+Bini 450 versus Enco 300, 191 PFS events were required to detect a HR of 0.667 with an 80% power using a log-rank test at a one-sided 2.5% level of significance. For the primary efficacy comparison of Enco+Bini 450 versus vemurafenib, 145 PFS events were required to detect a HR of 0.58 with a 90% power using a log-rank test at a one-sided 2.5% level of significance.

Conditional power calculations for OS were also performed (as OS would only be formally tested if primary and key secondary PFS comparisons were statistically significant). Based on results from the COMBI-v trial,[33] a 17-month median OS was expected to be observed in the vemurafenib arm and, accounting for an anticipated 5% loss to follow-up for OS, treatment with Enco+Bini 450 was expected to increase median OS to 22 months, corresponding to a HR of 0.7727.

The primary PFS analysis was to be performed when enrolment in Part 1 was complete and was event driven, according to the sample size calculation. According to the hierarchical approach of statistical testing, each test would be performed only if the prior test was statistically significant (i.e., $p<0.025$ at a one-sided 2.5% cumulative level of significance).

PFS for Enco+Bini 450 versus vemurafenib was statistically significant (see Test 1 within Figure 1, and see Section 4.6.2 of this ERG report for PFS results in the COLUMBUS trial). Statistical significance was not shown for PFS for Enco+Bini 450 versus Enco 300 at a one-sided 2.5% cumulative level of significance (see Test 2 within Figure 1, and see Section 4.6.3 of this ERG report). Therefore, according to the hierarchical approach of statistical testing, the interim OS analysis of Enco+Bini 450 versus vemurafenib (see Test 4a within Figure 1) could not be formally tested and nominal p-values for OS are provided for descriptive purposes only. The final OS analysis of Enco+Bini 450 versus vemurafenib (see Test 4b within Figure 1) was not available at the time the CS was submitted to NICE. This analysis is planned at approximately 62 months from first patient, first visit in the COLUMBUS trial, after 309 deaths have occurred for the Enco+Bini 450 versus vemurafenib comparison. According to the hierarchical approach of statistical testing, the company also confirmed in the response to the ERG clarification letter that the final OS analysis (Test 4b within Figure 1) cannot be formally tested and only nominal p-values for descriptive purposes will be provided at the time of final analysis.

4.5.2 ERG critique of statistical approach

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the COLUMBUS trial is provided in and appropriate.

Table 6. Having carried out these checks, the ERG considers that the pre-planned statistical approach employed by the company is adequate and appropriate.

Table 6 ERG assessment of statistical approach used to analyse data from the COLUMBUS trial

Item	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	The analysis populations are reported in Section 2.4.1 of the CS (p26). These populations were pre-defined in the COLUMBUS trial protocol[30] (Section 10.1, p51-52). Efficacy outcomes presented in the CS were analysed within the FAS, defined as all randomised patients, analysed according to the treatment and stratification factors they were assigned to at randomisation. No randomised patients were excluded from analysis. A PPS was also defined, including all patients from the FAS who had no major protocol deviations (listed in Section 10.1.2, p52 of the COLUMBUS trial protocol) and who received at least one dose of trial medication. Efficacy outcomes in the PPS were presented as a sensitivity analysis. Safety outcomes presented in the CS were analysed within the Safety Set defined as all randomised patients who received at least one dose of the trial medication and had at least one valid post-baseline safety evaluation. Seven patients (five in the vemurafenib arm and two in the Enco 300 arm) were randomised but did not receive trial drug and were excluded from the PPS and the Safety Set.
Were all protocol amendments carried out prior to analysis?	The protocol of the COLUMBUS trial (version 4) was available as supplement to the trial publication.[30] All protocol amendments were provided in the COLUMBUS trial protocol (version 4). The rationale for amendments and details of changes made to the protocol were provided in the COLUMBUS trial protocol (version 4, p14-29). The largest amendment (Amendment 3) related to the addition of Part 2 to the COLUMBUS trial, which is described in further detail in Section 4.5.1 of this ERG report and is not of direct relevance to the CS. The ERG is satisfied with the rationale for the amendments and that all amendments that have been made to date were made before the data cut-off date for the original analysis (19th May 2016) and updated analysis (interim analysis (7th November 2017)).
Was an appropriate sample size calculation pre-specified?	The sample size calculation of the COLUMBUS trial is reported in Section 2.4.4 of the CS (p31) and is described in more detail in Section 4.5.1 of this ERG report. The expected median PFS in the three arms of the COLUMBUS trial were based on results of the BRIM-3,[51] BRIM-2,[49] Combi-v[45] and Co-BRIM[33] trials for vemurafenib, a phase IV study of vemurafenib in patients with metastatic melanoma,[56] the dose-escalation and dose expansion results of an ongoing Phase I study for Enco 300,[57] and results from a phase Ib/II study for Enco+Bini 450.[58] The ERG is satisfied that the sample size calculations relating to all outcomes were appropriate and pre-specified in the COLUMBUS trial protocol (Section 10.8, p165-166).
Were modelling assumptions (e.g. proportional hazards) assessed?	It was pre-specified in the COLUMBUS TSAP version 5[55] (Section 7.5.1 and 7.5.2) that PFS and OS outcomes would be analysed using a Cox PH model. Log cumulative hazard plots for the comparison Enco+Bini 450 vs vemurafenib were presented in Appendix D.1.3 of the CS for investigator assessed PFS (Appendix D.1.3, Figure 10) and OS (Appendix D.1.3, Figure 3) and the company interpret that the PH assumption broadly holds for both of the outcomes for the COLUMBUS trial. The ERG agrees with this interpretation. The ERG notes a log cumulative hazard plot for the primary outcome of the COLUMBUS trial (i.e. PFS assessed by BIRC) is not presented, nor for PFS for the key secondary efficacy outcome PFS for Enco+Bini 450 vs Enco 300. However, from visual inspection of the K-M plots presented for these outcomes (Figure 3 and Figure 5 of the CS), the ERG is not concerned about any serious deviations from the PH assumption.
Were all subgroup analyses pre-specified?	The ERG is satisfied that all of the subgroup analyses presented within Section B.2.8 and Appendix E of the CS were pre-specified in the COLUMBUS TSAP version 5[55] (Section 7.5.1 and 7.5.2)
Were all sensitivity analyses pre-specified?	Several additional sensitivity and other supportive analyses were conducted for the primary PFS analysis and key secondary efficacy analyses are described in Section B 2.4.6 of the CS. Numerical results of the sensitivity analysis are very similar to those of the original analysis and no change to any conclusions (see Section 4.6.2 of this ERG report). The ERG is satisfied that of the sensitivity analyses presented in the CS were pre-specified in the COLUMBUS TSAP version 5[55] (Section 7.5.1 and 7.5.2).
Was the analysis	PROs reported in the CS were time to definitive 10% deterioration in the FACT-M subscale and global health status/HRQoL score, physical functioning, emotional functioning and social

approach for PROs appropriate and pre-specified?	functioning scale scores of the EORTC QLQ-C30, as well as change from baseline in the FACT-M subscale, EQ-5D-5L, and EORTC QLQ-C30 global health status and subscale scores. Time to definitive 10% deterioration was described using K-M methods and analysed using a stratified Cox regression model as per PFS. Descriptive statistics were used to summarise the FACT-M subscale, EQ-5D-5L index score and EORTC QLQ-C30 scores at each time point and change from baseline. A mixed-effect model for repeated measures (MMRM) was also used to compare the treatment arms in terms of change from baseline in the domain score over time. The ERG is satisfied that the company's approach to analysing PROs was pre-specified in COLUMBUS TSAP version 5[55] (Section 4.3, p22) and that the approach is appropriate.
Was the analysis approach for AEs appropriate and pre-specified?	AEs were assessed using the International CTCAE version 4.03. AEs were recorded based on severity grade, duration and outcome of the event, relationship to study treatment, whether dose adjustment or medication was required, timing of the event (pre-treatment, on treatment or post-treatment) and whether the event was an SAE. AEs of special interest were also recorded. Counts and percentages of AEs and SAEs according to a range of AE summaries, in addition to time to onset of first SAE, time to onset of first grade 3/4 AE, and time to onset of AE resulting in discontinuation of study drug (analysed by K-M methodology) were presented. The ERG is satisfied that the methodology for presenting AEs was pre-specified in the COLUMBUS TSAP version 5[55] (Section 7.6.5, p62-67) and that all summary tables and figures of AEs are presented within the CSR[54] (Section 14.3, p29615-30524).

AE=adverse event; CS=company submission; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQoL group 5 dimension five level; ERG=Evidence Review Group; FACT-M=functional assessment of cancer therapy – melanoma; FAS=full analysis set; HRQoL=health-related quality of life; K-M=Kaplan-Meier; QLQ-C30=quality of life questionnaire core 30; PH=proportional hazards; PPS=per-protocol set; PRO=patient-reported outcome; SAE=serious adverse events; TSAP=trial statistical analysis plan

Source: adapted from the CS, COLUMBUS CSR; COLUMBUS trial protocol and TSAP (supplementary file to the COLUMBUS trial publication[30]), the company's response to the ERG clarification letter, and ERG comment.

4.6 Efficacy results from the COLUMBUS trial

4.6.1 Patient flow through the COLUMBUS trial

In total, 1,345 patients were screened for entry into Part 1 of the trial. Of these, 768 patients (57.1%) were not randomised, mostly due to failure to meet at least one inclusion criterion or meet at least one exclusion criterion (727 patients [94.7%]). The most common exclusion criteria for 364 patients (47.4%) was not having the required presence of the BRAF V600E and/or V600K mutation in tumour tissue prior to enrolment per the central laboratory analysis.

In Part 1 of the trial, 577 patients were randomly assigned in a 1:1:1 ratio to receive either Enco+Bini 450 (n=192), Enco 300 (n=194) or vemurafenib (n=191). Seven patients (two in the Enco 300 arm and five in the vemurafenib arm) were randomised but did not receive the trial drug and were excluded from the per-protocol set (PPS) and the Safety Set.

At data cut-off date 19th May 2016, 141 patients (24.4%) were still participating in the treatment period of the trial (35.4% of the Enco+Bini 450 arm, 23.7% of the Enco 300 arm and 14.1% of the vemurafenib arm). The most common reason for discontinuation from trial treatment was progressive disease (43.2% of the Enco+Bini 450 arm, 44.8% of the Enco 300 arm and 52.9% of the vemurafenib arm) followed by AEs (8.3% of the Enco+Bini 450 arm, 12.4% of the Enco 300 arm and 13.6% of the vemurafenib arm).

At data cut-off date 7th November 2017, 80 patients (13.9%) were still participating in the treatment period of the trial (22.4% of the Enco+Bini 450 arm, 12.4% of the Enco 300 arm and 6.8% of the vemurafenib arm). The most common reason for discontinuation from trial treatment was progressive disease (51.6% of the Enco+Bini 450 arm, 51.5% of the Enco 300 arm and 57.1% of the vemurafenib arm) followed by AEs (10.4% of the Enco+Bini 450, 12.9% of the Enco 300 arm and arm 13.1% of the vemurafenib arm).

Following discontinuation of trial treatment, 41.7% of patients in the Enco+Bini 450 arm, 55.7% of patients in the Enco 300 arm and 62.3% of patients in the vemurafenib arm received a subsequent antineoplastic therapy, and [redacted] of the Enco+Bini 450 arm, [redacted] of the Enco 300 arm and [redacted] of patients in the vemurafenib arm received any BRAFi, MEKi or checkpoint drug therapy.

Detailed reasons for discontinuation of trial treatments at both data cut-off dates are provided in Table 13 and Table 14 and further details of antineoplastic treatments after discontinuation of trial treatment are provided in Table 15 of Appendix D.2.1 of the CS.

4.6.2 Primary efficacy outcome: PFS for Enco+Bini 450 versus vemurafenib

The primary objective of the trial was PFS (Enco+Bini 450 versus vemurafenib) assessed by BIRC. The results of this primary outcome are summarised in Table 7.

Table 7 Summary of PFS results (BIRC) for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19th May 2016

	Enco+Bini 450	Vemurafenib
Patients with events/patients included in analysis: n/N (%)	98/192 (51.0)	106/191 (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)
25th percentile of PFS (95% CI)[b]	[redacted]	[redacted]
50th (median) percentile of PFS (95% CI)[b]	14.9 (11.0 to 18.5)	7.3 (5.6 to 8.2)
75th percentile of PFS (95% CI)[b]	[redacted]	[redacted]
Event-free probability estimates (95% CI)[c]		
4 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
16 months	[redacted]	[redacted]
20 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
HR (95% CI), stratified one-sided log-rank p-value	0.54 (0.41 to 0.71); p<0.0001	

[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] Greenwood formula is used for CIs of Kaplan-Meier estimates
BIRC=blinded independent review committee; CI=confidence interval; FAS=full analysis set; HR=hazard ratio; NE=not estimable; PFS=progression-free survival; FAS=full analysis set
Source: CS, adapted from Table 10, the COLUMBUS trial publication[30]

There were 98 PFS events (51% of patients) in the Enco+Bini 450 arm and 106 PFS events (56% of patients) in the vemurafenib arm. The remaining patients were censored in the analysis, and the most common reasons for censoring were [redacted]) (see Table 30 of Appendix L.2 of the CS for detailed reasons for censoring).

Median PFS was more than doubled in the Enco+Bini 450 arm compared to the vemurafenib arm; median PFS 14.9 months (95% CI: 11.0 to 18.5) versus 7.3 months (95% CI: 5.6 to 8.2). There was a statistically significant difference in PFS in the Enco+Bini 450 arm relative to the vemurafenib arm; HR 0.54 (95% CI: 0.41 to 0.71); stratified one-sided log-rank test p<0.0001.

The PFS K-M data are provided in Figure 3 of the CS. The company's interpretation is that the curves separate early (approximately 1-2 months into treatment) and do not intersect until the end of follow-up, when the number of patients in each arm still at risk is less than four. The ERG agrees with this interpretation and has no concerns regarding violation of the PH assumption that is necessary to estimate a reliable HR (see and appropriate.

Table 6 of this ERG report for further details).

PFS by BIRC and by local investigator assessment

Investigator assessment of response was used to estimate PFS as a supportive analysis. PFS results by BIRC and by investigator assessment at the two data cut-off dates are presented in Table 8. The K-M data for investigator review and for updated analyses are shown in Section 2.6.2 (Figure 4), Appendix L.3.1 (Figure 35) and Appendix L.3.2 (Figure 36) of the CS. Detailed reasons for censoring PFS data, by BIRC and by investigator assessment, are shown in Table 30 and Table 31 of Appendix L.2.1 and Table 40 and Table 41 of Appendix L.3.3 of the CS.

Table 8 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; the 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 arm. 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 8) 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 8). Therefore, the discordance present between BIRC and investigator review does not seem to have impacted on the overall PFS results.

Sensitivity and supportive analyses of PFS for Enco+Bini 450 versus vemurafenib

A number of sensitivity analyses and other supportive analysis of PFS for Enco+Bini 450 versus vemurafenib were conducted as described in Section 4.5.1 of this ERG report at the two data cut-off dates. HRs and 95% CIs of these additional analyses are provided in Table 9. HRs and 95% CIs for PFS by BIRC and investigator review provided in Table 8 are also included for ease of comparison across all results of PFS. Results of sensitivity analyses and supportive analyses of PFS are consistent with the primary analysis, yielding very similar HRs ([redacted] to [redacted]) and nominal one-sided p-values ([redacted]). The ERG considers that the PFS results are robust to assumptions made within analyses.

Table 9 Summary of results for all analyses of PFS for Enco+Bini 450 versus vemurafenib

Analysis (all Part 1)	Data cut-off date	HR (95% CI), stratified one-sided log-rank p-value
BIRC, FAS (primary analysis)	19th May 2016	0.54 (0.41 to 0.71); p<0.0001
BIRC, FAS (updated primary analysis)	7th November 2017	0.51 (0.39 to 0.67); p<0.0001
Investigator review, FAS	19th May 2016	0.49 (0.37 to 0.64); p<0.0001[a]
	7th November 2017	[redacted]
BIRC, PPS[b,c]	19th May 2016	0.53 (0.40 to 0.70); p<0.0001[a]
BIRC, FAS, unstratified log-rank tests and Cox PH regression[c]	19th May 2016	0.58 (0.44 to 0.77); unstratified p<0.001[a]
BIRC, FAS, by eCRF stratification factors[c,d]	19th May 2016	[redacted][a]
BIRC, FAS, 'actual event' sensitivity analysis[e]	19th May 2016	[redacted][a]
	7th November 2017	[redacted][a]
BIRC, FAS, 'backdating' sensitivity analysis[f]	19th May 2016	[redacted][a]
	7th November 2017	[redacted][a]
BIRC, FAS, 'further anti-cancer treatment' sensitivity analysis[g]	19th May 2016	[redacted][a]
	7th November 2017	[redacted][a]

[a] P-values are nominal and for descriptive purposes only
[b] Number of patients included in PPS: 188 for Enco+Bini and 184 for vemurafenib
[c] Analysis in PPS, unstratified log-rank test and Cox PH regression analyses and analysis by eCRF stratification factors available only for data-cut off 19th May 2016
[d] Discordance rates ranging from 0.3% to 11.1% between randomisation stratification factors and eCRF stratification factors due to a time window of up to three weeks between registering randomisation factors and the registering stratification factors on the eCRF (see company response to ERG clarification letter for further details).
[e] 'Actual event' sensitivity analysis had a censoring rule that included a PFS event even if the event was recorded after two or more missing tumour assessments
[f] Backdating analysis has a censoring rule that backdated events occurring after one or more missing tumour assessments. Events were backdated to 8 weeks (or 12 weeks if the patient had been on treatment long enough) after the last adequate tumour assessment.
[g] 'Further anti-cancer treatment' sensitivity analysis for PFS including tumour assessments after initiation of subsequent antineoplastic therapy
BIRC=blinded independent review committee; CI=confidence interval; eCRF=electronic case report form; FAS=full analysis set; HR=hazard ratio; NE=not estimable; PH=proportional hazards; PFS=progression-free survival; PPS=per-protocol set
Source: CS, adapted from Section 2.6.2.3 and Table 14. CS, Appendix L.3.2, adapted from Table 37; company response to ERG clarification letter.

Subgroup analysis of PFS for Enco+Bini 450 versus vemurafenib

Subgroup analyses were performed at both dates of data cut-off, see Section 4.5.1 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 10.

Table 10 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	(0.56 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

reasons for censoring were [redacted]

[redacted])

(see Table 30 of Appendix L.2 of the CS for detailed reasons for censoring).

The HR for Enco+Bini 450 versus Enco 300 was 0.75 (95% CI: 0.56 to 1.00) but this PFS difference was not statistically significant (one-sided p=0.0256) by the one-sided stratified log-rank test according to the threshold for significance per the hierarchical testing approach as pre-defined in the protocol (p<0.025).

Additional PFS results for Enco+Bini 450 versus Enco 300 are summarised in Appendix 2, Section 8.2.1 of this ERG report.

Interim analysis of OS

The PFS of Enco+Bini 450 versus Enco 300 was not statistically significant according to the hierarchical approach of statistical testing (see Section 4.5.1 of this ERG report); all of the alpha of the trial has been spent and OS could not be formally tested. An interim analysis of OS was performed at the data cut-off date of 7th November 2017. OS results from this analysis for Enco+Bini 450 versus Enco 300 and versus vemurafenib are provided in Table 11. Nominal p-values for OS are provided for descriptive purposes only.

Table 11 Overall survival, Enco+Bini 450 versus Enco 300 and versus vemurafenib – FAS, Part 1, data cut-off 7th November 2017

	Event / N (%)	Median follow-up (95% CI)[a]	Median OS (95% CI)[b]	HR (95% CI)[c,d]	P-value (one-sided)[d,e]
Enco+Bini 450	[redacted]	37.2 (36.1 to 38.5)	33.6 (24.4 to 39.2)	NA	NA
Enco 300	[redacted]	36.3 (34.8 to 37.3)	23.5 (19.6 to 33.6)	0.81 (0.61 to 1.06)	0.0613
Vemurafenib	[redacted]	35.9 (34.9 to 38.0)	16.9 (14.0 to 24.5)	0.61 (0.47 to 0.79)	<0.0001

[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] Log-rank test and Cox proportional hazards model are stratified by AJCC stage and ECOG PS per randomisation. HRs and p-values are presented for Enco+Bini 450 compared to Vemurafenib and Enco 300
[d] HRs and CIs are derived from the Cox proportional hazards model using the Wald test
[e] P-value is based on the log-rank score test
CI=confidence interval; FAS=full analysis set; HR=hazard ratio; NA=not applicable
Source: CS, adapted from Table 17; the COLUMBUS trial publication[59]

By the data cut-off date of 7th November 2017, [redacted] of patients in the Enco+Bini 450 arm, [redacted] of patients in the Enco 300 arm and [redacted] of the patients in the vemurafenib arm had died. The remaining patients were censored in analysis, [redacted]

[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 8.2.2 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 8.1.2 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 Table 12. 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.

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 incidence of Grade 3 to Grade 4 AEs requiring dose interruption and/or adjustment

compared with the Enco 300 and vemurafenib arms ([redacted], respectively) and Grade 3 to Grade 4 AEs requiring additional treatment, compared with the single treatment arms ([redacted], respectively).

Most of the on-treatment deaths (occurring during treatment or within 30 days the last dose) were due to disease progression and the incidence was similar across the Enco+Bini 450, Enco 300 and vemurafenib arms ([redacted], respectively).

Table 12 Summary of deaths and AEs from the COLUMBUS trial, Part 1, data cut-off 9th November 2016

Category	Enco+Bini 450 N=192		Enco 300 N=192		Vemurafenib N=186	
	Median duration of exposure: [redacted]		Median duration of exposure: [redacted]		Median duration of exposure: [redacted]	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
On-treatment deaths[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose interruption and/or adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event

a Deaths occurring >30 days after end of treatment are not included

b Additional therapy includes all non-drug therapy and concomitant medications
Source: CS, Table 29

All grade adverse events

The full details of all grade AEs from the COLUMBUS trial are presented in Table 30 of the CS. The company has reported the AEs (≥10% of patients) regardless of relationship to study treatment.

The most common (≥10% in any treatment arm) any grade AEs in patients receiving Enco+Bini 450 were nausea ([redacted]), diarrhoea ([redacted]), vomiting ([redacted]), fatigue ([redacted]), arthralgia ([redacted]), increased creatine phosphokinase ([redacted]), headache ([redacted]), constipation ([redacted]), and asthenia ([redacted]). In the vemurafenib arm, the most common all grade AEs included arthralgia ([redacted]), alopecia ([redacted]), nausea ([redacted]), diarrhoea ([redacted]), fatigue ([redacted]), hyperkeratosis and rash (both [redacted]). The most frequent all grade AEs in the Enco 300 arm were alopecia ([redacted]), palmar-plantar

erythrodysaesthesia syndrome ([redacted]), 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 AEs 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

of Enco+Bini 450 versus Dab+Tram. The ERG notes, from the appraisal of Dab+Tram,[13] that the most frequently occurring Grade 3 and Grade 4 AEs and SAEs associated with Dab+Tram[13] were pyrexia, hypertension, headache, nausea, vomiting and diarrhoea.

4.8 Health-related quality of life

The COLUMBUS trial protocol included collecting HRQoL data using three tools (the Functional Assessment of Cancer Therapy-Melanoma[60] (FACT-M) subscale, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30[61] (EORTC QLQ-C30) and the EuroQol-5 dimensions-5 levels[62] (EQ-5D-5L) questionnaire. It is reported in the CS (p57) that compliance was high in each arm from baseline to Cycle 25, with [redacted] of evaluated patients completing the questionnaires. At the safety follow-up (30 days post-treatment), completion rates ranged from [redacted] Results are only available from the 19th May 2016 data cut-off.

Time to definitive deterioration (primary analysis)

Results show that treatment with Enco+Bini 450 significantly delayed deterioration in HRQoL compared with vemurafenib, as measured by median time to 10% deterioration on the FACT-M[60] melanoma subscale and EORTC-QLQ-C30[61] global health status (see Table 13 for details).

Table 13 Time to 10% deterioration in health-related quality of life

	FACT-M			EORTC QLQ-C30		
	Enco+Bini 450	**Vem**	**Enco 300**	**Enco+Bini 450**	**Vem**	**Enco 300**
Median, months	NE (22.1 to NE)	22.2 (15.2 to NE)	20.3 (15.0 to NE)	23.9 (20.4 to NE)	16.6 (11.9 to NE)	14.7 (9.2 to 18.4)
HR (95% CI)	0.46 (0.29 to 0.72)		0.48 (0.31 to 0.75)	0.55 (0.37 to 0.80)		0.45 (0.31 to 0.65)

CI=confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-M=Functional Assessment of Cancer Therapy-Melanoma; HR=hazard ratio; NE=not evaluable
Source: CS, p58

Score change post-baseline (primary analysis)

Based on the mixed-effect model for repeated measures (MMRM) analyses, compared with vemurafenib, treatment with Enco+Bini 450 was associated with higher post-baseline score estimates (FACT-M[60] scale [redacted] QLQ-C30[61] global health status +[redacted]; EQ-5D-5L[62] index score [redacted]). Compared with Enco 300, Enco+Bini 450 was associated with higher post-baseline score estimates (FACT-M[60] scale [redacted] QLQ-C30[61] global health status +[redacted]; EQ-5D-5L[62] index score [redacted]).

Score change from baseline (post-hoc analysis)

The company undertook post-hoc analyses[63] to estimate adjusted mean score changes from baseline, at each time point, up until Cycle 25 (week 95) for the comparison of treatment with Enco+Bini 450 with vemurafenib. Results were as follows:

- FACT-M[60] subscale: the minimal clinically important difference of two points[64] was reached at all visits [redacted]
- QLQ-C30[61]: the minimal clinically important difference of five points[65] was reached at all visits [redacted].
- EQ-5D-5L[62] questionnaire: index scores were [redacted].

[redacted]

4.9 ERG critique of the indirect evidence

In the absence of direct evidence for the comparison of the effectiveness of treatment with Enco+Bini 450 versus Dab+Tram (the comparator specified in the final scope[22] issued by NICE, see Section 3.3 of this ERG report), the company conducted Bayesian NMAs to indirectly estimate relative effects of treatment efficacy (PFS and OS), HRQoL and AEs for these two treatments.

4.9.1 Trials identified for inclusion in the NMAs

The company conducted broad clinical and HRQoL systematic searches to identify published evidence reporting efficacy and safety of available interventions for advanced (unresectable or metastatic) cutaneous melanoma and those reporting measures of HRQoL of patients with advanced (unresectable or metastatic) melanoma (see Section 4.1 of this ERG report for further details). RCTs of BRAFi therapies (BRAFi monotherapies and BRAFi/MEKi combinations licensed for use within the EU) and only doses of BRAFi therapies approved in EMA marketing authorisations were considered for inclusion in the NMAs.

The company identified seven RCTs (COLUMBUS, COMBI-v, COMBI-d, BRF113220 Part C, coBRIM, BREAK-3 and BRIM-3) investigating BRAFi therapies reporting clinical efficacy and safety data. Five of these seven RCTs (COLUMBUS, COMBI-v, COMBI-d, coBRIM and BREAK-3) also reported HRQoL data.

4.9.2 Methodological approach to the NMAs

The company first performed an assessment to determine the feasibility of the NMA and explored whether:

- a connected network of evidence for given outcomes of interest could be established

- comparability / transitivity held and the extent of between-trial heterogeneity arising from the comparability of:
    - trial design characteristics and the impact on outcomes of interest
    - patient baseline characteristics across trials.

Trial design and patient baseline characteristics across trials are further discussed in Section 4.9.3 of this ERG report.

Construction of networks of evidence for clinical efficacy and safety outcomes

Clinical efficacy outcomes of interest were PFS and OS and the safety outcome of interest was 'incidence of any Grade ≥3 AE.' The company considered the analysis of the incidence of specific AEs not be feasible due to low numbers of specific AEs. All seven trials included in the NMAs reported PFS, OS and incidence of any Grade ≥3 AEs. The general evidence network for clinical efficacy and safety outcomes is presented in Figure 2 and the networks for each outcome are shown in Figure 9, Figure 10 and Figure 14 of the CS.

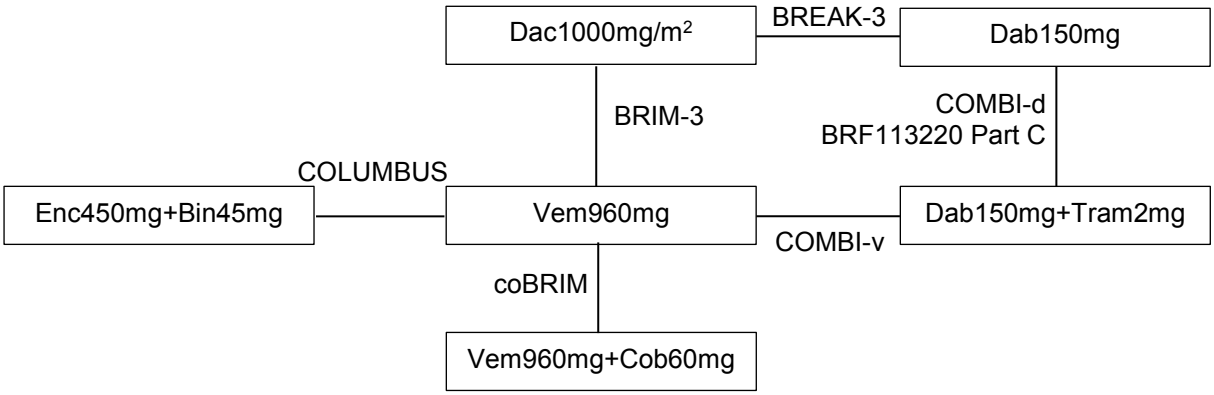

Figure 2 Evidence network for PFS, OS and incidence of any Grade ≥3 AEs

AE=adverse event; Bin=binimetinib; Cob=cobimetinib; Dab=dabrafenib; Dac=dacarbazine; Enc=encorafenib; PFS=progression-free survival; OS=overall survival; Tram=trametinib; Vem=vemurafenib
Source: CS, adapted from Figure 9, Figure 10 and Figure 14

The ERG notes that, under the assumption of 'transitivity', all treatments are 'jointly randomisable' in the network. In other words, all interventions within a network could feasibly be randomised in the same trial and any intervention which is not those a treatment arm in any given trial is 'missing at random.[67] Clinical advice to the ERG is that, as dacarbazine is not a BRAFi therapy and no longer seen as a standard of NHS care, inclusion of this treatment within the network may violate the important assumption of transitivity. However, the ERG appreciates the efforts made by the company to construct a 'connected' closed loop of evidence and is aware that this approach requires the inclusion of dacarbazine so that consistency (another important assumption of NMA) can be evaluated.

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 BICR 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 4.9.3 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 Table 14 and Table 15 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.

Construction of networks of evidence for HRQoL outcomes

HRQoL outcomes assessed for the NMA were EQ-5D utility scores pre-progression, difference in change from baseline at week 32 and difference in change from baseline at disease progression. Due to substantial variability in published HRQoL data and analyses across the included trials, the company did not use the published HRQoL data in the NMAs. Instead, utility scores were sourced from health technology assessment submissions for the COMBI-d, COMBI-v, coBRIM and BREAK-3 trials[12,13,69] and utility scores were determined, via a post-hoc MMRM analysis, for the COLUMBUS trial.

The company considered that the inclusion of both open-label and double-blinded trials in the same network would be methodologically inappropriate for these patient reported outcomes and limited the evidence network to the indirect comparisons between open-label COLUMBUS and COMBI-v trials. The general evidence network for the HRQoL outcomes is presented in Figure 3 and the evidence networks specific to each outcome are shown in Figure 11, Figure 12 and Figure 13 of the CS.

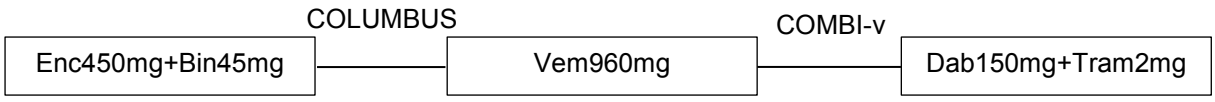

Figure 3 Evidence network for HRQoL outcomes

Bin=binimetinib; Dab=dabrafenib; Enc=encorafenib; HRQoL=health-related quality of life; Tram=trametinib; Vem=vemurafenib.
Source: CS, adapted from Figure 11, Figure 12 and Figure 13

Statistical approach to NMA

The company conducted Bayesian NMAs based on the methodology outlined in the NICE Decision Support Unit Technical Support Document 2[70] and the International Society for Pharmacoeconomics and Outcomes research task force on indirect treatment comparisons.[71,72] Further details of the Bayesian analysis approach, assessment of model convergence and the OpenBUGS programming language used by the company are provided in Appendix D.1.3.2 and Appendix D.1.3.3 of the CS. The ERG considers that, overall, the statistical approach used was appropriate.

The company fitted both fixed-effects and random-effects NMA models to the clinical efficacy and safety outcomes and presented results from fixed-effects NMA models. Model fit was determined by the Deviance Information Criterion and total residual deviance. The company considered the fixed-effects results to be most appropriate due to the sparseness of the evidence networks for clinical efficacy and safety outcomes as they consisted of only one or

two RCTs in each pairwise comparison. Only fixed-effects models were fitted for HRQoL outcomes due to the evidence network being limited to only two trials.

The ERG appreciates the computational difficulty of fitting random-effects NMA models to small networks, particularly very small networks with only two trials. Yet, the ERG notes that the model fit statistics provided in Appendix D.1.3.2, Table 10 of the CS were generally similar between fixed and random-effects models for the clinical efficacy and safety outcomes. Therefore, in the presence of heterogeneity of design, study duration and some patient baseline characteristics (as outlined in Section 4.9.2 and Section 4.9.3 of this ERG report), a random-effects approach to NMA may have been more appropriate for the assessment of clinical efficacy and safety outcomes. However, the ERG notes that, as uncertainty and wide CrIs are observed for the results of the fixed-effects NMAs, this uncertainty and imprecision would only become larger and the CrIs would become wider within random-effects NMAs. Therefore, the ERG considers that, for efficacy, safety and HRQoL, the same interpretation and conclusions would likely be made from examination of the result of fixed-effects and random-effects NMA models.

Inconsistency was assessed by the Bucher method,[73] comparing the fixed-effects direct estimates with the fixed-effects indirect estimates. No evidence of inconsistency was found within the closed loop of dabrafenib, dacarbazine, vemurafenib and Dab+Tram for PFS or OS (see Appendix D.1.3.2, Table 11 of the CS). However, the ERG notes that Enco+Bini 450 was not included within the closed loop of evidence within the network for PFS and OS, and no closed loops of evidence were present for the HRQoL outcomes. Therefore, the consistency of the indirect estimates of Enco+Bini 450 versus Dab+Tram for all outcomes is unknown. The ERG notes that, in addition to the Bucher method,[73] which is a 'local' approach to evaluating inconsistency of each comparison within a closed loop, the company could also have taken a 'global' approach to evaluating the presence of inconsistency across the entire network of evidence,[74] including the comparison of Enco+Bini 450 versus Dab+Tram.

4.9.3 Characteristics of trials included in the NMA

The trial design characteristics are summarised in Appendix D.1.3.1, Table 5 and patient baseline demographics from included trials are summarised in Appendix D.1.3.1, Table 6 of the CS.

The included trials were broadly similar in terms of general designs and inclusion criteria. Two notable differences in design across the trials were noted by the company. Firstly, six of the seven trials permitted treatment crossover of some description during the OS follow-up period (only the coBRIM trial did not permit any crossover at any point during OS follow-up). The

company investigated the potential impact of crossover in an additional crossover adjusted NMA (see Section 4.9.2 of this ERG report).

Secondly, five of the trials had an open-label design (COLUMBUS, COMBI-v, BRIM-3, BREAK-3 and BRF113220 Part C) and two of the trials had a double-blind design (COMBI-d and coBRIM). As described in Section 4.9.2 of this ERG report, the variability of open-label and double-blind design impacted on the reliability of the results derived from the NMAs of PFS and HRQoL.

The patient populations within the targeted BRAFi therapy studies consisted almost exclusively of patients with tumours with a BRAF mutation (although up to 22% of patient tumours could not be specifically subtyped in coBRIM). Age, gender, ethnicity, distribution of ECOG PS scores, tumour stage and number of metastatic sites were all comparable across trials. There was variability in the proportion of patients for whom LDH was greater than the upper level of normal at baseline, ranging from 27% to 58%, as noted by the company. The ERG notes that the proportions of patients who have received prior immunotherapies are quite variable across the studies, ranging from 15% to 30%.

The ERG agrees with the feasibility assessment of the company that most patient baseline characteristics, except for LDH level and prior immunotherapies, are broadly similar across the trials. The ERG notes that the variation in LDH level across trials should be taken into account when interpreting the results of the NMAs considering LDH level as a potential effect modifier,

[redacted] see Section 4.6.2 and Section 8.2.2 of this ERG report.

4.9.4 Assessment of risk of bias of the trials included in the NMA

A quality assessment of the trials included within the NMA is presented in Appendix D.1.3.4, Table 12 of the CS, based on the NICE technology appraisal checklist.[75] The quality assessment of the COLUMBUS trial is presented in Section 4.4 of this ERG report.

The company judges the risk of bias to be low for the randomisation method, baseline comparability, attrition, selective reporting and statistical analysis approach for all trials included in their NMAs. The ERG agrees with these judgements.

The company judges that only the COLUMBUS trial and the COMBI-d trial provide information regarding allocation concealment. From consultation of the published reports of all included trials, the ERG finds reference to interactive voice response systems used in randomisation

for five trials (COLUMBUS, COMBI-v, COMBI-d, coBRIM and BREAK-3) and reference to 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 4.9.2 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 5.3.2of 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 Figure 2). As described in Section 4.9.2 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 4.9.2 of this ERG report). Results for the base case analysis and sensitivity analyses of PFS are presented in Table 14.

Table 14 NMA results for investigator assessed PFS (fixed-effects model)

Analysis	Enco+Bini 450 vs Dab+Tram	Dab+Tram vs Enco+Bini 450
Base case	HR 0.77, 95% CrI (0.57 to 1.04)	HR 1.30 95% CrI (0.96 to 1.77)
Sensitivity analysis (open-label designed trials only)[a]	HR 0.79, 95% CrI (0.58 to 1.07)	HR 1.27, 95% CrI (0.93 to 1.72)
Sensitivity analysis (Cox PH model)	HR 0.74, 95% CrI (0.54 to 1.00)	HR 1.36, 95% CrI (1.00 to 1.84)
Sensitivity analysis (log rank)	HR 0.80, 95% CrI (0.59 to 1.09)	HR 1.25, 95% CrI (0.92 to 1.69)
Sensitivity analysis (trials violating PH assumption excluded)[b]	HR 0.77, 95% CrI (0.56 to 1.05)	HR 1.30, 95% CrI (0.95 to 1.77)

[a] Open-label designed trials were COLUMBUS, COMBI-v, BRIM-3, BREAK-3 and BRF113220 Part C
[b] Trials judged to violate the PH assumption for PFS were BRIM-3 and BREAK-3
Bini=binimetinib; CrI=credible interval; Dab=dabrafenib; Enco=encorafenib; HR=hazard ratio; PFS=progression free survival; PH=proportional hazards; Tram=trametinib
Source: CS, adapted from Table 22 and Table 26; company response to ERG clarification letter, Table 4 and Table 6

The results of the base case and sensitivity analyses are consistent, with the NMA results favouring Enco+Bini 450 (HR<1); however, the CrI crosses 1, indicating no statistically significant difference between Enco+Bini 450 and Dab+Tram.

NMA results for OS

The evidence network for the base case analysis of OS is provided in Figure 9 of the CS (and the general structure of this network is provided in Figure 2). Two sensitivity analyses were also performed (see Section 4.9.2 of this ERG report). Results for the base case analysis and sensitivity analyses of OS are presented in Table 15.

Table 15 NMA results for OS (fixed-effects model)

Analysis	Enco+Bini 450 vs Dab+Tram	Dab+Tram vs Enco+Bini 450
Base case	HR 0.89, 95% CrI (0.65 to 1.23)	HR 1.12, 95% CrI (0.81 to 1.53)
Sensitivity analysis (crossover adjustment via RPSFT model)	HR 0.90, 95% CrI (0.61 to 1.34)	HR 1.11, 95% CrI (0.75 to 1.65)
Sensitivity analysis (trials violating PH assumption excluded)[a]	HR 0.90, 95% CrI (0.70 to 1.17)	HR 1.11, 95% CrI (0.86 to 1.43)

[a] Trials judged to violate the PH assumption for PFS were BRIM-3, BREAK-3 and BRF113220 Part C
Bini=binimetinib; CrI=credible interval; Dab=dabrafenib; Enco=encorafenib; HR=hazard ratio; PH=proportional hazards; OS=overall survival; RPSFT=rank preserving structure failure time; Tram=trametinib
Source: CS, adapted from Table 21 and Table 25; company response to ERG clarification letter, Table 5

The results of the base case and sensitivity analyses are consistent with the NMA results favouring Enco+Bini 450 (HR<1); however the CrIs cross 1, indicating no statistically significant difference between Enco+Bini 450 and Dab+Tram.

NMA results for incidence of any Grade ≥3 AEs

The evidence network for the base case analysis of OS is provided in Figure 14 of the CS (and the general structure of this network is provided in Figure 2). An NMA result for 'serious AEs' was also presented in the CS; however, the networks were not presented for this analysis

so it is unclear which trials and which data contributed to this NMA. Results for safety outcomes are presented in Table 16.

Table 16 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 Figure 3 of this ERG report). Results for HRQoL outcomes are presented in Table 17.

Table 17 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 Enco+Bini 450 (Delta<0); however, the CrIs cross 0 for all analyses. The company also notes that the numerical improvements in favour of Enco+Bini 450 were also inferior to the minimal difference in EQ-5D-5L score considered to be clinically important (0.08 points).[76]

4.10 Conclusions of the clinical effectiveness section

4.10.1 Direct evidence

The direct clinical effectiveness evidence for Enco+Bini 450 was derived from the COLUMBUS trial. The ERG highlights the following points:

- The COLUMBUS trial is a well-designed and good quality trial with an appropriate, pre-defined, statistical approach to the analysis of efficacy, safety and patient reported outcomes.
- The COLUMBUS trial, however, did not include treatment with Dab+Tram, the comparator specified in the final scope issued by NICE.
- Clinical advice to the ERG is that, in the NHS, the treatment sequence for almost all patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive patients, is immunotherapy first-line, followed by Dab+Tram on disease progression. Only a small subgroup of patients with BRAF V600 mutation-positive melanoma who have highly symptomatic or rapidly progressing disease are treated with Dab+Tram at first-line. Clinical advice to the ERG is that the baseline characteristics of patients recruited to the COLUMBUS trial mean that, in NHS clinical practice, they would be treated with a PD-1 inhibitor before treatment with a BRAF inhibitor.
- Immunotherapies were not considered as comparators in the present appraisal; however, the rationale for that decision is unclear to the ERG.
- No treatment line is specified in either the final scope[22 222222] issued by NICE, the CS, or the EMA marketing authorisation for Enco+Bini 450.[23] 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 evidence presented in the CS for the clinical effectiveness of Enco+Bini 450 can be considered as being for its use as a first-line treatment option for patients with advanced disease.
- None of the patients recruited to the COLUMBUS trial had an ECOG PS of ≥2 and very few patients had brain metastases. This means that there is no clinical effectiveness evidence for the use of Enco+Bini 450 in patients with a PS of ≥2 in patients with brain metastases.
- There is a move, in the NHS, towards adjuvant treatment with immunotherapies. The impact of adjuvant treatment with immunotherapy on the treatment pathway in the advanced and metastatic setting for patients with melanoma is currently unknown
- The primary objective of the COLUMBUS trial was to compare PFS (BIRC assessed) of Enco+Bini 450 with vemurafenib. The results showed a statistically significant difference in PFS in the Enco+Bini 450 arm relative to the vemurafenib arm; HR 0.54 (95% CI: 0.41 to 0.71); stratified one-sided log-rank test p<0.0001. The duration of PFS was more than doubled in the Enco+Bini 450 arm compared to the vemurafenib arm; median PFS 14.9 months (95% CI: 11.0 to 18.5) versus 7.3 months (95% CI: 5.6 to 8.2).
- A key secondary efficacy objective was to compare PFS of Enco+Bini 450 with Enco 300 based on BIRC. The HR for Enco+Bini 450 relative to Enco 300 was 0.75 (95% CI: 0.56 to 1.00) but this PFS difference was not statistically significant (one-sided p=0.0256) by the one-sided stratified log-rank test according to the threshold for significance per the hierarchical testing approach as pre-defined in the protocol (p<0.025). An interim analysis of OS was performed at the data cut-off date of 7th November 2017. OS was doubled with Enco+Bini 450 compared with vemurafenib monotherapy (33.6 months versus 16.9 months; HR: 0.61, 95% CI: 0.47 to 0.79;

nominal one-sided p<0.0001 [presented for descriptive purposes]). The company explains that OS cannot be formally tested at any time point of the COLUMBUS trial (due to the use of the hierarchical testing procedure).

- 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. Therefore, the ERG interprets that the results of primary and key secondary efficacy outcomes are robust to assumptions made within the analysis.
- The AEs reported in the COLUMBUS trial show that treatment with Enco+Bini 450 appears to be as well-tolerated by patients as treatment with Enco 300 or vemurafenib.
- HRQoL results from the COLUMBUS trial demonstrated that treatment with Enco+Bini 450 significantly delayed deterioration in HRQoL compared with vemurafenib. The EQ-5D-5L index scores favoured Enco+Bini 450 versus vemurafenib, although the minimal clinically important difference was only reached at the time of the last patient visit.

4.10.2 Indirect evidence

In the absence of direct clinical evidence for the comparison of treatment with Enco+Bini 450 versus Dab+Tram, the company conducted NMAs to indirectly estimate relative effects of PFS, OS, HRQoL and safety. The ERG considers that the company's approach to conducting the NMAs is appropriate with regard to:

- The identification of trials for inclusion in the systematic literature review and NMA.
- The clinical efficacy, safety and HRQoL outcomes considered in the NMA.
- The statistical approach to NMA for each outcome, including the assessments of model fit of the NMA models and inconsistency within the network.
- The sensitivity analyses conducted by the company in consideration of treatment crossover, violation of proportional hazards, open-label and double blinded trial design and post-hoc adjustment of stratification factors in the COLUMBUS trial.
- The presentation of results from NMA models and the company interpretations of the relative treatment effects from the NMA.

However, the ERG considers that results from the company NMAs should be interpreted with caution due to the following points:

- The evidence networks were sparse and limited, particularly for HRQoL outcomes, with only one or two RCTs contributing to each link of the network.
- Clinical advice to the ERG is that dacarbazine is not a BRAFi therapy and is no longer seen as a standard of NHS care for this population. Therefore, inclusion of this treatment within the network may violate the important assumption of transitivity.
- The ERG appreciates the efforts the company has taken to construct a 'connected' closed loop of evidence of dabrafenib, dacarbazine, vemurafenib and Dab+Tram within networks for PFS and OS. The ERG also acknowledges that this requires the inclusion of dacarbazine in order that consistency (another important assumption of NMA) can be evaluated. However, the ERG notes that Enco+Bini 450 was not included within the closed loop of evidence and, therefore, the consistency of the indirect estimates of Enco+Bini 450 versus Dab+Tram for all outcomes is unknown.
- The ERG considers that the variability of the trial durations (which ranged from 2 years to 6 years) and data maturity (median follow-up for OS ranged from 11 months to 33.6

months) across the trials are sources of heterogeneity and add uncertainty to the generalisability of the results.

- A network of evidence to enable an indirect comparison of Enco+Bini 450 and Dab+Tram for PFS by BIRC could not be constructed, only an NMA of PFS by local investigator review was feasible. Five of the seven trials included within the NMA were of an open-label design and investigator assessment of PFS in open-label trials may be subject to bias.
- The company considered the fixed-effects results to be most appropriate due to the sparseness of the evidence networks. Results from fixed-effects NMAs showed improvements for Enco+Bini 450 in terms of PFS and OS compared to Dab+Tram, the incidence of Grade ≥3 AEs is higher for Enco+Bini 450 compared to Dab+Tram and the treatments are comparable for HRQoL.
- The ERG notes that fixed-effects sensitivity analyses were conducted by the company due to uncertainties with the indirect comparisons for the clinical efficacy outcomes (treatment crossover, violation of proportional hazards, open-label and double blinded trial design and post-hoc adjustment of stratification factors in the COLUMBUS trial). The ERG notes that the conclusions drawn from the base case analyses and the sensitivity analyses are consistent for the OS and PFS outcomes.
- High levels of uncertainty were present due to the sparse networks, and wide CrIs crossed 1 for all base case and sensitivity analyses for all outcomes. No statistically significant differences between Enco+Bini 450 and Dab+Tram were observed in the results of the fixed-effects NMAs for any outcomes.
- The ERG appreciates the computational difficulty of fitting random-effects NMA models to small networks, yet the model fit statistics were generally similar between fixed- and random-effects models for the clinical efficacy and safety outcomes. Therefore, in the presence of heterogeneity of design, study duration and some participant baseline characteristics, a random-effects approach to NMA may have been more appropriate for the clinical efficacy and safety outcomes.
- However, the ERG notes that, as uncertainty and wide CrIs are observed for the results of the fixed-effects NMAs, uncertainty and width of CrIs would only become larger for the random-effects NMAs. Therefore, the ERG considers that the same interpretation and conclusions would likely be made from the results of the fixed-effects and random-effects NMA models.

5 COST EFFECTIVENESS

This section includes a summary and structured critique of the economic evidence submitted by the company in support of the use of Enco+Bini 450 versus Dab+Tram for treating patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. Two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Systematic review for cost effectiveness evidence

5.1.1 Objective of the company's systematic review

The company performed a systematic search of the literature to identify published studies providing economic data for advanced (unresectable or metastatic) melanoma, including economic evaluations, resource utilisation, and costs. The company searched for articles that had been published since 1 January 2007. The databases listed in Table 18 were initially searched on 27 June 2017 and updated searches were carried out on 16 May 2018.

Table 18 Details of the databases searched for economic evidence

Database	Interface
Excerpta Medica Database (Embase®)	Ovid.com
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	Ovid.com
Cochrane Library	Ovid.com
Cost Effectiveness Analysis (CEA) registry database	Healtheconomics.tuftsmedicalcenter.org
EconLit®	Ebsco.com

Source: CS, adapted from Appendix G

The company also carried out searches to identify relevant proceedings from the following conferences:

- American Association for Cancer Research (AACR)
- American Society of Clinical Oncology (ASCO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and International Congress
- European Society for Medical Oncology (ESMO)
- Society for melanoma research (SMR).

Additionally, the NICE website was searched for potentially relevant technology appraisals. Details of the search strategies used by the company are provided in Appendix G of the CS.

5.1.1 Eligibility criteria used in study selection

The main inclusion and exclusion criteria used by the company to select studies are shown in Table 19. Only relevant studies published in English were included in the review.

Table 19 Economic review inclusion and exclusion criteria

Characteristic	Inclusion criteria	Exclusion criteria
Population	• Adults with advanced (unresectable or metastatic) melanoma	• Non-human populations • Patients below 18 years • Patients with other types of skin cancers (non-melanoma skin cancers), such as basal cell and squamous-cell cancers, Kaposi sarcoma, and lymphoma of the skin
Interventions	• The list of included interventions comprised of the following, whether alone or in combination with any other therapy: - encorafenib - dabrafenib - vemurafenib - trametinib - cobimetinib, - ipilimumab - nivolumab - pembrolizumab - atezolizumab - talimogene - dacarbazine - temozolomide - fotemustine - vindesine - interferon - interleukin-2 - taxanes - platinum derivatives	• Any intervention not listed in the inclusion criteria
Comparator	• Any treatment from the list of included interventions • Placebo or best supportive care	• Any comparator not listed in the inclusion criteria
Outcomes	• Incremental cost effectiveness ratio, net monetary benefits and other health economic analysis results	• Cost-only outcomes
Study design	• Full-economic evaluations (cost consequence, cost-effectiveness, cost utility, cost benefit) • Budget impact analysis, resource use studies or economic burden of illness studies • Cost-minimization analysis or cost analysis	• Editorials, notes, comments or letters • Case reports, case series or systematic reviews of economic evaluation studies
Country	• UK and Ireland	• Non-UK studies

LY=life years; QALY=quality adjusted life year
Source: CS, adapted from Appendix G, Table 18

5.1.2 Included and excluded studies

The company search identified nine cost effectiveness analysis studies. Five of the studies compared treatment with a BRAFi+MEKi combinations with BRAFi monotherapies,[76-80] whilst the remaining four studies compared treatment with a BRAFi monotherapy with chemotherapy[81,82] or immune-oncology therapy.[83,84] However, none of the nine studies included Enco+Bini 450 as a comparator. Details of the screening process and the reasons

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 20.

Table 20 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 tunnel states which are designed to account for primary treatment status (see Figure 4).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 tunnel 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 tunnel states.

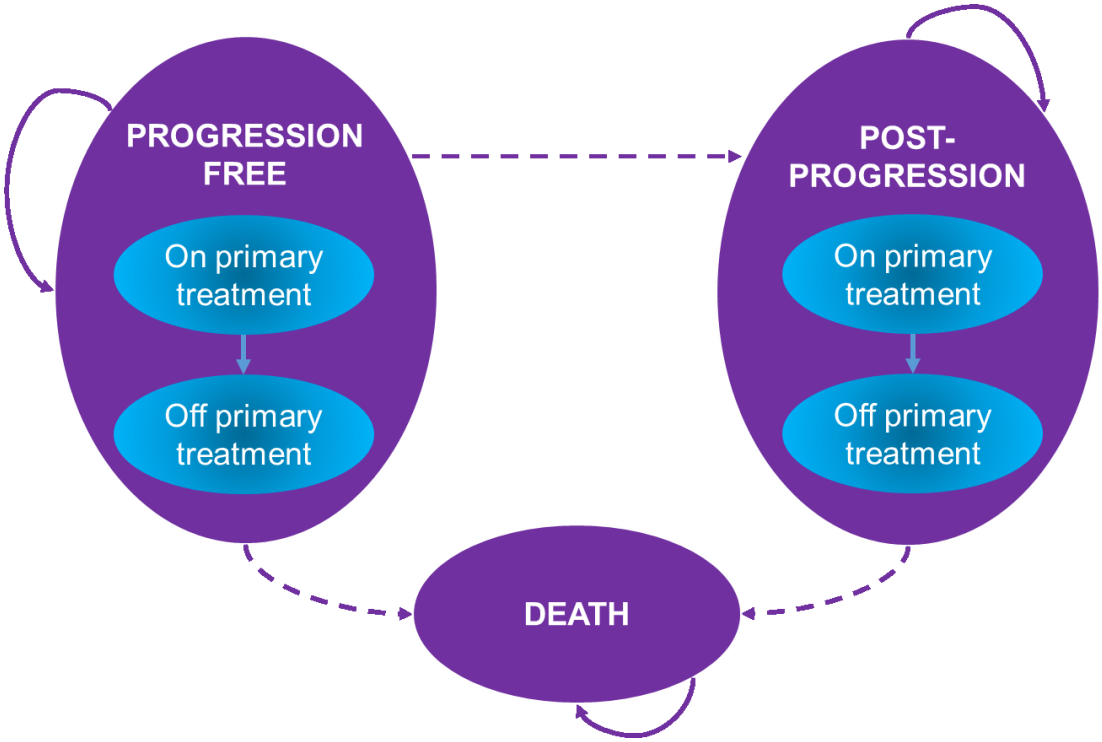

Figure 4 Health state structure of the company model
Source: CS, Figure 17

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 patient-level 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, an exponential 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 5 shows the OS K-M curve for both model arms.

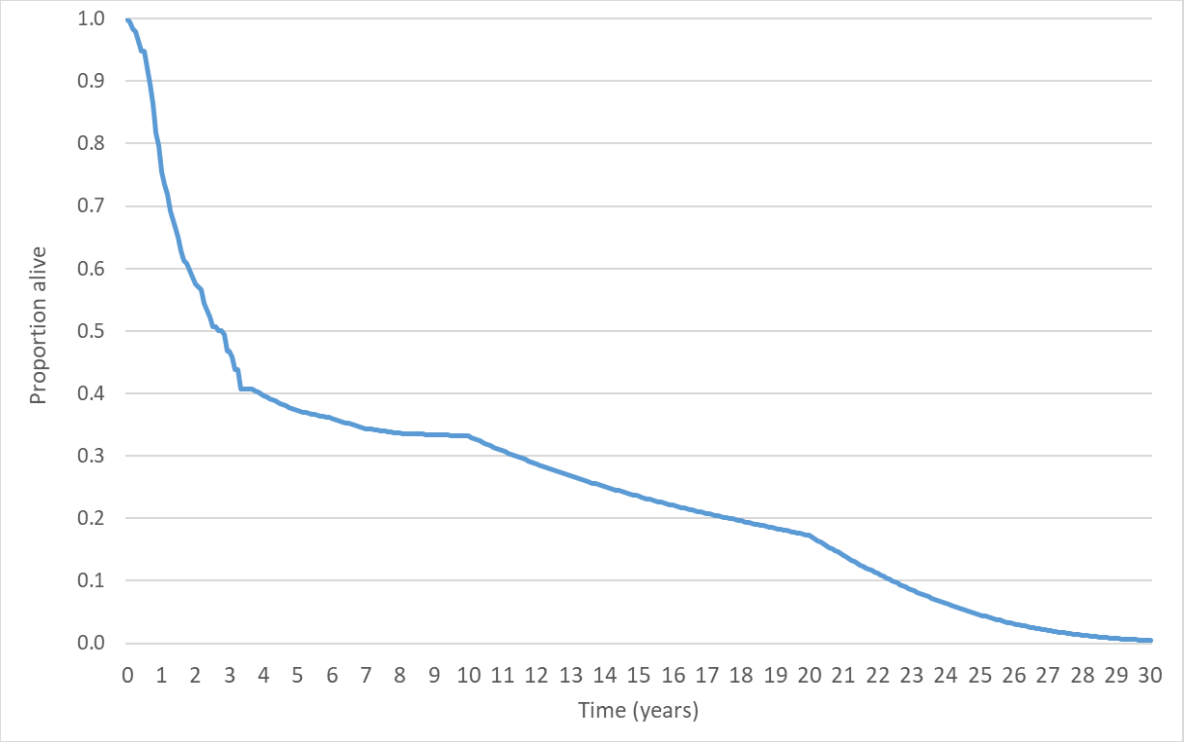

Figure 5 Reconstructed OS K-M curve for the Enco+Bini 450 and Dab+Tram arms used in the company model

Source: CS, Figure 18

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 pairwise PFS curves. The pairwise 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 pairwise 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 21).

Table 21 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 22. The company model includes relative dose intensity (RDI) multipliers to account for the fact that not all patients on treatment receive the full dose. 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 22 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	0.96	276.00	5,648.81
Trametinib	2mg once a day	£1,120.00	7 x 2mg	0.92	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 (Table 23). The one-off subsequent therapy cost was calculated as the sum of the weighted total cost for each subsequent therapy.

Table 23 Subsequent treatments expected cost per course of therapy

Subsequent therapy	Expected total subsequent therapy cost (including administration cost)	Proportion receiving therapy in Enco+Bini 450 arm of the COLUMBUS trial	Weighted total subsequent therapy cost (£)
Ipilimumab	£76,160	25.6%	£19,483
Pembrolizumab	£53,391	21.7%	£11,589
Nivolumab	£48,528	10.9%	£5,267
Chemotherapy	£3,478	10.1%	£350
Dabrafenib	£67,466	9.3%	£6,276
Dab+Tram	£121,473	4.7%	£5,650
Ipilimumab + nivolumab	£109,863	4.7%	£5,110
Other	£49,904	3.9%	£1,934
Vemurafenib	£84,291	3.9%	£3,267
Cobimetinib + vemurafenib	£135,842	3.1%	£4,212
Immunotherapy + others	£95,293	2.3%	£2,216
Enco+Bini 450‡	[redacted]	0.0%	£0
BRAFi + MEKi + others‡	£101,451	0.0%	£0
Protein kinase inhibitors + vemurafenib‡	£138,298	0.0%	£0
Total weighted cost			**£65,354**

BRAFi=serine/threonine-protein kinase B-Raf inhibitor; MEKi,=mitogen-activated extracellular signal-regulated kinase inhibitor
Source: CS, adapted from Table 51 and Table 52

Resource use by health state

The base case resource use categories and costs in the cost effectiveness model are shown in Table 24. A one-off terminal care cost of £7,608 was applied to individuals who transit to the death health state. Detailed death state resource use estimates and costs are available in Tables 54, 55 and 56 of the CS.

Table 24 Resource use and cost associated with model health states

Health state	Disease management	Cost
Progression free	Routine management during antineoplastic treatment	£576.20
Post-progression	Routine management during antineoplastic treatment	£576.20
	Management at progression (one-off cost)	£2,669.76
	Routine management part of best supportive care	£775.57

Source: CS, adapted from Table 53 and Table 56

Adverse event costs

Estimates of the cost implications to the NHS of Grade 3/4 AEs experienced by at least 5% of participants in the Enco+Bini 450 arm of the COLUMBUS trial (for Enco+Bini 450 model arm) or the Dab+Tram arm of the COMBI-v and COMBI-d (for the Dab+Tram model arm) were included in the company model. The company obtained outpatient and inpatient costs by referral to the literature and expert advice.[87,88] The total cost per AE was obtained by calculating the weighted average cost of inpatient and outpatient costs. Clinical advice to the

company was that all Grade 3 AEs were treated as outpatient care while Grade 4 AEs required an inpatient stay. The company, therefore, defined the proportions of individuals who required outpatient appointments and inpatient stays to be the proportions of people with Grade 3 and Grade 4 AEs in the COLUMBUS trial, respectively. Table 25 shows the model costs of treating AEs. Full details are available in Tables 57, 58 and 59 of the CS.

Table 25 Total costs associated with adverse events in the company model

Adverse event	Enco+Bini 450	Dab+Tram
Hypertension	£13.63	£30.93
Pyrexia	£9.44	£14.15
Blood creatine phosphokinase increased	£5.74	-
Gamma-glutamyl transferase increased	£24.57	£8.91
Alanine aminotransferase increased	£13.65	£9.17
Total	**£67.02**	**£63.16**

Source: CS, adapted from Table 59

5.2.8 Cost effectiveness results

Table 26 shows the ICER per QALY gained for the comparison of treatment with Enco+Bini 450 versus treatment with Dab+Tram. Company model results show that treatment with Enco+Bini 450 dominates treatment with Dab+Tram (is cheaper and more effective).

Table 26 Base case incremental cost effectiveness result– PAS discount applied to treatment with Enco+Bini 450

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Enco+Bini 450	[redacted]	5.88	4.22				
Dab+Tram	353,603	5.271	3.770	[redacted]	0.613	0.453	Dominant

LYG=life year gained; QALY=quality adjusted life year
Source: adapted from CS, Table 61

5.2.9 Sensitivity analyses

Deterministic sensitivity analysis

The company conducted one-way sensitivity analysis (OWSA) on several model parameters, using either 5% or 95% CI for each parameter (where available) or varying the mean

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 6).

Figure 6 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 +0.431) are similar to the model deterministic results (the cost effectiveness plane is presented in Figure 7). The cost effectiveness acceptability curve is provided in Figure 8 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%.

Figure 7 Cost effectiveness plane showing scatter plot of incremental cost and incremental QALY for treatment with Enco+Bini 450 versus treatment with Dab+Tram*

* Outer and inner eclipse represent 95% and 99% confidence eclipse
Incr=incremental; QALYs=quality-adjusted life years; PSA=probabilistic sensitivity analysis
Source: CS, Figure 29

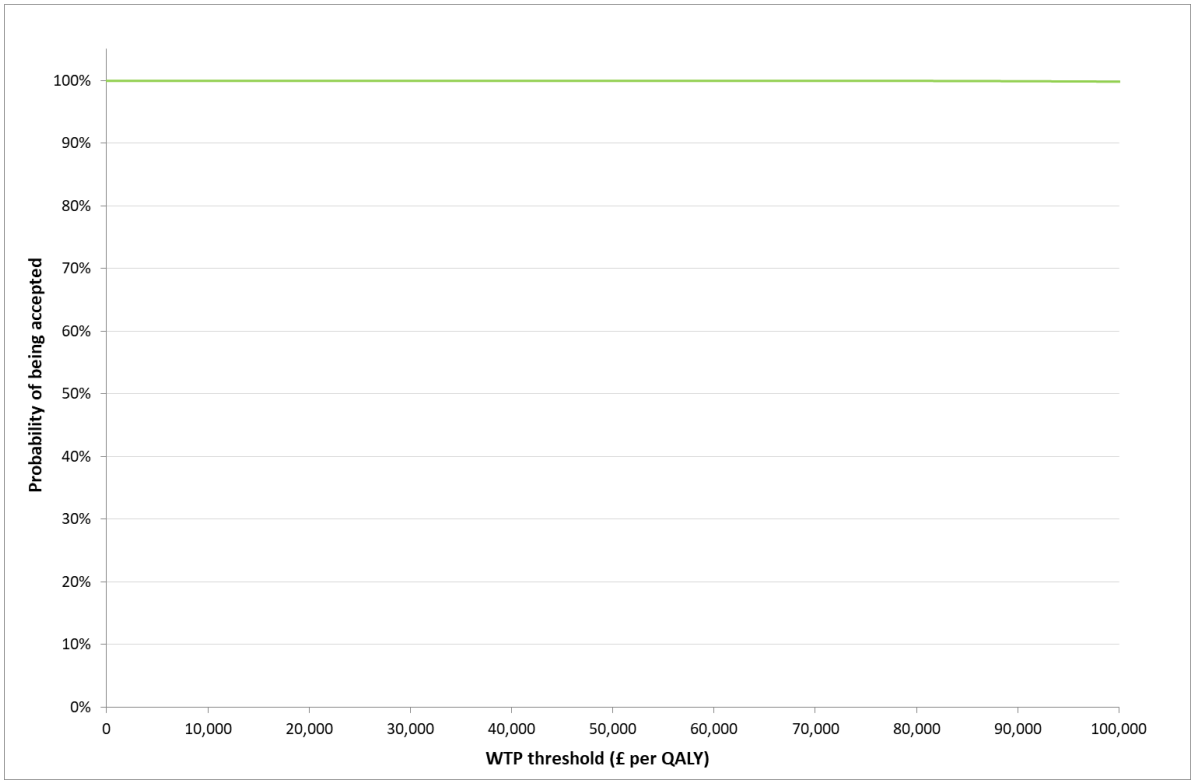

Figure 8 Cost effectiveness acceptability curve for treatment with Enco+Bini 450 versus treatment with Dab+Tram – based on 10,000 iterations

Source: CS, Figure 30

5.2.10 Scenario analyses

The company carried out a range of scenario analyses. Results from these analyses are largely robust to the changes to most model parameters (Table 27). The exceptions are when (i) a [redacted] discount was applied to the list price for Dab+Tram and (ii) OS, PFS, PF utility value and AE rates are assumed to be the same for treatment with Enco+Bini 450 and treatment with Dab+Tram.

Table 27 Scenario analyses results

Scenario	Incremental		ICER
	Costs	QALYs	
Base case	[redacted]	0.453	Dominant
Equal effectiveness for Dab+Tram and Enco+Bini 450 (OS, PFS, PF utility, AE rates)	[redacted]	0.000	Less costly, equal effectiveness
PF utilities equal for Dab+Tram and Enco+Bini 450	[redacted]	0.501	Dominant
HR for TTD for Dab+Tram vs Enco+Bini 450 = 0.9	[redacted]	0.453	Dominant
HR for TTD for Dab+Tram vs Enco+Bini 450 = 1.1	[redacted]	0.455	Dominant
Constant hazard approach for extrapolation of both TTD and PFS	[redacted]	0.418	Dominant
TTD any reason (not censored)	[redacted]	0.453	Dominant
HR adjustment for AJCC =1	[redacted]	0.366	Dominant
OS crossover adjustment applied	[redacted]	0.422	Dominant
RDIs all set to 1	[redacted]	0.453	Dominant
Remove utility decrement for age	[redacted]	0.461	Dominant
Subsequent treatment option 2	[redacted]	0.453	Dominant
Subsequent treatment option 3	[redacted]	0.453	Dominant
Vial wastage excluded	[redacted]	0.453	Dominant
Exclude terminal care cost	[redacted]	0.453	Dominant
Both grade 3 and 4 AEs hospitalised	[redacted]	0.453	Dominant
List price for both Enco+Bini 450 and Dab+Tram	[redacted]	0.453	Dominant
PAS price for Enco+Bini 450 and [redacted] discount applied to Dab+Tram (threshold analysis to reach ICER of £20,000)	[redacted]	0.453	[redacted]
Discount rates 0% for both costs and outcomes	[redacted]	0.664	Dominant
Discount rates 6% for both costs and outcomes	[redacted]	0.358	Dominant

AEs=adverse events; AJCC=American Joint Committee on Cancer; HR=hazard ratio; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity; TTD=time to treatment discontinuation
Source: CS, adapted from Table 62

5.2.11 Model validation and face validity check

The company states that an external health economist and a clinical expert checked the model structure, key assumptions, input data and implementation techniques (formula/functionality errors). Further input from the clinical expert was sought via a face to face meeting, with the main objective being to ensure the clinical plausibility of the model structure and assumptions. Specific assumptions were checked as necessary with follow-up emails and phone calls. Input from the health economist was sought via videoconference, with the main objective of ensuring

that the selected modelling approaches were methodologically sound and met the requirements of health technology assessment bodies.

5.3 ERG assessment of company economic model

Table 28 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=personal social services

5.3.1 Drummond checklist

Table 29 Economic analysis checklist completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness of Enco+Bini 450 was established versus vemurafenib (COLUMBUS trial), however, results from the company's NMAs did not establish effectiveness versus Dab+Tram
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

5.3.2 ERG's critique of the company's cost effectiveness analysis

Population

In line with the final scope[22] issued by NICE, the company has only generated cost effectiveness results for the comparison of treatment with Enco+Bini 450 versus Dab+Tram for patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. Evidence for the effectiveness of Enco+Bini 450 is available from the COLUMBUS trial and relates to patients receiving first-line treatment. However, 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 or combination treatment with nivolumab+ipilimumab 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 (generally Dab+Tram, with vemurafenib or dabrafenib being prescribed to patients who have contraindications to Dab+Tram). The ERG, therefore, considers that the results from the company model may be of limited relevance to the NHS.

Company model

The ERG considers that the company model is appropriately designed and is satisfied that accurate algorithms are employed within the model.

For the Enco+Bini 450 arm of the company model, values for OS, PFS, time on treatment, utility values in different heath states and AE rates were derived from the COLUMBUS trial. The ERG is satisfied that the COLUMBUS is a well-conducted trial and that the trial data were appropriately incorporated into the company model.

In the absence of direct evidence comparing the clinical effectiveness of Enco+Bini 450 versus Dab+Tram, the company carried out NMAs. Results showed no statistically significant difference between Enco+Bini 450 versus Dab+Tram for investigator-assessed PFS, OS, AEs and HRQoL (relevant results are displayed in Table 30). The ERG considers that the results of the NMAs should be viewed with caution due to numerous methodological limitations but highlights that clinical advice to the ERG is that Enco+Bini 450 and Dab+Tram are likely to be similar in terms of clinical effectiveness outcomes (see Section 4.10 of this ERG report).

Table 30 Summary of key results from the company's NMAs

	Hazard ratio (95% CrI)		Source in company submission
	Enco+Bini 450 vs Dab+Tram	**Dab+Tram vs Enco+Bini 450**	
OS	0.89 (0.65 to 1.23)	1.12 (0.81 to 1.53)	Table 21, p67
PFS (investigator assessed)	0.77 (0.57 to 1.04)	1.30 (0.96 to 1.77)	Table 22, p68
EQ-5D utility score, pre-progression	-0.02 (-0.05 to 0.01)	0.02 (-0.01 to 0.05)	Table 23, p70
EQ-5D utility score, DCFB at Week 32	-0.04 (-0.10 to 0.02)	0.04 (-0.02 to 0.10)	
EQ-5D utility score, DCFB at disease progression	-0.04 (-0.12 to 0.04)*	0.04 (-0.04 to 0.12)	
Grade ≥3 AEs	1.18 (0.70 to 1.98)	0.85 (0.51 to 1.43)	Table 24, p71

AE=adverse event; CrI=credible interval; DCFB difference in change from baseline; EQ-5D=EuroQol-5 dimensions; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival;
*CrI incorrectly reported as (-0.12 to-0.04) in CS

As the results of the 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, the ERG considers that, in the base case, it is inappropriate to model any difference in efficacy or utility.

The ERG highlights that the company did not use NMA AE results (which showed no statistically significant difference in the incidence of Grade ≥3 AEs between treatment with Enco+Bini 450 versus Dab+Tram) in their model. Instead, the company included data relating to specific Grade 3 and 4 AEs with an incidence of 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 (see Table 31). The ERG highlights that such a simple analysis is not robust as it fails to account for any differences in patient baseline characteristics between the three trials. No statistical testing of this simple 'between trial analysis' result was performed by the company or could be performed by the ERG.

Table 31 Incidences of Grade ≥3 AEs (≥5% in any relevant arm)

Grade 3/4 AEs (≥5% in either arm)	Enco+Bini 450	Dab+Tram		
	COLUMBUS trial Nov 2016 cut-off	COMBI-v trial March 2015 cut-off N=350†	COMBI-d trial 15 Feb 2016 cut-off N=209†	COMBI-d/ COMBI-v trials weighted average
	CS, Section B.2.10.1.2	NICE TA396[13]	LONG 2017[35]	Calculated
Hypertension	[redacted]	15.4% (54)	5.7% (12)	11.8%
Pyrexia	[redacted]	4.6% (16)	6.7% (14)	5.4%
Blood CK increased	[redacted]	NR (set to 0%)	NR (set to 0%)	0.0%
GGT increased	[redacted]	5.4% (19)	NR (set to 0%)	3.4%
ALT increased	[redacted]	2.6% (9)	2.4% (5)	2.5%

ALT=alanine aminotransferase; CK=creatine phosphokinase; CS=company submission; GGT=gamma-glutamyl transferase; NR=not reported
† Numbers provided to enable calculation of weighted averages
Source: CS Table 42, p116

The impact of AEs on utility values has been captured by the health state utility values employed in the company model. This means that any differences in incidence of Grade ≥3 AEs between the Enco+Bini 450 and Dab+Tram model arms do not affect the estimate of incremental QALYs generated by the company model. In terms of costs, in the company base case, the cost per patient of treating AEs was only £3 higher for patients in the Enco+Bini 450 arm than for patients in the Dab+Tram arm. As there is a lack of evidence to demonstrate any statistically significant difference in the incidence of any Grade ≥3 AEs when treatment with Enco+Bini 450 is compared with Dab+Tram, and as the impact of the cost of treating AEs on model cost effectiveness results is negligible, the ERG considers that the AE costs associated with Enco+Bini 450 and Dab+Tram can be assumed to be equal.

As OS, PFS, utility values and AEs can all be assumed to be equal for patients treated with Enco+Bini 450 and those treated with Dab+Tram, the only difference between the two treatment combinations that affects model results is treatment-related costs. In the company model, treatment-related costs are a function of time on treatment, administration costs, RDI multipliers 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 has assumed that the RDI multiplier associated with treatment with Enco+Bini 450 (Enco 0.91, Bini 0.88) is lower

than that associated with treatment with Dab+Tram (Dab 0.92, Tram 0.96). The company's assumption of differential RDI multipliers is based upon a simple 'between trial analysis' of RDI results from the COLUMBUS trial (for Enco+Bini 450) and from the COMBI-d and COMBI-v trials (for Dab+Tram). This 'between trials analysis' is not robust, as it does not account for any differences that may have existed in baseline patient characteristics between the three trials. The ERG considers this assumption is not consistent with the company assumptions that tolerability (in terms of frequency and severity of AEs) and time on treatment are the same for all patients, irrespective of whether they are treated with Enco+Bini 450 or Dab+Tram. Therefore, the ERG considers that the RDI multiplier should be the same for both treatments.

The ERG has run a scenario analysis (Table 32, Scenario B) where OS, PFS, utility values, AEs and RDI multipliers (set to 1) are the same for both drug combinations. This ERG scenario is similar to the company's scenario (CS, p144) where OS, PFS, PF utility and AEs are assumed to be equal; the company's results show that Enco+Bini 450 is cost-saving (generating equal QALYs) versus Dab+Tram.

The ERG, whilst assuming no difference in efficacy (PFS or OS), utility values or AEs between the two treatment combinations, has also generated results from a scenario analysis using the differential RDI multipliers that the company uses for the two drug combinations (Table 32, Scenario B1).

With time on treatment, administration costs and RDI being equal for both treatments, 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 a cost utility analysis is not required as the available clinical evidence supports the use of a simple cost-minimisation analysis.

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 32, 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 32, 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 32. The ERG model adjustments to the company base case analysis are described in Appendix 8.3 of this ERG report.

Table 32 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 PS >1 (the remainder had an ECOG of 30%), the treatments can be assumed to be delivered in the first-line setting to patients with a high PS.

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.

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8 APPENDICES

8.1 Appendix 1 Other efficacy outcomes in the COLUMBUS trial

8.1.1 Outcome definitions and statistical analysis approach

Other secondary efficacy outcomes which did not contribute to the economic model were response outcomes:

- Objective response rate (ORR), calculated as the proportion of patients with a best overall response of complete response (CR) or partial response (PR). ORR was to be calculated for confirmed and unconfirmed responses separately
- Disease control rate (DCR), calculated as the proportion of patients with a best overall response of CR, PR or stable disease
- Time to objective response (TTR), calculated as the time from date of randomisation until first documented CR or PR (CR or PR did not need to be confirmed)
- Duration of response (DOR), calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer

Response for all outcomes was derived according to RECIST version 1.1,[89] presented by treatment arm and were performed using BIRC assessments, with local Investigator's assessments being used for sensitivity analyses. ORR and DCR were defined as 'best overall response (BOR)' and as the first tumour assessment was performed 8 weeks after randomisation, the definition of a best overall response evaluation of 'progressive disease' or 'unknown' were applicable.[30]

ORR and, DCR were presented as proportions with exact 95% CI. TTR and DOR were described using Kaplan-Meier methods as per PFS (see Section 4.5.1 of this ERG report). No formal statistical tests were performed of response outcomes.

8.1.2 Results of other efficacy outcomes in the COLUMBUS trial

Best overall response: ORR and DCR

Results for ORR and DCR for all three treatment arms for the data-cut off dates of 19th May 2016 and 7th November 2017 (updated analysis) per BIRC and per investigator review are provided in are presented in

Table 33 of this ERG report. Further details of the type of response (complete response [CR], partial response [PR], stable disease [StD], non-progressive disease [Non-PD], non-complete response [Non-CR]) are provided in Table 18 of the CS and Table 32, Table 42 and Table 43 of the Appendix L of the CS.

Table 33 ORR and DCR results

	Enco+Bini 450 N=192	Enco 300 N=194	Vemurafenib N=191
BIRC, FAS, Part 1, data-cut off 19 May 2016			
Patients with measurable disease at baseline; n (%)[a]	[redacted]	[redacted]	[redacted]
Patients with non-measurable disease at baseline; n (%)[a]	[redacted]	[redacted]	[redacted]
Confirmed ORR: CR + PR; n (%)	121 (63.0)	98 (50.5)	77 (40.3)
95% CI[b]	(55.8, 69.9)	(43.3, 57.8)	(33.3, 47.6)
DCR: CR+PR+StD+Non-PD/Non-CR; n(%)	177 (92.2)	163 (84.0)	156 (81.7)
95% CI[b]	(87.4, 95.6)	(78.1, 88.9)	(75.4, 86.9)
Unknown[c]	11 (5.7)	25 (12.9)	22 (11.5)
Not assessed[d]	2 (1.0)	0	0
Investigator review, FAS, Part 1, data-cut off 19 May 2016			
Patients with measurable disease at baseline; n (%)	191 (99.5)	194 (100)	190 (99.5)
Patients with non-measurable disease at baseline; n (%)	1 (0.5)	0	1 (0.5)
Confirmed ORR: CR + PR; n (%)	144 (75.0)	112 (57.7)	94 (49.2)
95% CI[b]	(68.3, 81.0)	(50.4, 64.8)	(41.9, 56.5)
DCR: CR+PR+StD+Non-PD/Non-CR; n (%)	179 (93.2)	168 (86.6)	160 (83.8)
95% CI[b]	(88.7, 96.3)	(81.0, 91.1)	(77.8, 88.7)
Unknown	11 (5.7)	19 (9.8)	20 (10.5)
BIRC, FAS, Part 1, data-cut off 7 November 2017			
Patients with measurable disease at baseline; n (%)	[redacted]	[redacted]	[redacted]
Patients with non-measurable disease at baseline; n (%)	[redacted]	[redacted]	[redacted]
Confirmed ORR: CR + PR; n (%)	122 (63.5)	100 (51.5)	78 (40.8)
95% CI[b]	(56.3, 70.4)	(44.3, 58.8)	(33.8, 48.2)
DCR: CR+PR+StD+Non-PD/Non-CR ; n (%)	177 (92.2)	163 (84.0)	155 (81.2)
95% CI[b]	(87.4, 95.6)	(78.1, 88.9)	(74.9, 86.4)
Unknown[c]	[redacted]	[redacted]	[redacted]
Not assessed[d]	[redacted]	[redacted]	[redacted]
Investigator review, FAS, Part 1, data-cut off 7 November 2017			
Patients with measurable disease at baseline; n (%)	[redacted]	[redacted]	[redacted]
Patients with non-measurable disease at baseline; n (%)	[redacted]	[redacted]	[redacted]
Confirmed ORR: CR + PR; n (%)	145 (75.5)	112 (57.7)	94 (49.2)
95% CI[b]	(68.3, 81.4)	(50.4, 64.8)	(41.9, 56.5)
DCR: CR+PR+StD+Non-PD/Non-CR; n (%)	178 (92.7)	168 (86.6)	160 (83.8)
95% CI[b]	(88.1, 96.0)	(81.0, 91.1)	(77.8, 88.7)
Unknownc	[redacted]	[redacted]	[redacted]

a. Does not include the 2 patients who were not assessed by BIRC;
b. The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson's method;
c. Unknown response: Not included in BOR assessment but included in denominator for ORR and DCR. Progression has not been documented and one or more lesions have not been assessed or have been assessed using a different method than baseline;
d. Not included in BOR assessment but included in denominator for ORR and DCR. No assessment has occurred by BIRC; not included in patients with measurable or non-measurable disease at baseline.
Bini=binimetinib; BIRC, blinded independent review committee; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; Enco=encorafenib; FAS, full analysis set; ORR, overall response rate; PD, progressive disease; PR, partial response; StD, stable
Source: CS, adapted from Table 18; Appendix L, CS, adapted from Table 32, Table 42 and Table 43.

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] 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 [redacted] 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 4.6.2 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 4.6.2 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 4.6.2 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 34 ERG revisions to submitted company model

ERG revisions	Implementation instructions
Setting all efficacy parameters and RDI sto be the same for Dab+Tram and Enco+Bini 450	In Sheets 'Exec summary' Insert value in cell R9 = P9 Select value in cell K26 = "Do not include RDI" In Sheets 'Clinical' Select value in box 'Drop Down 5': 'Assign HR and OR = 1' In Sheets 'QoL' Set value in cell E11 = 0.80

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 1 November 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Missing information for licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 "Encorafenib combined with binimetinib (Enco+Bini 450) is licensed in Europe for treating (unresectable or metastatic) BRAF V600 mutation-positive melanoma"	The text should be corrected to: "Encorafenib combined with binimetinib (Enco+Bini 450) is licensed in Europe for treating adult patients with unresectable or metastatic BRAF V600 mutation-positive melanoma**.**"	"adult patients" should be added to be fully consistent with the licensed indication. The brackets around 'unresectable or metatsatic' have been added in error by the ERG and should be removed.	This is an error and the ERG report will be amended

Issue 2 Description error in AE data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 "The most frequently reported Grade 3 and Grade 4 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 text should be corrected to: "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 following text should also be added: "The most frequently reported Grade 3 and Grade 4 AEs in ≥5% of patients treated with Enco+Bini 450 were elevated gamma-glutamyl transferase ([redacted]), blood creatine phosphokinase increased ([redacted]), hypertension ([redacted]) and elevated alanine aminotransferase ([redacted]) and in the vemurafenib arm was arthralgia ([redacted])."	Current text incorrectly attributes rates to Grade 3 and Grade 4 AEs. However, the rates quoted are for **serious** AEs and this should be corrected. For balance and also clarification the rates of common Grade 3 and Grade 4 AEs should be added.	This is an error and the ERG report will be amended so that 'serious' is added to the text as requested. The request for additional text is not a factual error and no amendment is required

Issue 3 Consistency error in terminology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11; Page 12; Page 54 "BICR"	The text should be corrected to: "BIRC"	Typographical error. BIRC is used in the majority of cases throughout the report. The three occurrences of BICR should be amended to BIRC for consistency.	This is an error and the ERG report will be amended

Issue 4 Accuracy of description of eligible patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 "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 text should be corrected to: "The company expects that if Enco+Bini 450 is recommended for use in the NHS, 86 patients would receive treatment with Enco+Bini 450 during the first year after a positive recommendation, rising to 486 patients by the 5th year (CS, Document A, p23)."	The patient numbers detailed in Document A, p23 are based on the patient population eligible for treatment (858 in Year 1 rising to 972 in Year 5), to which an expected market share is then applied. As such, the numbers are not estimates of the population **eligible** for treatment with Enco+Bini 450 but rather estimates of the population anticipated to **receive** treatment with Enco+Bini 450.	This is not a factual error. No amendment required

Issue 5 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 "The ERG is unable to comment on the company's estimate as the methods used to calculate the estimate were not included in the CS."	The text should be corrected to: "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."	The statement is misleading as full methodology was provided in the budget impact template with appropriate cross reference to the budget impact template made in the CS, Document A, p23.	For clarity, the ERG report will be amended

Issue 6 Clarification of PAS description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 "Results using the PAS agreed with the Department of Health are presented in the company's PAS addendum."	The text should be corrected to: "Results using the PAS agreed with the Department of Health for Enco+Bini 450 are presented in the company's base case."	For clarity it should be stated that the PAS referred to is for Enco+Bini 450. It should also be clarified that the PAS was presented in the base-case analysis in the main body of the CS; a PAS addendum was not provided as part of the company submission	This is an error and the ERG report will be amended

Issue 7 Inaccuracy on ECOG status

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 "The ERG notes that most patients (70%) in the COLUMBUS trial were of ECOG PS 0 and the	The text should be corrected to: "The ERG notes that most patients (72%) in the COLUMBUS trial were of ECOG PS	The percentages presented by the ERG are for the Enco+Bini 450 arm specifically. These should be corrected to reflect	This is an error and the ERG report will be amended

remainder (30%) were of ECOG PS 1”	0 and the remainder (28%) were of ECOG PS 1”	the overall trial population, as per CS, table 6.	

Issue 8 Inaccuracy on event discordance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 “The ERG asked the company for clarification regarding discordance between BIRC and investigator for [redacted] ‘death’ events in the Enco+Bini 450 arm.”	The text should be corrected to: “The ERG asked the company for clarification regarding discordance between BIRC and investigator for [redacted] ‘death’ events across the Enco+Bini 450 and vemurafenib arms.”	This statement is factually incorrect in making reference to the Enco+Bini 450 arm alone. The subsequent text provided in the ERG report correctly refers to six death events distributed across the Enco+Bini 450 and vemurafenib arms (total of four Enco+Bini 450 arm and two vemurafenib arm).	This is an error and the ERG report will be amended

Issue 9 Missing hazard ratio

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46, table 10, last row “(0.56 to 1.00); p=0.0256”	Correct table entry to: “0.75 (0.56 to 1.00); p=0.0256”	The hazard ratio is currently missing and needs to be inserted to allow full interpretation of results	This is an error and the ERG report will be amended

Issue 10 Incorrect AE data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48 “Slightly more of the patients in the Enco+Bini 450 arm ([redacted]),	The text should be corrected to: “Slightly more of the patients in the Enco+Bini 450 arm ([redacted]), compared with	Vemurafenib rate is incorrect.	This is an error and the ERG report will be amended

compared with the vemurafenib ([redacted]) and Enco 300 ([redacted]) arms experienced Grade 3 to Grade 4 AEs leading to treatment discontinuation"	the vemurafenib ([redacted]) and Enco 300 ([redacted]) arms experienced Grade 3 to Grade 4 AEs leading to treatment discontinuation"		

Issue 11 Description error in AE data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50 "The most frequently reported Grade 3 to Grade 4 AEs 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])."	The text should be corrected to: "The most frequently reported Grade 3 to Grade 4 serious AEs in ≥2% of patients in the Enco+Bini arm were pyrexia ([redacted]) and anaemia ([redacted]). 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])."	Current text incorrectly attributes rates to Grade 3 and Grade 4 AEs. However, the rates quoted are for **serious** AEs and this should be corrected.	This is an error and the ERG report will be amended

Issue 12 Description error in NMA interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 "…and a delta<0 indicates a result in favour of Enco+Bini 450 for HRQoL outcomes"	The text should be corrected to: "…and a delta>0 indicates a result in favour of Enco+Bini 450 for HRQoL outcomes"	Direction of effect in favour of Enco+Bini 450 is incorrectly stated and requires correction to allow correct interpretation of results.	This is an error and the ERG report will be amended

Issue 13 Description error in NMA interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 "For all HRQoL outcomes, the NMA results favour Enco+Bini 450 (Delta<0); however, the CrIs cross 0 for all analyses. The company also notes that the numerical improvements in favour of Enco+Bini 450 were also inferior to the minimal difference in EQ-5D-5L score considered to be clinically important (0.08 points)."	The text should be corrected to: "For all HRQoL outcomes, the NMA results favour Dabra+Tram (Delta<0); however, the CrIs cross 0 for all analyses. The company also notes that the numerical improvements in favour of Dabra+Tram were also inferior to the minimal difference in EQ-5D-5L score considered to be clinically important (0.08 points)."	Direction of effect in favour of Enco+Bini 450 incorrectly stated and requires correction to allow correct interpretation of results.	This is an error and the ERG report will be amended. The text referred to by the company appears on page 60 of the ERG report

Issue 14 Terminology of 'tunnel states'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 (3 mentions), Page 66 (1 mention), Page 67 (2 mentions)	The text should be corrected to: "sub-states"	These states are used only to account for the differential costs for patients on or off primary treatment. There is no impact	This is an error and the following pages of the ERG report will be amended:

"Tunnel states"		on quality of life. These states should not be considered as health states but rather just a way of capturing the relevant costs. Tunnel states imply that patients must transition through this state before moving onto another and therefore the use of this wording could be misleading.	3 on page 15 1 on page 66 2 on page 67

Issue 15 Description error in PAS discount

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 "the PAS price for Enco+Bini 450 was reduced to [redacted]%"	The text should be corrected to: "the list price for Dab+Tram was reduced by [redacted]%" or "a discount of [redacted]% was applied to the list price for Dab+Tram"	Using the wording "reduced to" has a different meaning to "reduced by". In addition, the discount is applied to the list price of Dab+Tram **not** the PAS price of Enco+Bini 450.	This is an error and the ERG report will be amended

Issue 16 Reason for applying RDI

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 "The company's rationale for this approach is that the two populations experience different incidences of Grade 3 and 4 AEs." ***Page 18*** "On the basis that patients treated with Enco+Bini 450 and Dab+Tram experience different incidences of Grade 3 and 4 AEs, the company has assumed that different RDI multipliers should be applied to the two model treatment arms." ***Page 71*** "The company model includes relative dose intensity (RDI) multipliers to account for the fact that not all patients on treatment receive the full dose."	The text should be corrected to: ***Page 17*** "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." ***Page 18*** "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." ***Page 71*** "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."	The differences in Grade 3 and 4 AEs is not the only reason for including RDI. The efficacy estimates derived from COLUMBUS are based upon patients receiving reduced doses. Therefore, applying the RDIs ensures consistency with the actual doses which were used in the trial to derive the efficacy estimates. Using full doses may have resulted in different efficacy results in the trial.	Page 17. This is an error and the ERG report will be amended Page 18. This is an error and the ERG report will be amended Page 71. This information was not provided in the CS. For clarity, the ERG report will be amended

Issue 17 Error in ERG's base case cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 "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." and "results in treatment with Enco+Bini 450 costing [redacted]less than treatment with Dab+Tram." ***Page 85*** "leads to a [redacted] per person." ***Page 86, Table 32*** "[redacted]", "£373,318" "[redacted]" ***Page 87*** "results in treatment with Enco+Bini 450 costing [redacted] than treatment with Dab+Tram." ***Page 89***	After setting Enco+Bini 450 AE rates equal to Dab+Tram AE rates in the model, all instances of Enco+Bini 450 cost and cost difference highlighted for this issue should be amended as follows: Enco+Bini 450 cost: "[redacted]Dab+Tram cost: "£373,318" (unchanged) Cost difference: "[redacted]	AE rates do not appear to have been altered correctly by the ERG in their base-case analysis (see Issue 29). We have set our version of the model to assume equal AEs for the two treatments and generated updated results for inclusion in the ERG report (see proposed amendment column). **Note:** AE rates appear to have been altered correctly in the ERG scenario where RDI is applied.	This is an error and the ERG report will be amended

"results in treatment with Enco+Bini 450 costing [redacted] than treatment with Dab+Tram."			

Issue 18 Patient level data not used directly in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68 "The company model has been constructed using patient-level data from COLUMBUS trial"	The text should be corrected to: "The company model has been constructed using data from the COLUMBUS trial" or "The company model has been constructed using K-M data from COLUMBUS trial"	The current wording implies that patient level data was used directly in the model, which is not the case.	This is an error and the ERG report will be amended

Issue 19 Constant hazard used instead of exponential

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68 "Then, an exponential extrapolation of the digitised OS K-M curves from the AJCC[2] melanoma registry data were used from year 10 to year 20."	The text should be corrected to: "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."	A constant hazard extrapolation was used, not exponential.	This is an error and the ERG report will be amended

Issue 20 OS K-M curve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69 "Figure 5 shows the OS K-M curve for both model arms." "Figure 5 Reconstructed OS K-M curve for the Enco+Bini 450 and Dab+Tram arms used in the company model" "Source: CS, Figure 18"	The text should be corrected to: "Figure 5 shows the OS K-M curve for Enco+Bini 450." "Figure 5 Reconstructed OS K-M curve for the Enco+Bini 450 arm used in the company model" "Source: CS, Figure 25" Alternatively. figure 19 from the company submission can be presented which does show both treatment arms.	The current graph shows the K-M curve for Enco+Bini 450 only. In addition, this chart is Figure 25 in the CS Document B, not Figure 18.	This is an error and the ERG report will be amended

Issue 21 Terminology of "pairwise"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 "Pairwise" (3 mentions)	The text should be corrected to: "Piecewise"	The approach where K-M data is used, followed by a parametric extrapolation, should be referred to as "piecewise". The wording "piecewise" is used for example in TA396.	This is an error and the ERG report will be amended

Issue 22 List prices for Enco+Bini 450 shown in Table 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, Table 22 "Encorafenib: £1,400.00	The text should be corrected to: "Encorafenib: £[redacted]	PAS prices are used in the base case so these should be shown in this table rather than list	This is an error and the ERG report will be amended

Binimetinib: £2,240.00”	Binimetinib: £[redacted]”	prices. Also, the cost per model cycle in the last column is based on PAS prices so PAS prices per pack should be displayed. **Note:** PAS prices should be marked as CIC; list prices do not need to be marked CIC.	

Issue 23 RDIs for dabrafenib and trametinib switched

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, Table 22 “Dabrafenib: 0.96 Trametinib: 0.92”	The text should be corrected to: “Dabrafenib: 0.92 Trametinib: 0.96”	The RDIs for dabrafenib and trametinib are the wrong way round. Note: they are written correctly on page 84 of the ERG report.	This is an error and the ERG report will be amended

Issue 24 PSA results require update

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 “(increment cost of [redacted] and incremental QALY gain of +0.431)”	The text should be corrected to: “(incremental cost of [redacted] and incremental QALY gain of +0.432)”	The PSA was re-run when the company corrected for the error in RDIs for dabrafenib and trametinib. Therefore, the updated PSA results which were supplied to NICE should be reported.	This is an error and the ERG report will be amended

Issue 25 Inaccuracy on ECOG status

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 88 "As 94% of patients in the COLUMBUS trial had had no previous treatment and, at baseline, ≥70% had an ECOG PS >1 (the remainder had an ECOG of 30%), the treatments can be assumed to be delivered in the first-line setting to patients with a high PS"	The text should be corrected to: "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)."	The clinical evidence for Enco+Bini 450 from the COLUMBUS study is predominantly in the first-line setting for patients with good performance status (ECOG PS 0/1); however, the licence is not restricted to this population and as such the ERG's assumption is incorrect and misleading. This should be corrected as proposed. Factual inaccuracies in ECOG PS status are very misleading and should be corrected.	This is an error and the ERG report will be amended

Issue 26 CIC mark up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99 • Enco+Bini 450 arm: per BIRC 16.6 months; 95% CI: 12.2 to 20.4; range [redacted] month and per investigator assessment [redacted] months; [redacted]; with	All yellow highlighted text requires underlining	Text requires correct AIC mark up as per the company submission.	This is an error and the ERG report will be amended

[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 [redacted] responders ongoing.			

Issue 27 Inaccuracy on event discordance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100 "Further, at data cut-off time 7th November 2017, an "event type" discordance occurred for [redacted] in the Enco	The text should be corrected to: "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)."	Current text is incorrect.	This is an error and the ERG report will be amended

300 arm (see Appendix L.3.2, Table 35 of the CS)."			

Issue 28 Description error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101 "Most subgroups demonstrated [redacted]"	The text should be corrected to: "Most subgroups demonstrated [redacted]"	HRs referred to are for OS not PFS.	This is an error and the ERG report will be amended

Issue 29 Error in the way revisions were applied to company model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102 "In Sheets 'Exec summary' Insert value in cell R9 = P9 Select value in cell K26 = "Do not include RDI In Sheets 'Clinical' Select value in box 'Drop Down 5': 'Assign HR and OR = 1' "	"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' "	Cells R9 and P9 in the exec summary are linked up to the results Page, so they will not have an impact on the overall results. To set the AEs equal, please use the clinical sheet as described in proposed amendment.	This is an error and the ERG report will be amended

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

This report was commissioned by the NIHR HTA Programme as project number 17/109/14

Completed 18th October 2018

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.

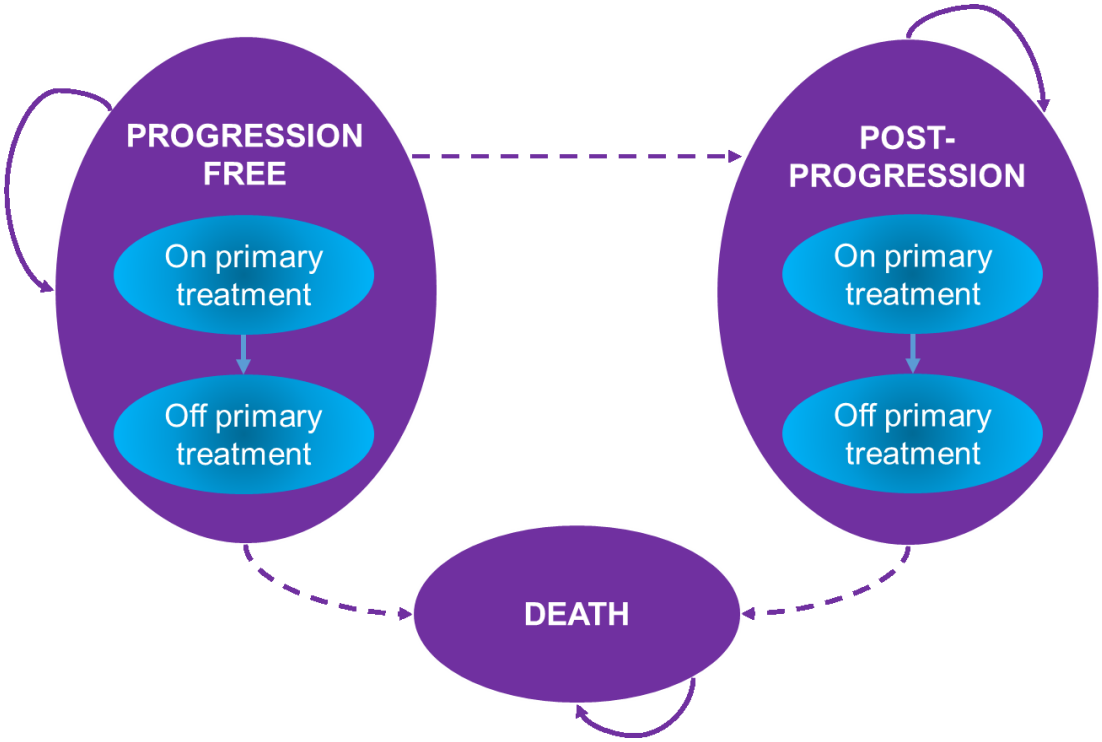

Figure 1 Health state structure of the company model
Source: CS, Figure 17

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.

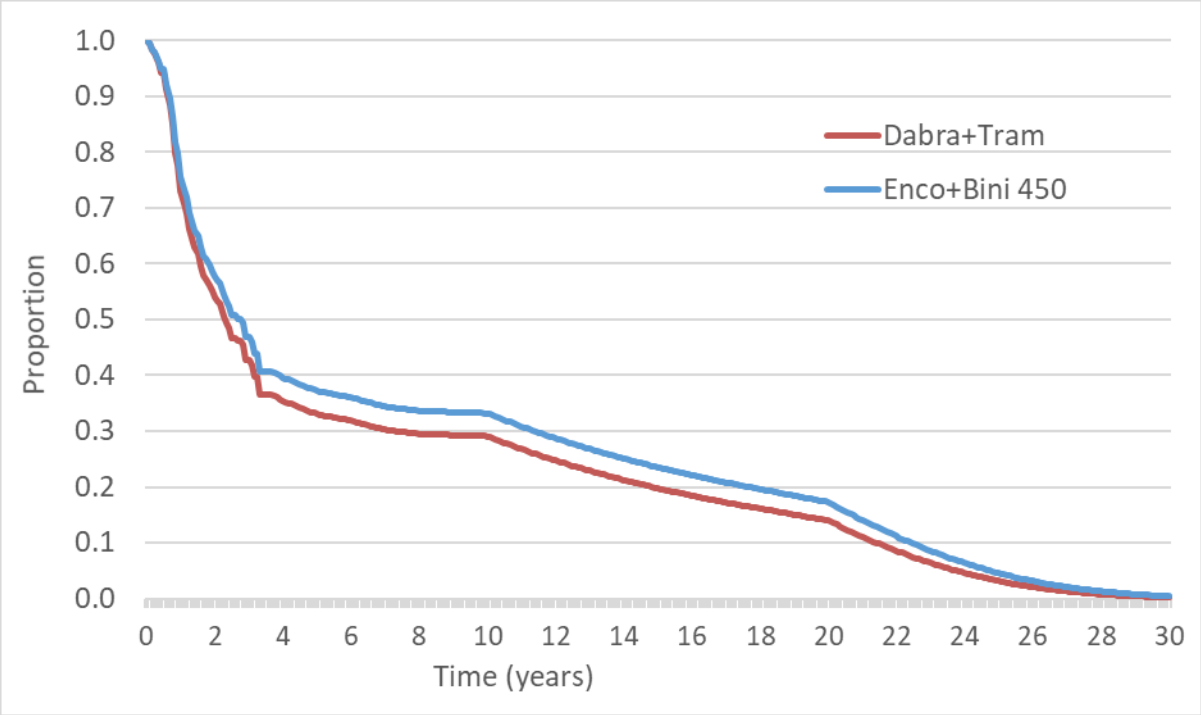

Figure 2 Reconstructed OS K-M curve for the Enco+Bini 450 and Dab+Tram arms used in the company model

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