NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

Contents:

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

Pre-meeting briefing

Dabrafenib in combination with trametinib for adjuvant treatment of resected stage III BRAF V600 positive mutation melanoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Key issues - clinical effectiveness

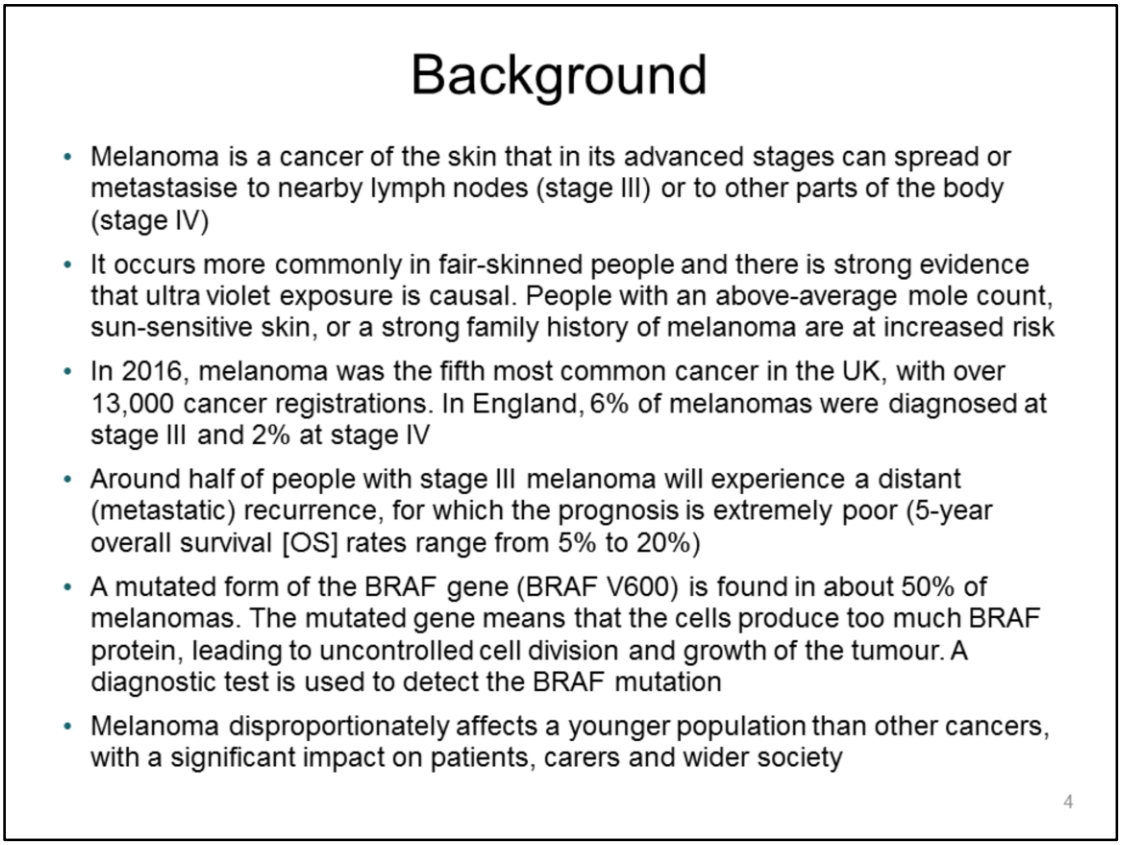
- What are the committee's conclusions on COMBI-AD?
  - quality, risk of bias and generalisability?
- What is the committee's view on the results of the trial using the company's Kaplan-Meir analysis compared with the ERG's alternative competing risk analysis?
- What conclusions can be drawn about relapse free survival and overall survival given the immaturity of the data?
- A key uncertainty is whether treatment with dabrafenib and trametenib mainly postpones disease recurrence or permanently cures the disease. What is the committee's view on this?
- The American Joint Committee on Cancer (AJCC) 8th edition has redefined stage III groupings and included an additional stage IIID subgroup. Does the committee consider this will affect the generalisability of COMBI-AD to clinical practice in England in the future?

2

Key issues - cost effectiveness

- Is it appropriate to use data from a study comparing adjuvant ipilimumab to placebo to model long-term RFS after the observed period of COMBI-AD instead of extrapolation using parameterised curves from COMBI-AD?
  - are results from a population with unknown BRAF status generalisable to a BRAF positive population?
- What is the committee's view on the choice of RFS curves?:
  - company's log logistic (U) cure base case model, which suggests that treatment will permanently cure a larger proportion of patients
  - company's log logistic (R) cure model, suggesting that treatment postpones recurrence
  - ERG's flexible parametric fit and competing risks models also suggest that treatment postpones recurrence - should competing risks be considered?
- Is it appropriate that outcomes after a distant recurrence (DR) were applied as one-off costs and QALYs at the point of entry into the DR health state, making overall survival disconnected from the model outcomes?
- What are the committee's conclusions on possible underestimation of costs associated with adverse events and monitoring?
- Is the technology innovative?

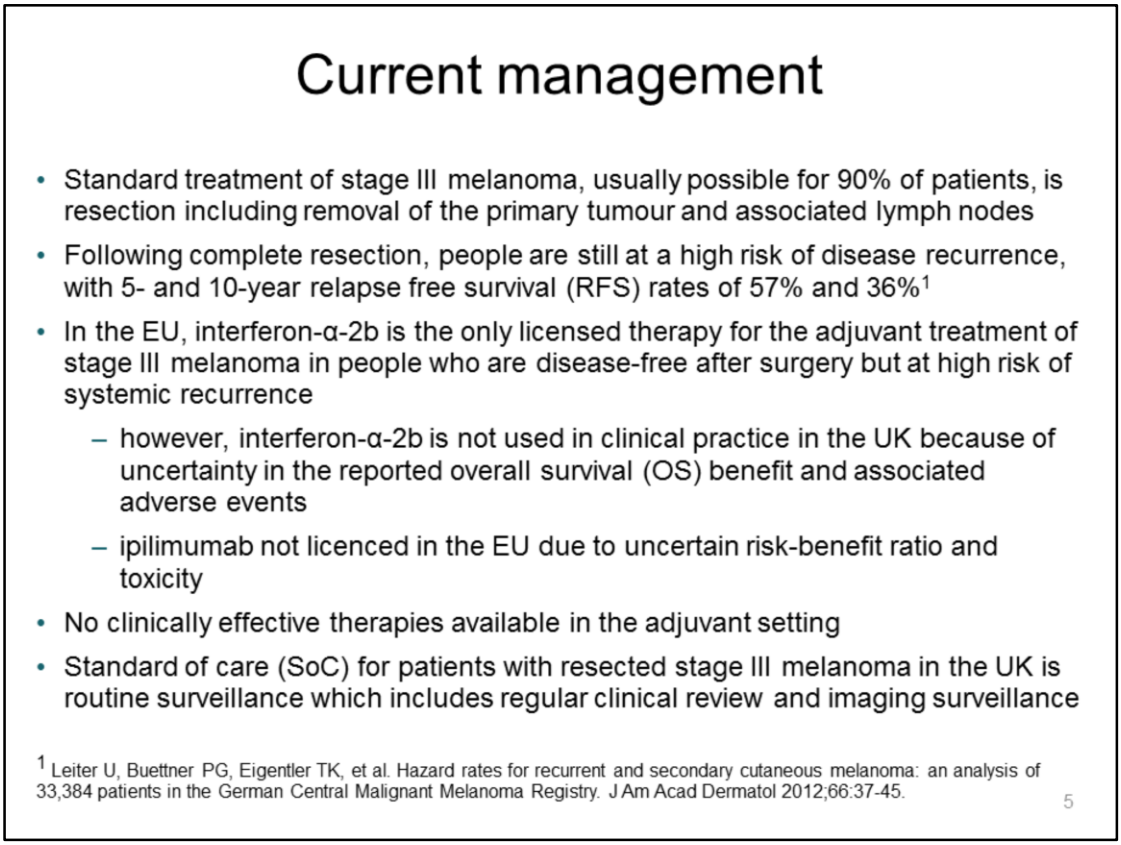
3



Please see pages 15-21 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.



Please see pages 21-24 of the company submission for more information.

Clinical guidelines from British Association of Dermatologists (BAD) do not recommend the use of adjuvant interferon-α-2b. This is because its effect on disease free survival is of uncertain clinical relevance and although a meta-analysis of interferon studies showed a significant improvement in OS, the effect was small and associated with significant drug toxicity. In addition, patients with stage IIIA melanoma should be seen 3-monthly for 3 years, then 6-monthly to 5 years (stage IIIA–IIIC), then annually to 10 years (stage IIIB–IIIC).

The European Society Medical Oncology (ESMO) clinical practice guidelines (2015) state that there is no consensus on the optimal schedule of frequency of follow-up visits, or on the utility of imaging and blood tests for patients with resected melanoma.

NICE clinical guidelines for the management of melanoma (NG14, 2015) recommends clinical follow-up with imaging for people with stage III disease following complete resection, at a schedule of every 3 months for the first 3 years post resection, then every 6 months for the next 2 years, and discharge at the end of 5 years. It states that adjuvant radiotherapy should not be offered in stage IIIA melanoma and should only offered in stage IIIB or IIIC melanoma, if a reduction in the risk of local recurrence outweighs the risk of

significant adverse events.

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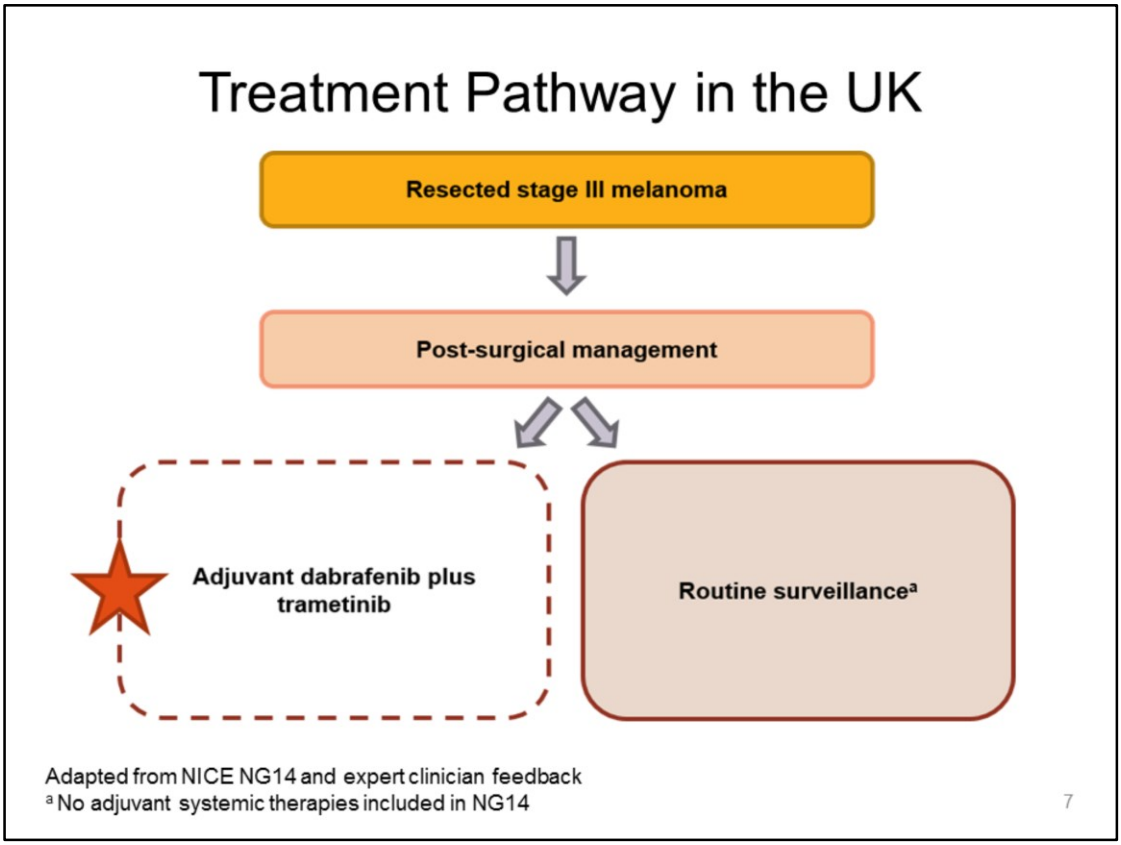
Details of the technologies

	Dabrafenib (Tafinlar; Novartis)	Trametinib (Mekinist; Novartis)
Anticipated MA	[redacted]	
Mechanism of action	Selective inhibitor of BRAF V600 kinase activity and blocks the activity of mutant protein 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,150 mg (two 75 mg capsules) twice daily	2 mg (one tablet) once daily
Duration of treatment	12 months or less if there is disease recurrence or unacceptable toxicity	12 months or less if there is disease recurrence or unacceptable toxicity
Cost	List price for 28 capsules of dabrafenib 75 mg: £1,400	List price for 30 tablets of trametinib 2 mg: £4,800
	Patient access schemes agreed for each technology involving a single confidential discount applied to the list price of dabrafenib and trametinib	
Avg cost of course of treatment	Based on average number of packs in COMBI-AD: List price: £[redacted] PAS price: £[redacted]	
Other licensed indications	Licensed as monotherapies or in combination for treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation. Recommended in NICE TA 396 (combination) and TA321 (Dabrafenib)	

Please see pages 11-14 of the company submission for more information.

Concurrent inhibition of the MAPK pathway by dabrafenib plus trametinib has demonstrated efficacy in the metastatic setting and in 2016, dabrafenib plus trametinib was licensed and approved by NICE for the treatment of unresectable or metastatic melanoma in adults with a BRAF V600 mutation (TA396). In addition, dabrafenib monotherapy has been recommended by NICE for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321)

In order to initiate treatment with dabrafenib in combination with trametinib, 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 dabrafenib plus trametinib, 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.



Source: Figure 4 (page 23) of the company submission.

Concurrent inhibition of the MAPK pathway with dabrafenib plus trametinib represents a targeted approach to mitigate the risk of disease recurrence in patients with a BRAF V600 mutation.

The company estimates that in 2018, the number of patients eligible for treatment with dabrafenib and trametinib in the proposed adjuvant indication will be 427.

Decision problem

	NICE scope	Company submission
Population	People with completely resected, stage III melanoma with BRAF V600 positive mutations	Adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection
Intervention	Dabrafenib plus trametinib	Dabrafenib plus trametinib
Comparator	Routine surveillance	Routine surveillance
Outcomes	Overall survival Relapse-free survival Distant metastases free survival Adverse effects of treatment Health-related quality of life	Relapse-free survival Overall survival Distant metastases free survival Freedom from relapse Adverse effects of treatment Health-related quality of life

8

Source: Table 1 (page 9) of the company submission.

Clinical expert comments

- Aim of the new treatment is to reduce the risk of people diagnosed with primary melanoma developing metastatic disease, thereby improving overall survival
- No adjuvant treatment currently available. Standard of care is observation with additional scanning for patients at high risk of developing metastases – there is a major unmet need
- Adjuvant treatment with dabrafenib and trametinib will require additional resource use in the form of more staff, outpatient visits and investigations with subsequent effects on additional appointments, blood tests and imaging
- Treatments are generally well tolerated and side effects are manageable with quality of life maintained
- A clinically significant treatment response would be a reduction in the risk of relapse or death by more than 10%
- Expectation that significant numbers of patients will be cured with adjuvant treatment

9

Patient perspective

- No patient expert comments received

10


Clinical effectiveness
11

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Company's clinical evidence: COMBI-AD

Design	Randomised, double-blind, placebo-controlled, phase III
Population (n= 870)	Adults with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high risk (defined as stage IIIA [lymph node metastasis >1 mm], IIIB or IIIC) cutaneous melanoma; patients with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were also eligible
Intervention	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily for 12 months **(n=438)**
Comparator	Two matched placebos for 12 months **(n=432)**
Location	169 international study sites in 26 countries from Europe (including 13 sites in the UK), North and South America, Asia and Oceania. This included 86 patients from the UK: [redacted]
Primary endpoint	Relapse free survival (RFS) - investigator assessed
Key secondary endpoints	• Overall survival (OS) • Distant metastasis free survival (DMFS), • Freedom from relapse (FFR) • Safety
Duration of study and follow-up	Treatment period 12 months. Discontinuation could occur earlier due to disease recurrence, death, unacceptable toxicity or withdrawal of consent. Median follow-up time was [redacted] in the dabrafenib plus trametinib arm and [redacted] in the placebo arm at data cut-off for the primary analysis (30th June 2017) 12

Please see pages 26-34 of the company submission for more information.

Patients with resected BRAF V600 positive, stage III melanoma were screened for eligibility for inclusion within the trial and staging was completed as per the seventh edition (2009) of the American Joint Commission on Cancer (AJCC) staging system which was the most recent available at the time of the trial. An eighth edition of the AJCC was released in January 2018 and UK clinical practice is currently in the process of adopting this. The minor difference between the two is a shift in the distribution of patients categorised with stage II melanoma to stage III melanoma. This change means more patients will be categorised as stage IIIC and in addition there is a new pathologic sub-stage (stage IIID) representing patients with poorer outcomes.

RFS was defined as the time from randomisation to disease recurrence or death from any cause, assessed by clinical examination and imaging by means of computed tomography (CT), magnetic resonance imaging (MRI), or both. Company state that RFS is a direct measurement of anti-tumour effect because it will not be subject to confounding from subsequent therapy (as OS may). Since relapses are associated with disease- and treatment-related morbidity, RFS is a true measure of patient benefit. Health related quality of life was an exploratory outcome.

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Baseline characteristics in COMBI-AD

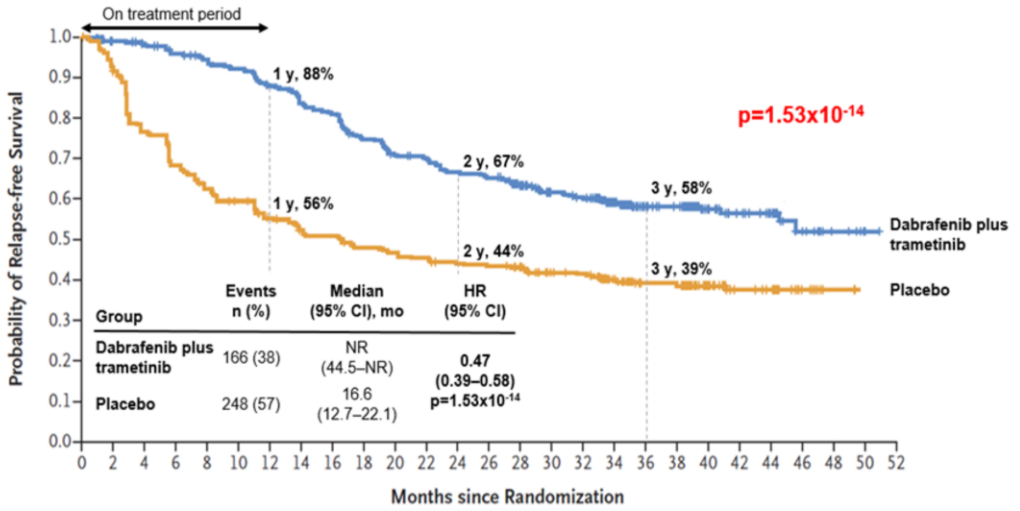
Characteristic	Dabrafenib plus trametinib (N=438)	Placebo(N=432)
Demographics		
Age, median years (range)	50 (18–89)	51 (20–85)
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Disease characteristics		
BRAF mutation status, n (%)		
V600E	397 (91)	395 (91)
V600K	41 (9)	37 (9)
Disease stage, n (%)		
IIIA	83 (19)	71 (16)
IIIB	169 (39)	187 (43)
IIIC	181 (41)	166 (38)
III unspecified	5 (1)	8 (2)
Prior therapy		
Sentinel lymphadenectomy, n (%)	[redacted]	[redacted]
Lymph node dissection, n	[redacted]	[redacted]
Median number of lymph node removed	[redacted]	[redacted]
Median time from initial diagnosis (months)	[redacted]	[redacted]

13

Source: Table 9 (page 28-32) of the company submission for more information.

Demographic characteristics (such as age, sex, race) were well balanced between treatment arms. Mean age was 50.5 years. Disease characteristics (such as BRAF mutation status, performance status and disease stage) were also well balanced. In addition, prognostic indicators for melanoma such as number of nodal metastases, primary tumour ulceration and micrometastasis versus macrometastasis were also roughly similar for the two treatment groups.

Primary efficacy results: investigator assessed RFS (ITT population)



No. at Risk

Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reached; RFS: relapse-free survival. 14

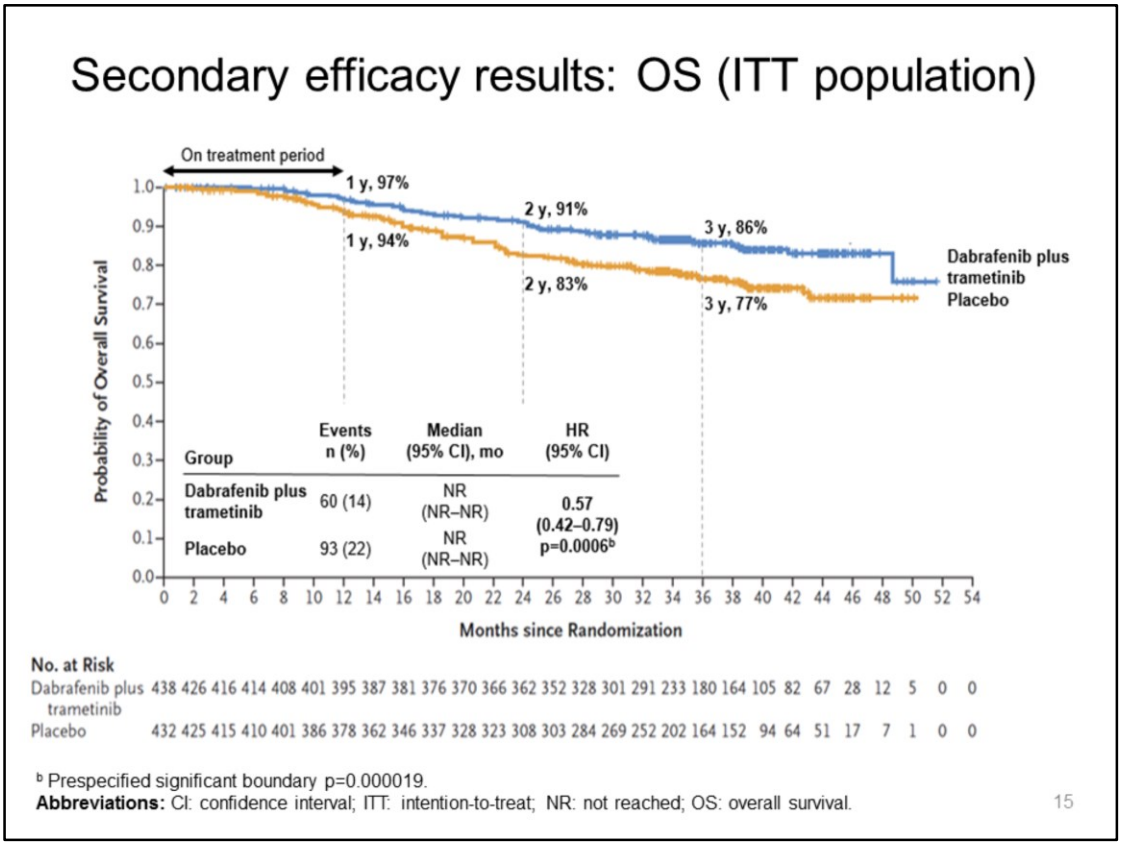
Source: Figure 6 (page 37) of company submission reporting investigator-assessed RFS in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population). Please see pages 34-37 for more information.

RFS events were defined as:

- Occurrence of loco-regional or distant metastases,
- Identification of a new primary melanoma,
- Occurrence of death without prior documentation of tumour recurrence (and not censored in the statistical analysis)

RFS events (disease recurrence or death) had occurred in 166 (38%) of 438 patients in the dabrafenib plus trametinib arm and in 248 (57%) of 432 patients in the placebo arm.

- RFS analysis only included the first recurrence event and as such, if a patient experienced a loco-regional recurrence first followed by a distant recurrence at a later time point, only the former one was counted as an event.
- At the time of first recurrence, 54 patients (12%) in the dabrafenib plus trametinib arm had experienced loco-regional recurrence, 7 (2%) had both local and distant recurrence and 96 (22%) had a distant recurrence, as compared with 107 (25%), 7 (2%) and 126 (29%), respectively, in the placebo group



Source: Figure 7 (page 39) of company submission reporting OS in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population). Please see pages 37-39 for more information.

The estimated HR for OS was 0.57 (95% CI: 0.42–0.79; p=0.0006). Despite this low p-value, the between-arm difference was not statistically significant because it did not cross the pre-specified conservative interim boundary of p=0.000019. The company states that this result nonetheless still shows a clinically meaningful improvement in OS.

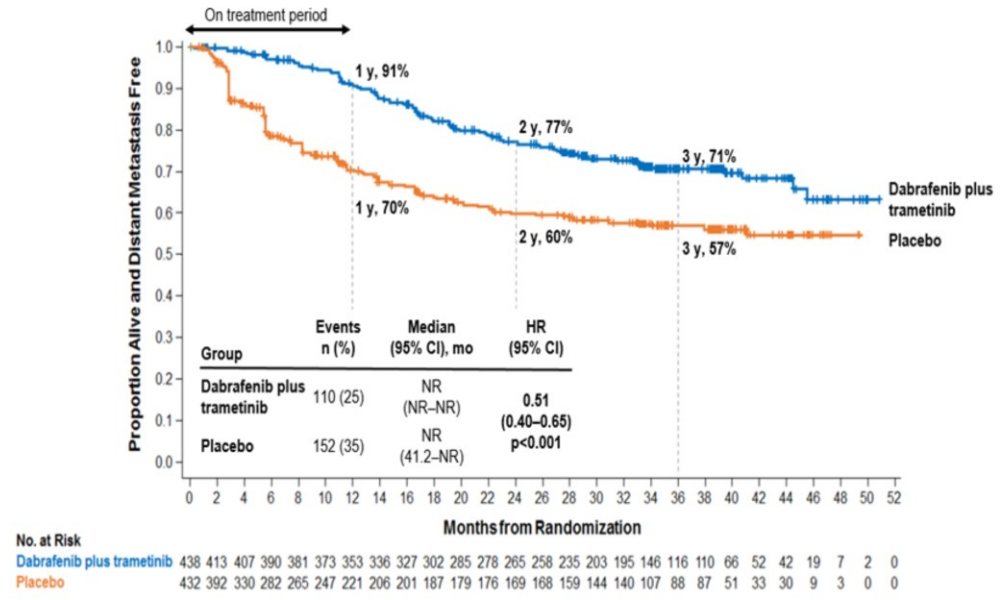
At the time of the data cut-off, 153 deaths had occurred; 60 (14%) in the dabrafenib plus trametinib arm and 93 (22%) in the placebo arm, representing 26% of the total targeted 597 deaths required for the final OS analysis. The most common cause of death was melanoma, which occurred in 54 patients (12%) in the dabrafenib plus trametinib arm and 77 patients (18%) in the placebo arm. For all other deaths, 6 in the dabrafenib plus trametinib arm and 16 in the placebo arm, the cause of death was listed as “other”, which includes pneumonia, haemorrhage, trauma, suicide, other cancer and heart failure, or unknown

331 (76%) patients in the dabrafenib plus trametinib arm and 277 (64%) patients in the

placebo arm were censored and are still being followed for OS events. Censoring was performed using the date of the last known contact for those who were alive at the time of analysis. Follow-up for the remaining 47 patients (11%) and 62 patients (14%) in the dabrafenib plus trametinib arm and placebo arms, respectively, has ended.

TheOS curve remains consistently higher for the dabrafenib plus trametinib treatment arm relative to placebo at all subsequent time points, thereby indicating a sustained OS advantage with dabrafenib plus trametinib versus placebo

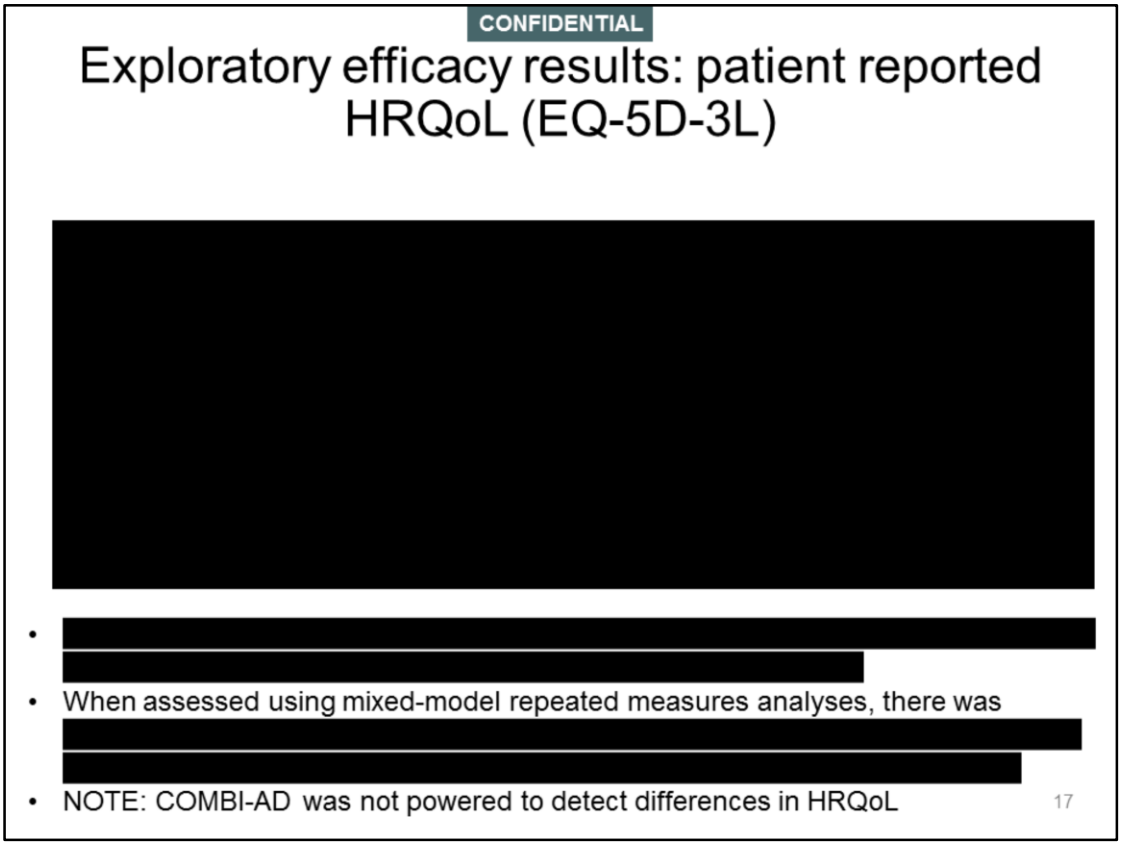
Secondary efficacy results: distant metastasis-free survival (ITT population)



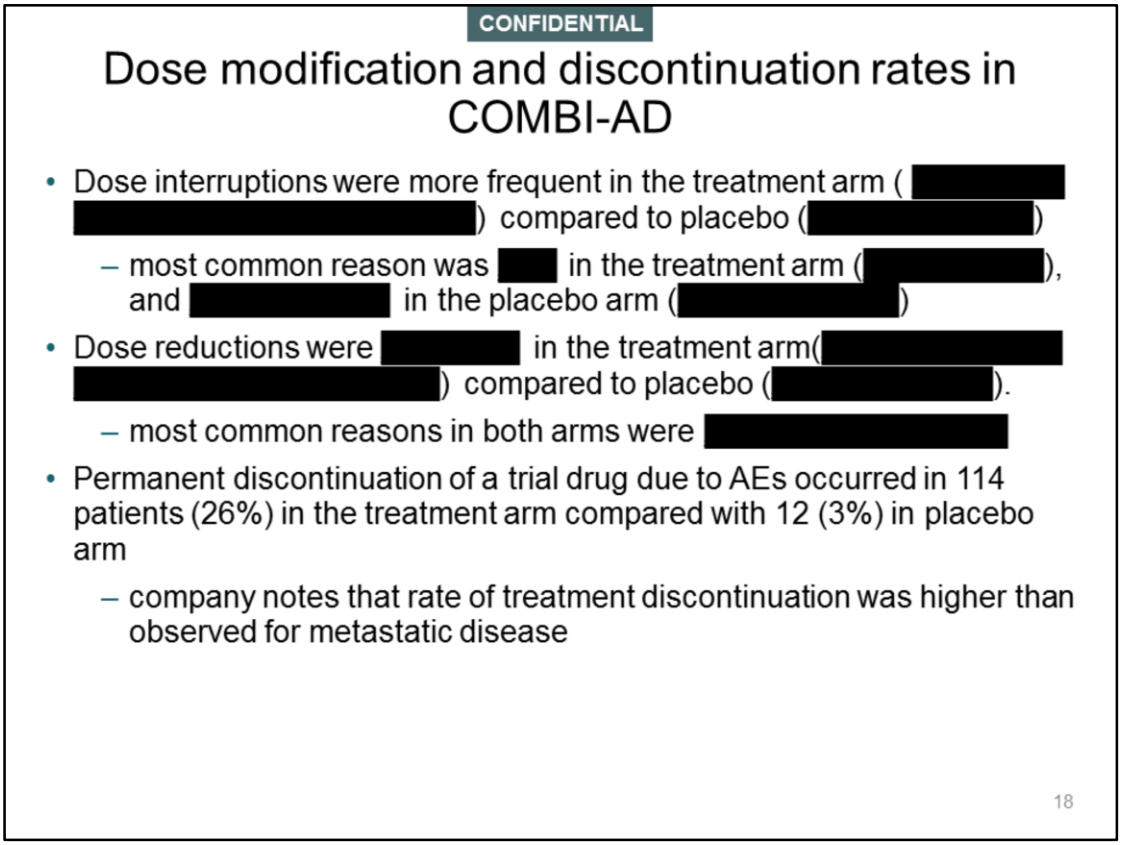
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat.

16

Source: Figure 8 (page 40) of company submission reporting distant metastasis-free survival (DMFS) in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population). Please see pages 39-41 for more information.



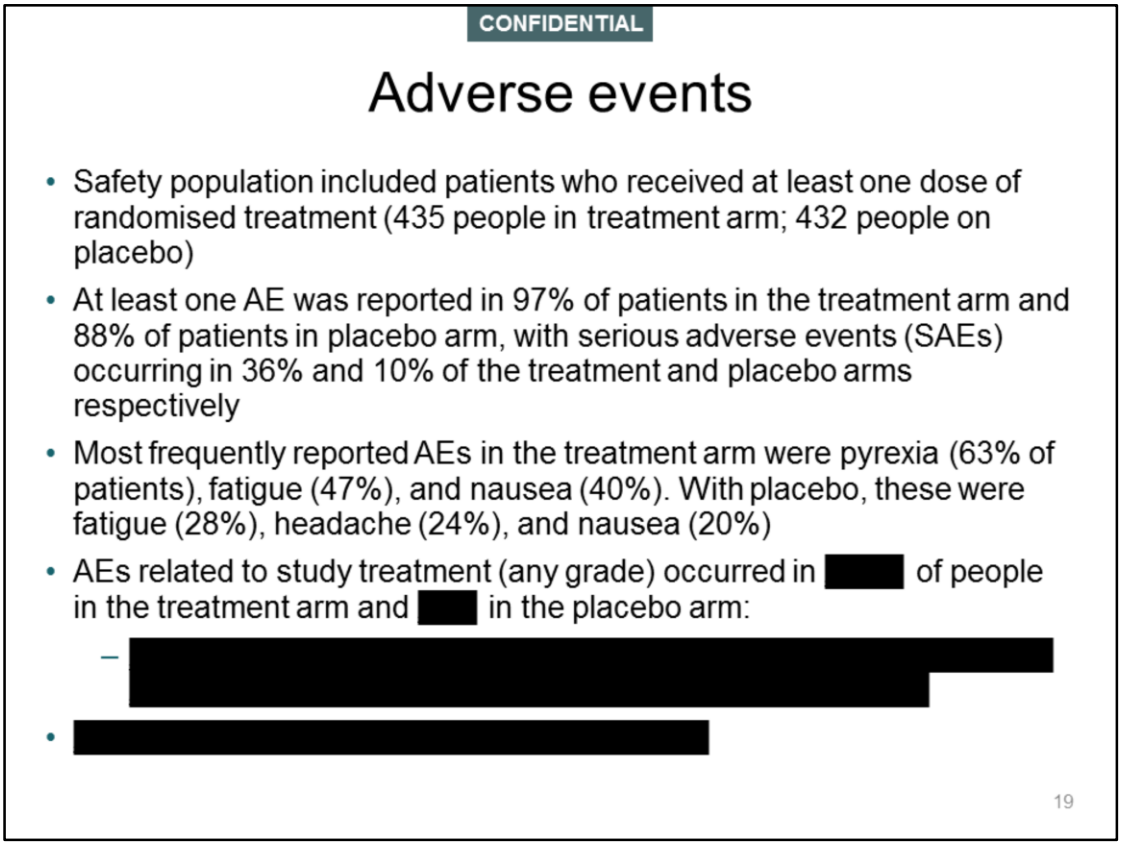
Source: Figure 10 (page 43) of the company submission. See pages 42-43 for more information and Table 16 for a summary of EQ-5D-3L utility scores in COMBI-AD as of the latest data cut-off.



Please see pages 48-51 of the company submission for more information and Table 19 for a summary of treatment duration and dose interruptions in COMBI-AD as of latest data cut-off for the primary analysis.

At the time of cut-off of COMBI-AD, 272 patients (63%) had completed all scheduled doses of dabrafenib and 163 patients (37%) had discontinued treatment with dabrafenib. Out of the 163 patients who discontinued, 108 were due to AEs, 23 due to disease recurrence and 32 for other reasons.

Similarly, 277 patients (64%) had completed all scheduled doses with trametinib and 158 patients (36%) had discontinued treatment, due to AEs (n=104), disease recurrence (n=23) or other reasons (n=31). In the placebo arm, 227 patients (53%) completed treatment and 205 (47%) discontinued, due to AEs (n=12), disease recurrence (n=175) or other reasons (n=18)



Please see pages 52-56 of the company submission for more information and tables 21-24 for a full breakdown of the AEs reported in COMBI-AD.

ERG's comments on clinical evidence

- COMBI-AD was well conducted, quality is reasonable, and baseline demographic characteristics of patients are comparable to patients in the UK, however:
  - potential bias from imbalance between study arms in numbers and timing of patients ending follow-up before study cut-off may influence outcomes, especially those involving time to event analysis
  - higher rate in placebo arm of deaths from non-melanoma or unknown causes may be suggestive of poorer health at baseline or differences in post recurrence treatments
  - some outcomes were investigator-assessed when they could have been assigned to an Independent Review Committee masked to treatment assignments
  - imaging to detect recurrence was only performed every 3 months during the first 24 months and every 6 months thereafter. Accuracy of RFS may be limited due to this
- Data is immature for both RFS and OS:
  - a major uncertainty is whether dabrafenib and trametinib delays disease recurrence, so that recurrence incidence in the intervention arm eventually catches up with that in the control arm, or whether treatment leads to a proportion of patients being "cured"
  - pattern of recurrence is not well served by the composite outcome (RFS) used in most adjuvant trials

20

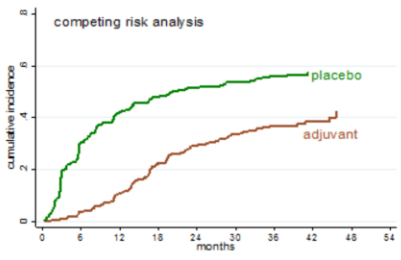
Please see pages 29-40 and 64-65 of the ERG report for more information.

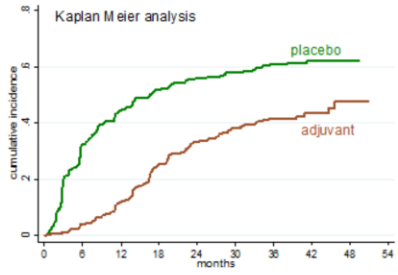
The ERG interpret "cure from recurrence" to mean a permanent delay in recurrence. Adjuvant treatment may have no effect on recurrence, it may only temporarily delay it, it may temporarily delay it in some patients and permanently delay in others (i.e. cure), or it may only cure in selected patients.

ERG's competing risk analysis

- ERG conducted a competing risk (CR) analysis because of CR events that preclude the occurrence of death/recurrence (differences between arms in premature end to follow-up and new primary melanomas)
- ERG's analysis indicates that:
  - RFS estimated by the company's KM analysis is overestimated by approximately 11%
  - OS is overestimated by approximately 21%

ERG's competing risk analysis - RFS





21

Please see pages 43-47 and 54-56 of the ERG report for more information

Competing risk analysis offers an alternative approach sometimes used in circumstances where multiple outcomes are recorded (as in COMBI-AD), and offers an alternative estimate of the incidence of an event of particular interest to that of a KM analysis.

Restricted mean survival was estimated to 41 months for RFS and 42 months for OS since this was the longest follow up common across analyses and arms.

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ERG comments on adverse events

- Concern that, in [redacted] patients in the placebo arm who had serious side effects, these were related to study treatment
  - ERG had serious reservations about the safety, chemical composition and pharmacodynamics of the placebo substance
  - remaining patients in the placebo arm were assumed to have experienced a SAE due to underlying disease morbidities
  - therefore, difficult to decipher whether AEs in the intervention arm were also due to progression of the underlying disease/patient comorbidities, or the treatment itself
- Concern that side effects which may potentially be responsible for malabsorption of drugs, such as diarrhoea, reported in 115 patients in the treatment arm, may preclude compliance and efficacy of treatment
- Costs for some AEs may be underestimated as they are difficult to predict in a non-trial setting (costs discussed further under cost effectiveness)

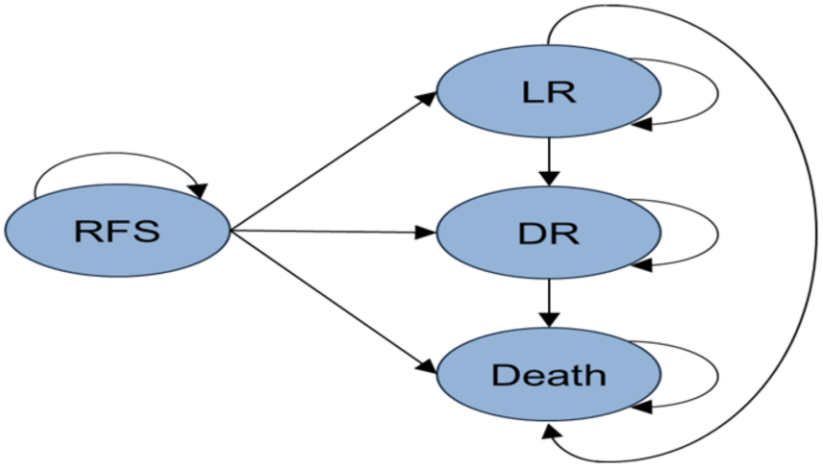
22

Please see pages 51-53 of the ERG report for more information

Cost effectiveness

23

Company's 4 state-transition model



Factor	Chosen values
Time horizon	50 years (lifetime assumed)
Perspective	NHS and PSS
Discount rate	3.5% per year
Cycle length	One month

Abbreviations: DR: distant recurrence; LR: loco-regional recurrence; RFS: relapse-free survival.

24

Source: Figure 12, page 63 of the company submission

The partitioned-survival model approach commonly seen in appraisals of oncology interventions was not considered appropriate by the company given the difficulty in (a) extrapolating OS with a low number of events (despite evidence of a survival advantage in the COMBI-AD) and (b) appropriately assigning costs and utility values (for different events such as LR and DR) when transitions are not modelled explicitly.

The economic model includes two death states: one for death due to melanoma, and another for death due to other causes but has been represented as one state for simplicity in the diagram.

Company model details

- Patients in RFS health state either remain in this state or develop loco-regional recurrence (LR), distant recurrence (DR) or die from melanoma/other causes
  - divided into on an off treatment phases to reflect the treatment duration, drug acquisition costs and differences in HRQoL
- After treatment patients undergo same schedule of routine surveillance as placebo arm
- Patients in LR health state either remain in this state until death with a small reduction in QoL, develop a DR or a new LR, or die from melanoma/other causes
- Patients in the DR health state remain until death and have a mix of treatments for metastatic disease in line with UK clinical practice
- Model is segmented into 2 periods: 1st 50 months, corresponding to the maximum follow-up in COMBI-AD, and the period subsequent to this
  - curves fitted to the model and the splitting of events into LR, DR and deaths differ in the 2 segments

25

Please see pages 62-68 of the company submission for more information.

Clinical inputs to company model

Efficacy and clinical data inputs used in the model derived from COMBI-AD:

- Patient baseline characteristics
- Probability of RFS during the observed trial period and the proportion of LR, DR and death events in RFS
- Probability of recurrence (LR or DR) or death following a LR
- Cumulative dose for drug costs
- Health related quality of life (EQ-5D-3L)
- Incidence of adverse events

Clinical data from other sources:

- Proportion of LR, DR and death events following a LR during observed period of COMBI-AD: from study by White et al. (2002) of 2,505 melanoma patients with regional lymph node metastasis
- Probability of RFS and the proportion of LR, DR and death events in RFS after the observed trial period: estimated from EORTC 18071 of adjuvant ipilimumab
- Time to death following a distant metastasis: from previous NICE appraisals in the first-line treatment of metastatic disease
- General population mortality in England by single year of age from Office for National Statistics

26

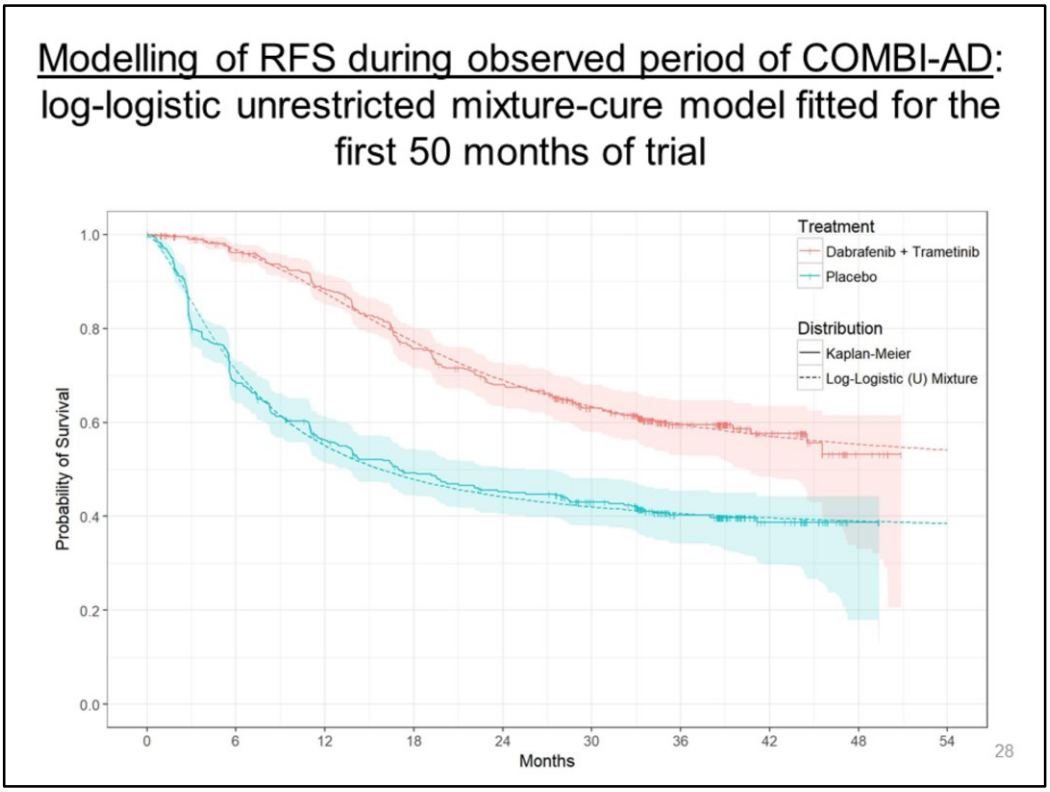
Please see pages 68-70 of the company submission for more information.

Company's modelling up to first 50 months

- A parametric function was fitted for the first 50 months of the trial to reflect the last censoring point
- The following parametric functions were considered for extrapolation: exponential, Weibull, Gompertz, lognormal, log-logistic, gamma, generalised-F and restricted cubic spline
  - non-mixture cure and mixture cure versions of these models were also explored
- Company considered that the log-logistic unrestricted mixture model provided the best visual fit to both treatment arms throughout the trial follow-up and also provided a good statistical fit in terms of AIC and BIC
- Company's clinical experts also considered that the log-logistic unrestricted mixture-cure model was an accurate prediction of the RFS observed in the trial

27

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



Source: Figure 15 (page 75 of the company submission).

Individual patient-level data (IPD) based on a median follow-up of 2.8 years from COMBI-AD was used to estimate RFS during the trial period. A parametric function was fitted for the first 50 months of the trial to reflect the last censoring point (51 months in adjuvant dabrafenib plus trametinib arm and 50 months in the placebo arm). The following parametric functions were considered for extrapolation: exponential, Weibull, Gompertz, lognormal, log-logistic, gamma, generalised-F and restricted cubic spline (RCS). Non-mixture cure and mixture cure versions of these models were also explored.

Based on the AIC and BIC, the generalised-F provided the best (statistical) fit to the data for both arms, followed by the generalised gamma unrestricted mixture, log-logistic unrestricted mixture and lognormal restricted mixture. However, the generalised-F models did not provide a good visual fit at the beginning of the curve. The company considered that the log-logistic unrestricted mixture model provided the best visual fit to both treatment arms throughout the trial follow-up and also provided a good statistical fit in terms of AIC and BIC.

The company noted that clinical experts also considered that the log-logistic unrestricted

mixture-cure model was a more accurate prediction of the RFS observed in the trial.

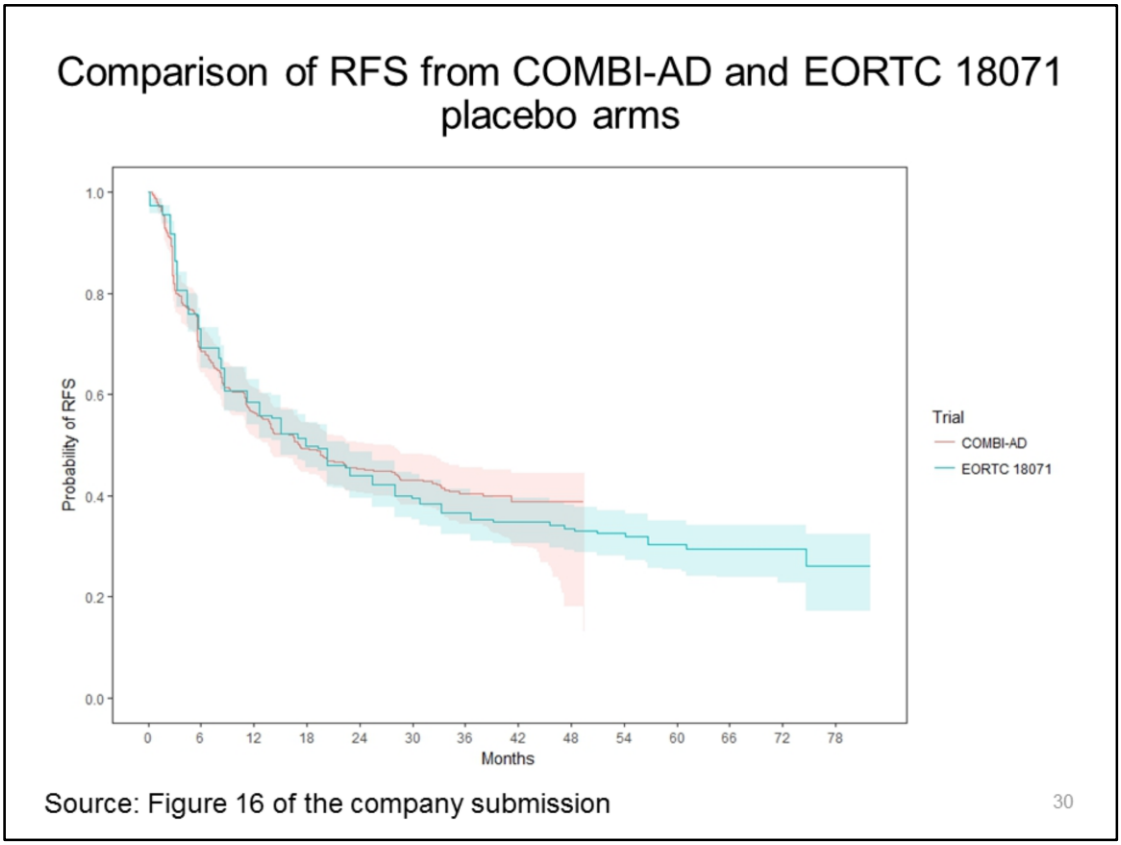
A parametric function was used in the base case instead of the non-parametric direct KM curve to (a) facilitate the probabilistic sensitivity analysis and (b) because the use of parametric functions is less influenced by events at the tail of the distribution.

Company's extrapolation of the short term observed RFS in COMBI-AD beyond 50 months

- Company extrapolated the results from COMBI-AD beyond 50 months using the placebo arm of the international EORTC 18071 trial that compared adjuvant ipilimumab with placebo in people with completely resected stage III melanoma (n=951)
- Company reported that its clinical experts considered the baseline characteristics of the patient population to be generally similar to that of the COMBI-AD trial:
  - although data on BRAF status was not reported in the EORTC 18071 trial, the exact prognostic role of BRAF V600 mutations in melanoma remains uncertain
  - data on the efficacy of immunotherapies in the metastatic setting have provided little evidence of a difference in outcomes for BRAF positive and BRAF wild-type patients
- In the absence of evidence of a difference, company assumed that outcomes in EORTC 18071 would be similar irrespective of BRAF status
- Company reports that this assumption is supported by comparison of RFS from the EORTC 18071 and COMBI-AD placebo arms

29

Please see pages 75-82 of the company submission for more information.



Source: Figure 16 (page 76) of the company submission

The company reports that the Kaplan-Meier curves were relatively similar up to month 24–30, after which a large number of patients were censored in COMBI-AD. Despite the visual separation after month 24–30, the confidence intervals overlap, indicating that the separation may be attributable to the number of patients at risk and censoring in the COMBI-AD trial.

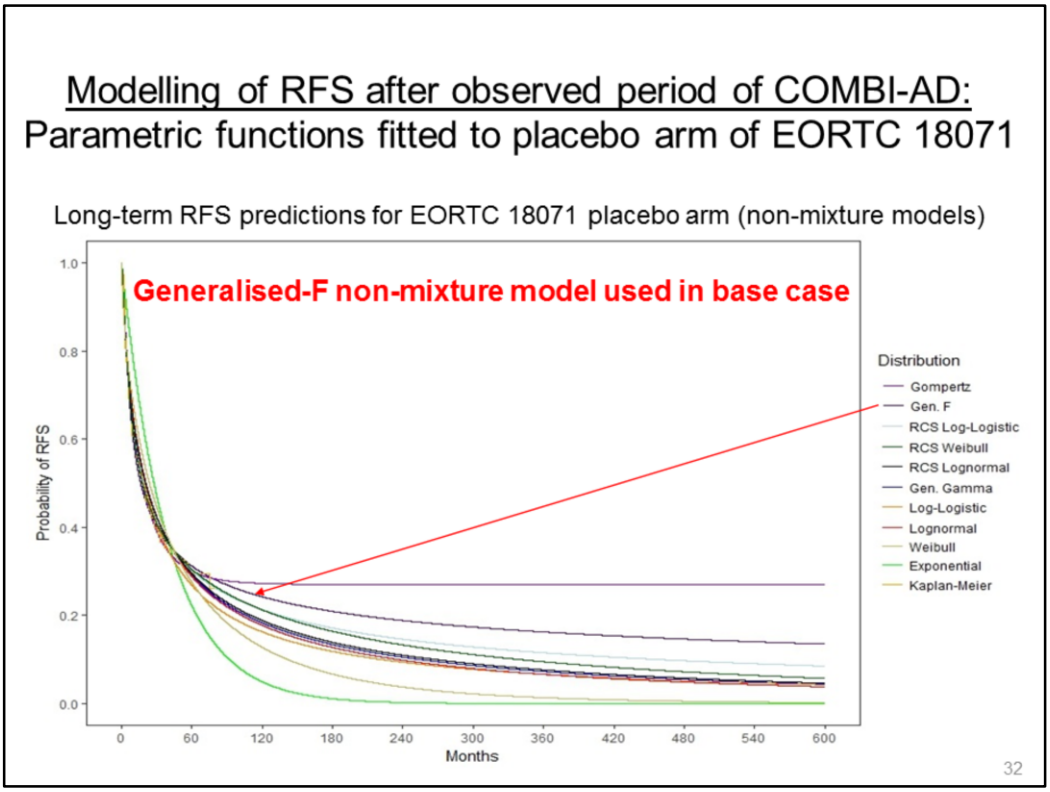
Data for RFS from the placebo arm of the EORTC 18071 trial were available for up to 7 years.

ERG comments on company's extrapolation of the short term observed RFS in COMBI-AD using EORTC 18071

- Assumption of equivalence between a trial with a mixed BRAF population and one with an exclusively BRAF+ population is open to question - seems odd to justify an assumption of equivalence on the basis of no evidence
- Company itself reports that BRAF V600 mutations drive disease progression
- No exploration of other sources such as AVAST-M (trial of adjuvant bevacizumab in patients with stage IIB, IIC and III melanoma)
  - extrapolation using AVAST-M is more likely to be generalisable to clinical practice in England as it is a larger (n=1347) and longer trial (8 years) that was conducted in UK patients; control arm received "observation" and would likely reflect the current UK alternative to a licenced adjuvant treatment
  - ERG reconstructed the KM for disease free survival in AVAST-M and reported that the experience of control participants in AVAST-M and EO-18071 differs, hence the choice of external data source will influence extrapolation
- However, ERG sees more merit in using parameterised curves derived from COMBI-AD for extrapolation (discussed further under cost effectiveness)

31

Please see pages 57-64 of the ERG report for more information



Source: Figure 20 (page 80 of the company submission). Please see page 75-82 for more information.

In the absence of long term data from COMBI-AD, the company used data from EORTC 18071: a phase III RCT comparing adjuvant ipilimumab to placebo in patients with completely resected stage III melanoma. Data for RFS from the placebo arm of the EORTC 18071 were available for up to 7 years, providing median follow-up of 5.3 years compared to 2.8 year median follow up in COMBI-AD trial.

To estimate hazard of recurrence over time, the company fitted parametric functions to the placebo arm of the EORTC 18071 RFS data from randomisation until the end of the observed period. The estimated hazard was then applied to the COMBI-AD RFS data (to both the placebo and treatment arms) from the end of the observed period in the COMBI-AD (approximately 50 months).

- The company considered this approach reasonable in the absence of evidence suggesting the hazard could be different between the two treatment arms after the observed period in the trial. They also noted that clinical experts did not believe that the hazard of recurrence in people who received adjuvant treatment would be greater than that observed in the placebo arm as literature suggests that people with stage III disease

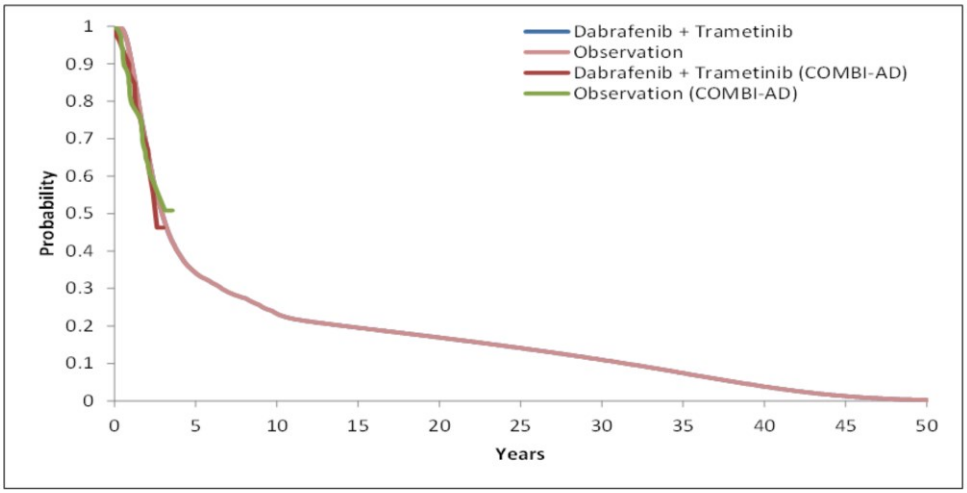
that don't receive adjuvant treatment have a very high risk of recurrence for the first three years, with risk of recurrence reducing significantly thereafter. Therefore, the hazard of recurrence reduces naturally with time.

The company fitted parametric functions to RFS from the placebo arm of the EORTC 18071, separating the distributions into two broad families (a) mixture-cure models and (b) non-mixture models. Although the generalised-F was considered the best fit statistically using the BIC and was also a good fit visually, the company noted that clinical experts considered the most clinically plausible curve for the EORTC 18071 placebo data in the non-mixture model family was likely to be in between the Gompertz and generalised-F distributions. Within the mixture models, the clinical experts considered that the generalised-F distribution provided a lower bound estimate for long-term RFS, with the remaining mixture models considered to be more plausible.

As a conservative measure, the base case for long term extrapolation of the COMBI-AD trial used the hazard for recurrence from the generalised-F **non-mixture** model from the end of the COMBI-AD trial (approximately 50 months) out to the lifetime of the model. The base case analysis also incorporated age-specific mortality data from UK specific life tables to account for the increased risk of dying due to older age.

Transition from LR health state: post-LR survival data from COMBI-AD used to approximate transitions by calibrating a HR to RFS so that OS post-LR predicted by model matched data observed in COMBI-AD

Calibrated post LR OS vs observed post-LR OS



Source: Figure 24 (page 86 of the company submission). Please see pages 85-86 for more information.

Since follow-up for disease recurrence in COMBI-AD only continued until the first recurrence (and thereafter, patients were followed for survival), transitions from the LR health state to the DR health state or subsequent LR were not directly available from COMBI-AD. Due to limited data on the risk of subsequent LR or DR following a previous LR in a population similar to the COMBI-AD trial, the company considered survival to follow the same distribution as RFS (i.e. high hazard initially which decreases with time). This assumption was supported by a study looking at recurrence in early stage melanoma (Salama et. al) showing that the hazard of recurrence following a previous LR was higher compared with the hazard of recurrence in patients without a previous LR up to month 40, after which the hazard was broadly similar.

Therefore, the placebo arm of the RFS curve was adjusted by a HR that yielded a model prediction for post-LR OS similar to that observed in the COMBI-AD trial. The HR was only applied to the RFS curve during the observed period (up to month 50), after which the hazard of recurrence for LR was assumed to be the same as for RFS. The calibration process estimated a HR of 2.53, suggesting that the risk of recurrence following a LR was

approximately 2.5 times higher in patients who had experienced a LR compared with those who had not experienced a LR during the first 50 months. The company noted that clinical experts considered this estimate to be plausible and it was supported by the HR reported in Salama et al.

Distribution of LR, DR and death

Distribution of RFS events

RFS event category	COMBI-AD observed period		After COMBI-AD observed period (estimated from EORTC 18071)	
	Dabrafenib plus trametinib N (%)	Placebo N (%)	Dabrafenib plus trametinib N (%)	Placebo N (%)
LR	54 (33.8)	107 (44.4)	114 (35.3)	114 (35.3)
DR	103 (64.4)	133 (55.2)	199 (61.6)	199 (61.6)
Death	3 (1.9)	1 (0.4)	10 (3.1)	10 (3.1)
Total	160 (100)	241 (100)	323 (100)	323 (100)

Note: for the purposes of the economic model, patients who experienced both LR and DR were considered to have experienced a DR, and SPM were excluded from the economic analysis

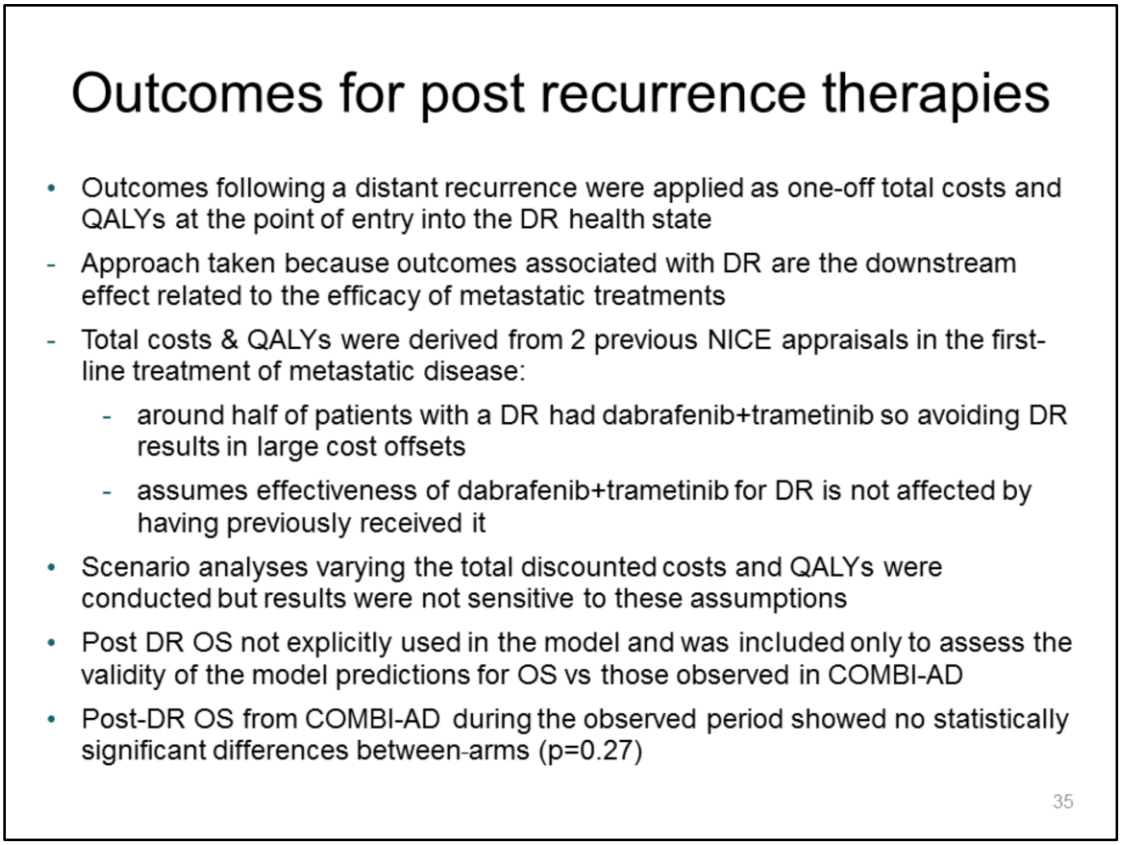
Distribution of events following a LR – (from White et al. 2002)

LR event category	Number of Events	Distribution
LR	541	32.0%
DR	1,067	63.1%
Death	83	4.9%
Total	**1,691**	**100%**

34

Source: Table 28 (page 84 of the company submission) and Table 29 (page 87). Please see pages 84 and 87 for more information.

There is limited evidence on the distribution of recurrence events following a LR. Clinical expert advice suggested that patients who had experienced a LR event were more likely to experience a DR compared with patients with no previous LR. As such, clinical experts expected the proportion of patients in the LR health state that experienced a DR to be greater compared with the proportion of patients in RFS that experienced a DR.



Please see pages 65-66 and pages 87-88 of the company submission for more information.

Although some data on post-recurrence therapies were collected in the COMBI-AD trial, data were incomplete and insufficient to robustly model the outcomes (costs and QALYs) following a DR with each potential treatment, without relying on a series of assumptions based on a limited clinical evidence. The company also note that optimal sequencing of post-recurrence treatments in UK clinical practice is unclear and given these uncertainties, explicitly modelling the treatment pathway in the DR health state would increase the complexity of the model and potentially introduce further unnecessary uncertainty.

A similar proportions of patients in both treatment arms of the COMBI-AD trial received any type of systemic anti-cancer therapy post-recurrence, but more patients in the treatment arm received immunotherapy compared to placebo. The company noted that the visual difference in post-DR OS could be explained by the different mix of treatments (e.g. immunotherapies or targeted therapies) received at the point of recurrence, but that clinicians expected the long-term to be similar irrespective of the starting treatment.

A log-logistic function was fitted to the data from COMBI-AD up to month 30, after which it assumed the weighted hazard reported in TA366 for pembrolizumab and TA396 for

dabrafenib plus trametinib. The proportions of patients receiving immunotherapy and targeted therapy were taken from COMBI-AD and were used to calculate the one-off cost and QALYs for immunotherapy and targeted therapy at the point of recurrence.

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Health state utilities

- [redacted]
- Utility values for the RFS and LR health states were from COMBI-AD
- Utility value for DR from COMBI-AD not used in model; instead one-off costs and QALYs at the point of entry into the DR health state

State	Utility value: mean (SE)	95% confidence interval	Justification
RFS on treatment	0.854 (0.006)	0.8426–0.8653	Based on statistical models fitted to EQ-5D-3L data collected in COMBI-AD
RFS off treatment[a]	0.869 (0.005)	0.8601–0.8786	Based on statistical models fitted to EQ-5D-3L data collected in COMBI-AD
LR	0.836 (0.013)	0.8100–0.8616	Based on statistical models fitted to EQ-5D-3L data collected in COMBI-AD

[a] RFS off treatment includes post-treatment dabrafenib plus trametinib and all placebo.
Abbreviations: DR: distant recurrence; EQ-50-3L: EuroQol 5-Dimensions 3-Levels; RFS: relapse-free survival; SE: standard error.

36

Source: Table 32 (page 91 of the company submission). Please see pages 90-92 for more information.

Since HRQoL was directly measured in the trial, decrements for adverse events were already implicitly included in the analysis.

Costs and resource use

- Base case estimates of the costs and resource use for routine surveillance were taken from consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by melanoma clinicians

Drug costs

- Drug acquisition costs were applied for on-treatment phase (12 months) of the RFS health state
- Cumulative doses were used to calculate drug costs as this takes into account dose interruptions and dose reductions
- Total number of packs of dabrafenib and trametinib per patient were estimated by dividing cumulative dose by total number of mg in a pack (including drug wastage)

Administration costs:

- No administration costs applied because both drugs are oral therapies

AE costs:

- Costs of serious adverse events (SAE) leading to hospitalisation included.
- Assumed that other events would not be associated with any meaningful management costs or impact on HRQoL.

37

Please see pages 92-98 of the company submission.

NICE clinical guidelines for the management of melanoma specify that genetic testing should be offered to all patients if a targeted systemic therapy, such as dabrafenib plus trametinib, is a possible treatment option. Therefore, the costs of BRAF testing were excluded from the model.

After completion of treatment, resource utilisation for patients receiving dabrafenib plus trametinib was assumed to be the same as patients receiving routine surveillance. Patients who discontinued treatment early were assumed to have follow-up and monitoring equal to routine surveillance for the remainder of the first year.

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Subsequent therapy costs and resource use

Costs associated with LR

- One-off cost assuming 90% of patients have surgery or, if unresectable, systemic therapy (immunotherapy (70%); targeted therapy (30%))
- Costs of monitoring were based on 2016/2017 NHS reference costs, and costs of immunotherapy or targeted therapy were based on the costs of medication, administration, and AEs for a course of pembrolizumab from TA366 or dabrafenib and trametinib from TA396

Costs associated with DR (incl. terminal care)

- Included as one-off costs and QALYs at the point of DR using estimates from previous NICE appraisals (TA366 and TA396):

	Immuno-therapy	Targeted therapy	Source	Combined
Proportion of patients starting first-line treatment in metastatic disease	43.9%	56.1%	COMBI-AD CSR	-
Total discounted costs (including PAS)	£83,282	[redacted]	TA366 ERG report, TA396	**£142,699**
Total discounted QALYs	2.960	3.443	TA366, TA396	**3.23**

38

Source: Table 38 (page 100 of the company submission). Please see pages 98-101 for more information.

Costs associated with LR

TA366 was used since the cost reported included the PAS price for pembrolizumab, and therefore more likely reflects the true cost to the NHS. Expert clinical opinion suggested that whilst it was reasonable to assume the cost of pembrolizumab as monotherapy immunotherapy, the combination ipilimumab/nivolumab would be likely to be used first-line in patients with a LR that are fit enough.

The company noted that the cost (including PAS) associated with a course of combination immunotherapy is not publicly available and it is likely that the cost associated with immunotherapy may be higher than the cost estimated.

Costs associated with DR

- Costs reported for pembrolizumab in TA366 and dabrafenib and trametinib in TA396 weighted according to relative receipt of the pooled proportions of immunotherapies and targeted therapies

received as first-line post-DR systemic anti-cancer therapies in COMBI-AD. In this approach, TA396 for dabrafenib plus trametinib was used to represent targeted therapies since clinical advice indicated that combination targeted therapies have largely replaced targeted monotherapies in the UK and TA366 for pembrolizumab was used to represent immunotherapies.

- Pooled distribution of therapies from COMBI-AD used and applied to both treatment arms in the model to reduce biasing the results toward one treatment or another if it were assumed that outcomes were associated with the initial treatment arm (i.e. different costs and QALYs following a DR according to the initial arm).
- The reasoning behind the approach taken is described in detail on pages 100-101 of the company submission

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Company's base case results (deterministic)

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/QALY)
Dabrafenib plus trametinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance (Placebo)	104,755	9.99	7.66	[redacted]	[redacted]	[redacted]	**20,039**

Note: Probabilistic ICER is £20,037

Scenario analyses showed that results are most sensitive to:

- different extrapolations for the estimation of the hazard of recurrence after the observed period (ICER **decreased** with alternatives as base case is most conservative)
- alternative parametric functions for RFS during observed period and through lifetime horizon of the model (ICER **decreased** with all distributions showing that using data solely from COMBI-AD yielded low ICERs)
- assuming a lower HR (1.5) than in base case (2.53) for calculating the transition probabilities from the LR health state increased the ICER to £24,548
- assuming costs and QALY's post DR solely from NICE TA366 increased the ICER to £23,803

39

Source: Table 44 (page 113 of the company submission). Please see pages 121-131 for more information.

Company's deterministic sensitivity analyses

10 most influential parameters	ICER (lower bound)	ICER (Upper bound)
Expected discounted cost of DR ±25%	£22,574	£17,504
Hazard for RFS after 50 months ±25%	£17,825	£22,239
HR applied to RFS events for LR vs RFS ±25%	£22,204	£18,882
Expected discounted QALYs after DR ±25%	£18,951	£21,259
Disutility for RFS on treatment vs off treatment ±25%	£18,991	£21,209
LR as a % of all RFS events ±25%	£19,331	£20,790
Follow-up and monitoring costs ±25%	£19,562	£20,516
Acute treatment of LR recurrence costs ±25%	£20,288	£19,789
Deaths as a % of all RFS events ±25%	£20,141	£19,936
Utility value in LR 95% CI	£19,938	£20,140

40

Source: Table 48 (page 119 of the company submission). Please see pages 119-120 for more information.

ERG comments – model structure

Model structure is unusual for 3 reasons:

- Results are not reliant on any modelled OS despite anticipated differences between arms. Company fits parameterised curves to COMBI-AD data but does not use for extrapolation, instead applies common risks from placebo arm of EORTC 18071:
  - generalisability concerns, and essentially freezes the proportionate OS gain at 50 months, with survival in the placebo arm being around 80% of survival in the treatment arm from months 50 to 600
- Patients who have a distant recurrence are not modelled explicitly. Instead, total costs and QALYs are taken from NICE STAs of treatments for metastatic disease
  - these have typically been viewed as satisfying End of Life (EoL) criteria and the total costs that are applied are large compared to the total QALYs accrued. Drugs meeting EoL criteria become disastrous from a cost effectiveness viewpoint when their costs and QALYs are appended to the current model
  - argument for valuing these costs & QALYs at EoL willingness to pay threshold
- Model fits an OS curve to post-DR patients but only for validation purposes:
  - not obvious how a competing risks analysis could be taken into account in the economics given that the modelled OS does not affect the results

41

Please see pages 72-75 and 15-18 of the ERG report for more information

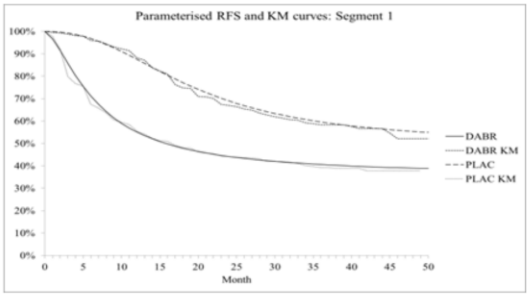
ERG comments – curve selection

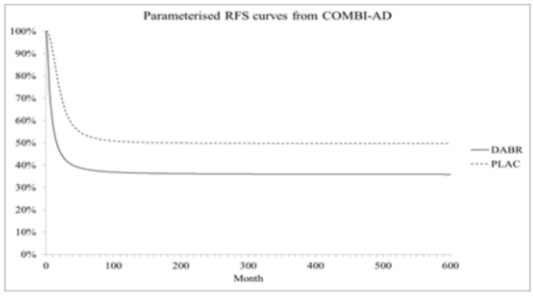
- Key uncertainty in the modelling is which curves should be applied, and the extent to which they should be extrapolated and whether competing risks should be considered
- Company rejects a number of parameterisations of the COMBI-AD RFS data as the dabrafenib+trametinib curve falls below the placebo curve
  - for a number of curves this does not occur until well into extrapolation, and is minimal and inconsequential
  - company has not properly justified why these curves should be rejected
  - ERG's preference is for parameterised curves derived from COMBI-AD
- Curve choice depends on whether treatment cures disease or postpones recurrence: ERG's clinical experts suggest postponement is most likely
  - company's log logistic (U) cure model (base case) suggests that treatment will permanently cure a larger proportion of patients
  - company's log logistic (R) cure model and the ERG's flexible parametric fit and competing risks models suggest treatment will postpone recurrence and the cure rate will eventually converge with placebo, leading to a worsening of the cost-effectiveness estimate

42

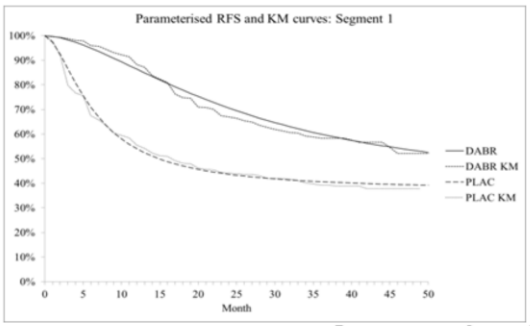
Please see pages75-78, 86-89 and 90-97of the ERG report for more information.

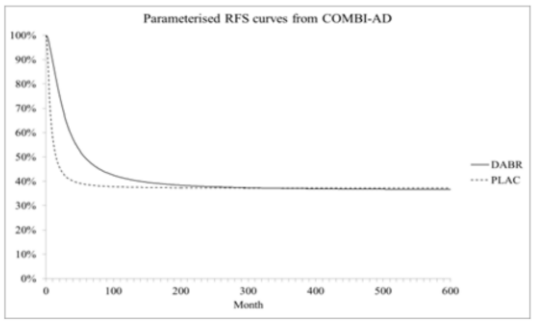
Company choice of RFS curves





Company Log-Logistic (U) Mixture (base case)



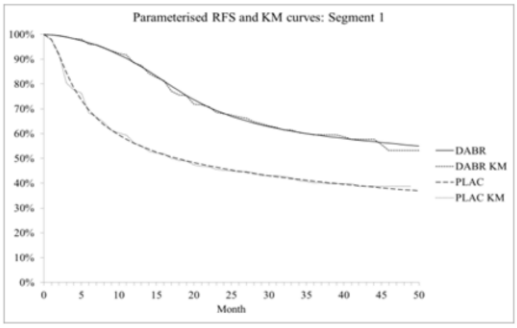


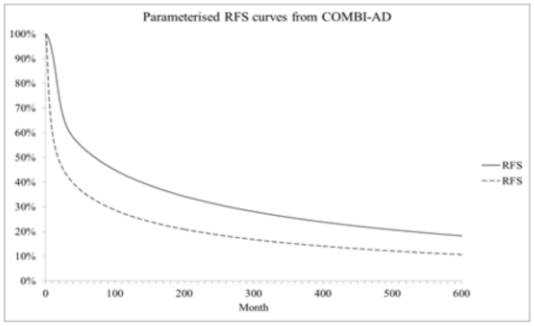
Company Log-Logistic (R) Mixture

43

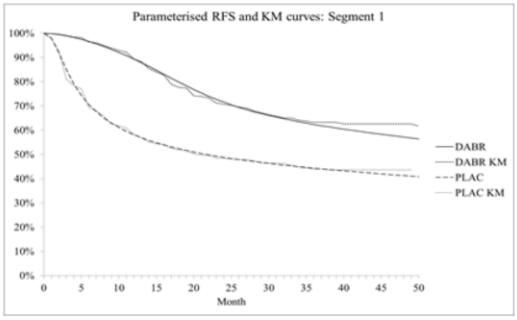
Source: Figure 17 (page 92) and Figure 19 (page 93) of the ERG report.

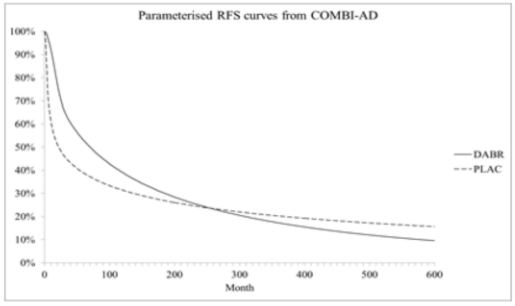
ERG alternative RFS curves





ERG flexible parametric fit





ERG flexible competing risk parametric fit

44

Source: . Figures 23 and 24 (page 95) of the ERG report.

ERG comments – other issues

- Calculation of the calibrating hazard ratio for post-LR events suggests >90% of those with a 1st recurrence will experience a 2nd recurrence within 50 months - no external data provided to support this
- The proportion on treatment is applied in the utility calculations but data supplied at clarification suggests that a higher proportion should be modelled as being on treatment - **only slightly worsens the cost effectiveness estimate**
- For a significant proportion of patients on treatment, time to treatment discontinuation was censored at day 364 and end of trial. If treatment continued beyond day 364, **this could affect costs considerably**
- Uncertainty about drug wastage during COMBI-AD - company's method is likely to underestimate wastage, as it applies the minimum number of packs that are consistent with individual patients' cumulative doses
  - prescriptions at times other than 4-weekly, dose interruptions, dose escalations and dose reduction are all likely to increase wastage
  - ERG's estimates are based upon company data supplied at clarification but may overestimate wastage

45

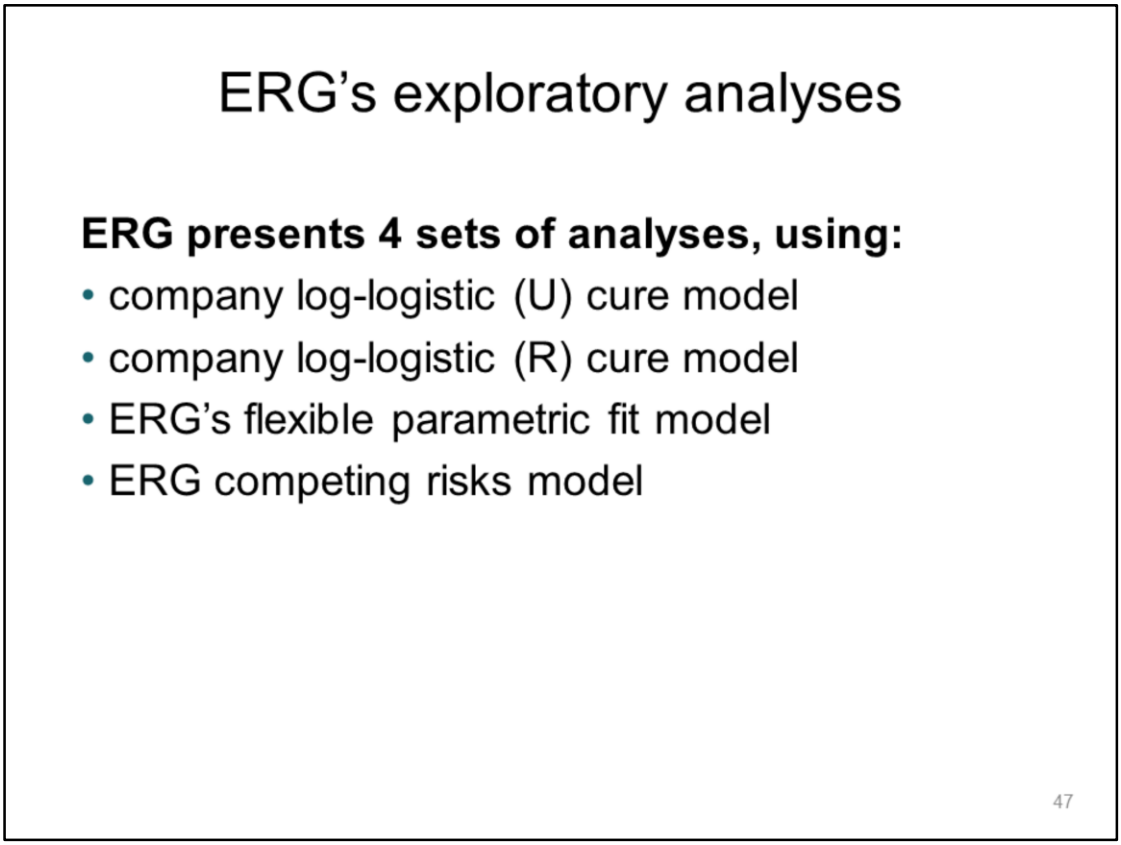
Please see pages 101-114 of the ERG report for more information.

ERG comments – other issues

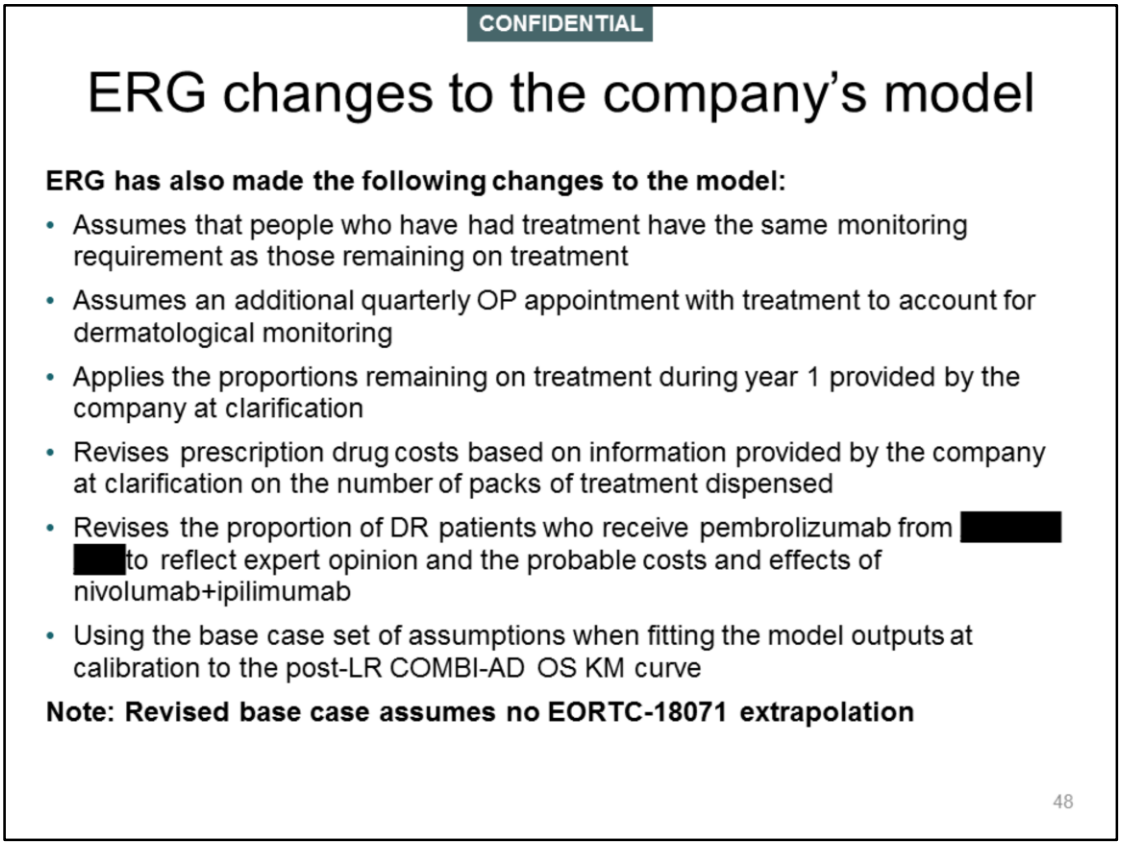
- Only SAE hospitalisation costs have been included but there is evidence of higher AEs, more prophylactic medication of AEs and more active medication of AEs in the treatment arm
  - **costs would have to rise significantly to have a major effect** on cost effectiveness
  - differentiating quality of life values for RFS by arm appears to have some effect, which may suggest that the company base case has not entirely taken into account the quality of life effects of AEs
- Company assumes a high proportion of stage IV patients will receive dabrafenib+trametinib for stage IV disease, the costs of which are high - **avoiding these costs improves the cost effectiveness estimate**
  - ERG expert opinion suggests that a lower proportion of stage IV patients will receive dabrafenib+trametinib, and that some will receive nivolumab+ipilimumab
  - The ERG's proportions worsen the cost effectiveness estimate

46

Please see pages 101-114 of the ERG report for more information.



Please see pages 114-128 of the ERG report for more information.



Please see pages 114-115 of the ERG report for more information.

ERG scenario analyses

- Applying the EQ-5D regression that splits on and off treatment by arm
- Varying the intercept term of the EQ-5D regressions by ±25% for both the base case regression and the regression that splits on and off treatment by arm, resulting in an approx ±0.1 change in the QoL values applied
- Extending the monitoring requirement for dabrafenib+trametinib by 50%
- Varying the proportion of LR events needing resection from 10% to 0% and to 20%
- Deriving the balance between LR, DR and death events in the post-LR modelling from the same source as used for RFS i.e. EORTC 18071
- Valuing health benefits of DR treatments at the end of life willingness to pay of £50k/QALY
- EORTC 18071 extrapolation from month 50 for RFS and post-LR RFS (both arms)

49

Please see pages 114-128 of the ERG report for more information.

ERG's exploratory analyses - results

	L-Log (U)	L-Log (R)	ERG CR	ERG Flex
ERG's revised base case	£20,701	£62,853	£46,161	£20,167
SA01: EQ-5D RFS split by arm	£21,734	£70,752	£49,492	£20,814
SA02a: EQ-5D intercept -25%	£24,134	£72,018	£53,061	£23,447
SA02b: EQ-5D intercept +25%	£18,134	£55,790	£40,873	£17,703
SA02c: SA01 + EQ-5D intercept -25%	£25,697	£83,032	£57,814	£24,461
SA02d: SA01 + EQ-5D intercept +25%	£18,830	£61,636	£43,264	£18,114
SA03: DABR monitoring +50%	£21,929	£65,675	£48,347	£20,404
SA04a: LR resection 0%	£21,329	£63,847	£46,954	£20,770
SA04b: LR resection 20%	£20,073	£61,859	£45,369	£19,564
SA05: LR évents balance EORTC 18071	£20,764	£63,716	£46,530	£20,181
SA06: DR costs & benefits reflect EoL	£24,980	£61,487	£46,589	£24,274
SA07: EORTC extrapolation*	£26,258	£30,866	£27,432	£23,513

*Results for SA07 are similar because applying common risks from EORTC to each arm from month 50 to 600 effectively freezes the proportionate OS gain at 50 months

50

Source: ERG addendum

Equality issues

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

51

Innovation: company comments

- First targeted therapy for resected BRAF V600 positive stage III melanoma, and the first active treatment for patients currently managed only through routine surveillance
  - represents a step change in the management of resected BRAF V600 positive stage III melanoma
- Consistent results across all pre-specified sub-groups
- As melanoma disproportionately affects a younger population, who are of working age and may have young families, this treatment has the potential to significantly impact patients, their carers and wider society which is not captured in the QALY
- Granted Breakthrough Therapy Designation on 23rd October 2017 by the Food and Drug Administration in the United States and has been included in the 2018 update of the National Clinical Comprehensive Cancer Network Guidelines for melanoma

52

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53

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma
ID1226

Document B
Company evidence submission

Novartis Pharmaceuticals Ltd

April 2018

File name	Version	Contains confidential information	Date
ID1226 **Document B**	**Final**	**Yes**	**16th April 2018**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

List of tables

List of figures

List of abbreviations

Abbreviation	Definition
AESI	Adverse event of special interest
AIC	Akaike information criterion
AJCC	American Joint Commission on Cancer
ASCO	American Society of Clinical Oncology
ATP	Adenosine triphosphate
BAD	British Association of Dermatologists
BIC	Bayesian information criterion
BID	Twice daily
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAB	Dabrafenib
DMFS	Distant metastasis-free survival
DNA	Deoxyribonucleic acid
DR	Distant recurrence
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D-3L	EuroQol Five Dimensions Three levels
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FFR	Freedom from relapse
GEE	Generalised estimation model
GP	General practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSU	Health state utility
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
ITT	Intention to treat
LR	Loco-regional recurrence
LVEF	Left ventricular ejection fraction
LY	Life year
LYG	Life years gained
MDT	Multidisciplinary team
MedDRA	Medical Dictionary for Regulatory Activities

MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition scan
NCCN	National Clinical Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OD	Once daily
OS	Overall survival
PAS	Patient access scheme
PBO	Placebo
PET	Positron emission tomography
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
QC	Quality control
QD	Once daily
R	Restricted
RCS	Restricted cubic splines
RCT	Randomised controlled trial
RFS	Relapse-free survival
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SPM	Secondary primary melanoma
STA	Single technology appraisal
TAF	Tafinlar
TNM	Tumour, Node, Metastasis
U	Unrestricted
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
WHO	World Health Organisation
WTP	Willingness-to-pay threshold

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

B.1.1 Decision problem

This submission covers the full marketing authorisation for the technology dabrafenib plus trametinib for the indication of [redacted].

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal as outlined in Table 1.

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	People with completely resected, stage III melanoma with BRAF V600 positive mutations	Adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection	In line with final NICE scope
Intervention	Dabrafenib plus trametinib	Dabrafenib plus trametinib	In line with final NICE scope
Comparator(s)	Routine surveillance	Routine surveillance	In line with final NICE scope
Outcomes	• Overall survival • Relapse-free survival • Distant metastases free survival • Adverse effects of treatment • Health-related quality of life	• Relapse-free survival • Overall survival • Distant metastases free survival • Freedom from relapse • Adverse effects of treatment • Health-related quality of life (EQ-5D-3L)	In line with final NICE scope
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 • 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	• The cost-effectiveness of the treatments evaluated in this appraisal is expressed in terms of incremental cost per quality-adjusted life year • A lifetime time horizon was adopted to capture all relevant costs and health-related utilities • All costs and utilities were discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal	In line with final NICE scope

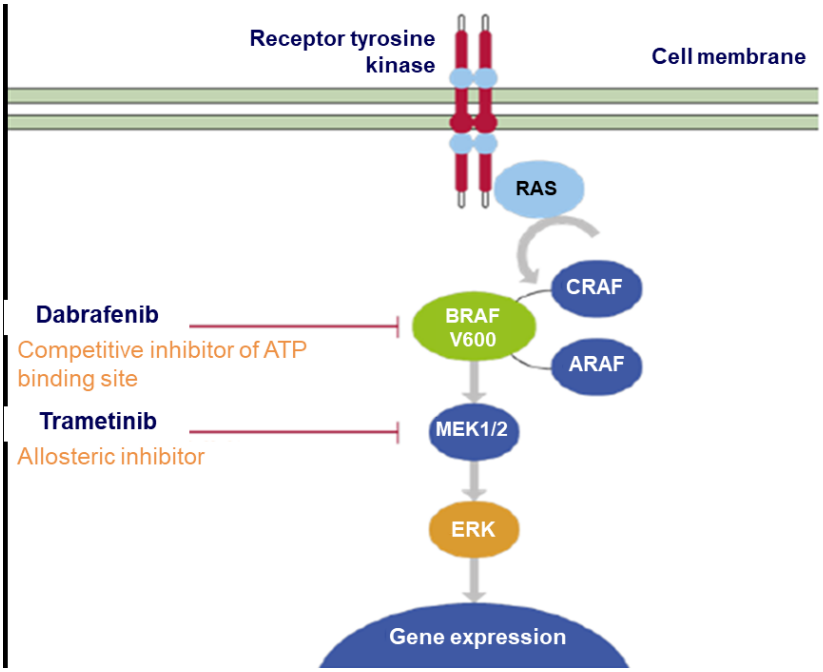
	• Costs will be considered from an NHS and Personal Social Services perspective • The availability of any patient access schemes for the intervention or comparator technologies will be taken into account	• Costs were considered from an NHS and Personal Social Services perspective	
Other considerations	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 granted by the regulator	Dabrafenib plus trametinib is presented within the full proposed marketing authorisations for both treatments for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection	In line with final NICE scope

Abbreviations: EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; N/A, not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence.
Source: NICE Final Scope for ID1226.[1]

B.1.2 Description of the technology being appraised

A description of the technology (dabrafenib plus trametinib for the adjuvant treatment of adult patients with resected BRAF V600 positive stage III melanoma) is presented in Table 2, together with a summary of the mechanism of action, marketing authorisation status, costs and administration requirements.

Table 2: Technology being appraised

UK approved name and brand name	Dabrafenib (Tafinlar®) plus trametinib (Mekinist®)
Mechanism of action	The mitogen-activated protein kinase (MAPK) signalling pathway plays a critical role in regulating the growth, proliferation and survival of normal cells, including melanocytes.[2, 3] In melanoma, dysregulation of the MAPK pathway caused by genetic mutations leads to increased signalling activity which in turn promotes malignant cell proliferation, invasion, metastasis, survival and angiogenesis.[3] Oncogenic mutations in BRAF V600 are one of the most common genetic mutations in melanoma; they are found in approximately 41% of melanomas and result in the constitutive activation of the MAPK pathway, thus driving disease progression.[4-17] Dabrafenib is an oral, selective, competitive inhibitor of BRAF V600 and trametinib is an oral, selective, allosteric inhibitor of MEK 1/2.[18, 19] Together, dabrafenib plus trametinib provide concurrent inhibition of the MAPK pathway by simultaneously targeting these two discrete kinases (Figure 1). **Figure 1: Mechanism of action of dabrafenib plus trametinib**  **Abbreviations:** ATP: adenosine triphosphate. **Source:** NICE TA396[20], dabrafenib SmPC[18] and trametinib SmPC[19] Concurrent inhibition of the MAPK pathway by dabrafenib plus trametinib has already demonstrated efficacy in the metastatic setting and in 2016, dabrafenib plus trametinib was licensed and approved by NICE for the treatment of unresectable or metastatic melanoma in adults with a BRAF V600 mutation.[18, 19, 21-26]

	The BRAF V600 mutation has shown early and continued involvement throughout the course of disease progression in melanoma, and is often found to be present in the primary lesion and corresponding metastatic lesions.[8] It therefore stands to reason that the concurrent inhibition of the MAPK pathway could provide disease control regardless of disease stage and, indeed, the efficacy of dabrafenib plus trametinib has now been demonstrated in the adjuvant setting, as presented within this submission.[27]
Marketing authorisation/CE mark status	Dabrafenib (Tafinlar®) plus trametinib (Mekinist®) does not currently have a UK marketing authorisation for the proposed indication of the [redacted]. A marketing authorisation application was made to the European Medicines Agency (EMA) [redacted] in [redacted] for the proposed indication, and the anticipated date of a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is [redacted]. The anticipated date of EMA regulatory approval is [redacted]. In the United States, dabrafenib plus trametinib was granted a priority review by the Food and Drugs Administration (FDA) for the proposed indication, in which the FDA is expected to issue its decision within 6 months of the license application submission as opposed to the 10-month standard review. This follows the Breakthrough Therapy Designation granted to dabrafenib plus trametinib in this indication in October 2017.[28] Treatments that receive Breakthrough Therapy Designation are those that treat a serious or life-threatening disease or condition and demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints based on preliminary clinical evidence.[29]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Dabrafenib and trametinib are currently licensed as monotherapies and combination therapies in the following indications: • *"Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation"[18] (26th August 2013)* • *"Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation"[19] (30th June 2014)* • *"Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation"[18, 19] (25th August 2015)* Both dabrafenib and trametinib are contraindicated in patients with hypersensitivity to the active substances or to any of the excipients.[18, 19] Treatment with dabrafenib plus trametinib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products and in order to initiate treatment with dabrafenib plus trametinib, patients must have confirmation of BRAF V600 mutation using a validated test.[20]
Method of administration and dosage	Both dabrafenib and trametinib are oral therapies and the recommended dose for the proposed indication is the same as the existing licensed indications: dabrafenib 150 mg (two 75 mg capsules) twice daily, plus trametinib 2 mg (one tablet) once daily. Patients should be treated for a period of 12 months, unless there is disease recurrence or unacceptable toxicity.[18, 19]

	As oral therapies, there are no special administration requirements for dabrafenib plus trametinib and the treatment may be simply administered by patients or their carers at home. Full details of any dose modifications required for dabrafenib plus trametinib are reported in the respective SmPCs.[18, 19]
Additional tests or investigations	In order to initiate treatment with dabrafenib in combination with trametinib, patients must have confirmation of the BRAF V600 mutation using a validated test. This is also in line with NICE clinical guidelines for the management of melanoma, which specify that genetic testing should be offered to all patients if a targeted systemic therapy, such as dabrafenib plus trametinib, is a possible treatment option.[20, 30] BRAF testing facilities are available nationally and BRAF testing is already part of routine clinical care for high-risk patients, which includes all stage III patients and those with unresectable or metastatic melanoma.[30] Since the majority of multi-disciplinary teams currently test high-risk patients, no new or additional diagnostic tests are required for the proposed indication. The monitoring requirements for patients who start treatment with dabrafenib plus trametinib in the proposed indication are expected to be the same as those in the metastatic setting, full details of which are reported in the SmPC.[18, 19]
List price and average cost of a course of treatment	The list prices for dabrafenib and trametinib are reported below.[31,32] **Drug** / **Pack size** / **List price** Dabrafenib 50 mg — 28 capsules — £933.33 Dabrafenib 75 mg — 28 capsules — £1,400.00 Trametinib 0.5 mg — 30 tablets — £1,200.00 Trametinib 2 mg — 30 tablets — £4,800.00 **Source:** British National Formulary 2018.[33] Patients should be treated for a period of 12 months, unless there is disease recurrence or unacceptable toxicity.[18, 19] The mean duration of treatment with dabrafenib plus trametinib in the COMBI-AD trial (the pivotal clinical trial for dabrafenib plus trametinib in this indication was [redacted] months with dabrafenib and [redacted] months with trametinib.[34] The mean number of packs of dabrafenib and trametinib received during the COMBI-AD trial was [redacted] and [redacted], respectively.[34] (calculated from the total cumulative dose for each patient divided by the total number of mg in a pack with rounding up to the nearest whole number). Based on these values, the average cost of a course of treatment at list price is [redacted] per patient as described below: • Dabrafenib: [redacted]* packs of 28 x 75 mg would be expected to be used, corresponding to 32.19 x £1,400.00 = [redacted] • Trametinib: [redacted]* packs of 30 x 2 mg would be expected to be used, corresponding to 8.50 x £4,800.00 = [redacted] *Note these values have been rounded. The exact values can be found in the economic model.
Patient access scheme (if applicable)	A confidential simple patient access scheme (PAS) exists for dabrafenib plus trametinib, in which the NHS will be able to procure both dabrafenib and trametinib at net prices lower than the current list prices. Should the list prices of either dabrafenib or trametinib change, the percentage

	discount will change accordingly to maintain a confidential fixed net price. Dabrafenib is provided to the NHS with a [redacted] discount off the current list price and trametinib is provided with a [redacted] discount off the current list price. As such, the confidential PAS net prices for dabrafenib and trametinib are reported below.

Drug	Pack size	PAS Net price
Dabrafenib 50 mg	28 capsules	[redacted]
Dabrafenib 75 mg	28 capsules	[redacted]
Trametinib 0.5 mg	30 tablets	[redacted]
Trametinib 2 mg	30 tablets	[redacted]

Abbreviations: ATP: adenosine triphosphate; CHMP: Committee for Medicinal Products for Human Use; LVEF: left ventricular ejection fraction; MAPK: mitogen-activated protein kinase; SmPC: Summary of Product Characteristics.

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

Disease overview

- Malignant melanoma is an aggressive form of skin cancer arising from the malignant transformation of melanocytes.[35-40]
- A mutation in BRAF V600 is the most common oncogenic mutation in melanoma (identified as driving the development of approximately 41% of melanomas).[4-17]
- Melanoma is classified according to the American Joint Commission on Cancer (AJCC) system: stage I or II tumours are localised, stage III tumours have spread to the lymph nodes and stage IV tumours are advanced (metastatic).[41]

Epidemiology

- In 2016, malignant melanoma was the fifth most common cancer in the UK, with over 13,000 cancer registrations.[42]
- Of melanoma cases in England with a recorded stage at diagnosis, 66% are diagnosed at stage I, 20% at stage II, 6% at stage III, 2% at stage IV and 5% with stage unknown.[42]
- In contrast to other cancer types, melanoma disproportionately affects a younger population than other cancers, with a significant impact on patients, carers and wider society.[43]

Morbidity and mortality

- Patients with stage III melanoma have a poorer prognosis (five-year overall survival [OS] rates of 50–55%)[43] compared to stage I and II melanoma (five-year OS rates of 100% and 75–85%, respectively).[43]
- Furthermore, since patients with stage III disease have lymph node involvement, they are considered at high risk of disease recurrence, with five-year relapse-free survival (RFS) rates of ~57% compared with 93% and 66% for stages I and II.[44]
- Prevention of disease recurrence following resection remains a priority in the management of stage III melanoma.[45] Of stage III patients who experience disease recurrence, 51% will experience distant (metastatic) recurrence, with an extremely poor prognosis (five-year OS rates 5%–20%) and substantial reductions in health-related quality of life (HRQoL).[46-52]

Clinical pathway of care

- In the EU, interferon-α-2b is the only therapy licensed for the adjuvant treatment of stage III melanoma patients that are free of disease after surgery but at high risk of systemic recurrence.[53] However, interferon-α-2b is not used in UK clinical practice because of the inconsistency seen in the OS benefit and associated substantial toxic effects.[54, 55]
- The standard of care (SoC) for patients with resected stage III melanoma in the UK is routine surveillance (comprising regular clinical review and imaging surveillance).[30, 56]
- Since disease recurrence reduces life expectancy, and there is an OS benefit associated with delayed disease progression,[57] there is universal agreement on the high unmet medical need for clinically effective and well tolerated treatments in the adjuvant setting to reduce the risk of progression to metastatic disease.[58]
- Dabrafenib plus trametinib is already licensed and NICE approved as a targeted therapy for the treatment of unresectable or metastatic melanoma in adults with a BRAF V600 mutation.[18, 19, 21-26] The proposed licence extension to the adjuvant setting would provide a step change in the management of melanoma, offering a clinically effective treatment with a manageable safety profile to reduce the morbidity and mortality burden associated with progression to metastatic disease.[55]

B.1.3.1 Disease overview

Malignant melanoma is an aggressive type of skin cancer that arises from the malignant transformation of melanocytes, the melanin-producing cells of the skin responsible for skin pigmentation and photoprotection.[35-37] Most melanomas (90%) arise in the skin (cutaneous melanoma) and are most likely to appear on sun-exposed areas, including the trunk, legs, face and neck, but may also arise from mucosal, ocular or other sites.[38-40] Malignant melanoma is the most aggressive form of skin cancer and can be fatal, particularly if not detected and treated at an early stage.[36] Furthermore, malignant melanoma has high metastatic potential and may spread to any organ (most commonly the lymph nodes, lungs, liver, bones, brain and abdomen).[59] Of stage III patients who experience disease recurrence, 51% will experience a distant (metastatic) recurrence, for which the prognosis is extremely poor (five-year OS rates range from 20% to just 5%).[46, 49-52] Therefore, the early detection and treatment of melanoma to avoid progression to metastatic disease is critical.

Risk factors for developing melanoma include environmental factors, such as acute and intermittent exposure to sunlight and UV radiation, and genetic factors, which include having a high number of moles, being fair skinned (especially with fair or red hair), having lighter eye colour and a family history of melanoma.[54, 60] The most important warning sign of melanoma is the appearance of a new mole or a change in size, shape, or colour of an existing mole. A lesion that deviates from the typical appearance of moles on an individual's body should also be investigated. Additional warning signs and symptoms include moles or skin patches that are itchy, bleeding, painful, asymmetric or inflamed.[40]

BRAF V600 positive melanoma

Multiple genetic alterations have been reported to play a role in melanoma disease progression, and dysregulation of MAPK signalling has been shown to be a key driver of the disease.[61] The BRAF V600 mutation has been identified as driving the development of approximately 41% of melanomas[4-17] and the BRAF protein is a critical component of the MAPK pathway that regulates normal cell growth, differentiation and survival.[2, 3]

Mutated BRAF is more active than the wild type protein and results in the constitutive activation of the downstream MAPK pathway, including MEK, leading to melanocyte proliferation and subsequent tumour growth. This is consistent with the observation that MAPK pathway inhibition increases progression-free survival (PFS) and OS in patients with metastatic melanoma.[18, 19, 21-26] Inhibition of this critical proliferation pathway is therefore a highly desirable target in the treatment of malignant melanoma. Concurrent inhibition of the MAPK pathway with dabrafenib plus trametinib represents a targeted approach to mitigate the risk of disease recurrence inpatients with a BRAF V600 mutation.

Diagnosis, staging and genetic testing

The American Joint Commission on Cancer (AJCC) system is the most widely used classification system for melanoma and the staging system is important in determining prognosis and an appropriate treatment strategy.[30] Tumours are classified using the Tumour, Node, Metastasis (TNM) staging system, which describes the Breslow depth (i.e. thickness of the tumour), the appearance of microscopic ulceration, the tumour's mitotic rate, whether there is lymph node involvement, and the degree of loco-regional or distant metastasis. Tumours classified as stage I or II are localised tumours, stage III tumours have spread to the lymph nodes and stage IV tumours are metastatic.[41, 62]

The seventh edition of the AJCC system (Table 3)[41] was used in the pivotal clinical trial for dabrafenib plus trametinib in this proposed indication ([redacted]). It should be noted that an eighth edition of the AJCC was released in January 2018 and UK clinical practice is currently in the process of adopting this. The key (albeit minor) difference between the seventh edition (used in the COMBI-AD trial) and the recently published eighth edition (2018) is a shift in the distribution of patients categorised with stage II melanoma to stage III melanoma.[41, 63] This change means more patients will be categorised as stage IIIC and in addition there is a new pathologic sub-stage (stage IIID) representing patients with poor outcomes [41, 63] Since the COMBI-AD trial was based on the classification system in version 7, this submission subsequently only discusses version 7.

Table 3: TNM staging system in cutaneous melanoma (AJCC seventh edition, 2009)[a]

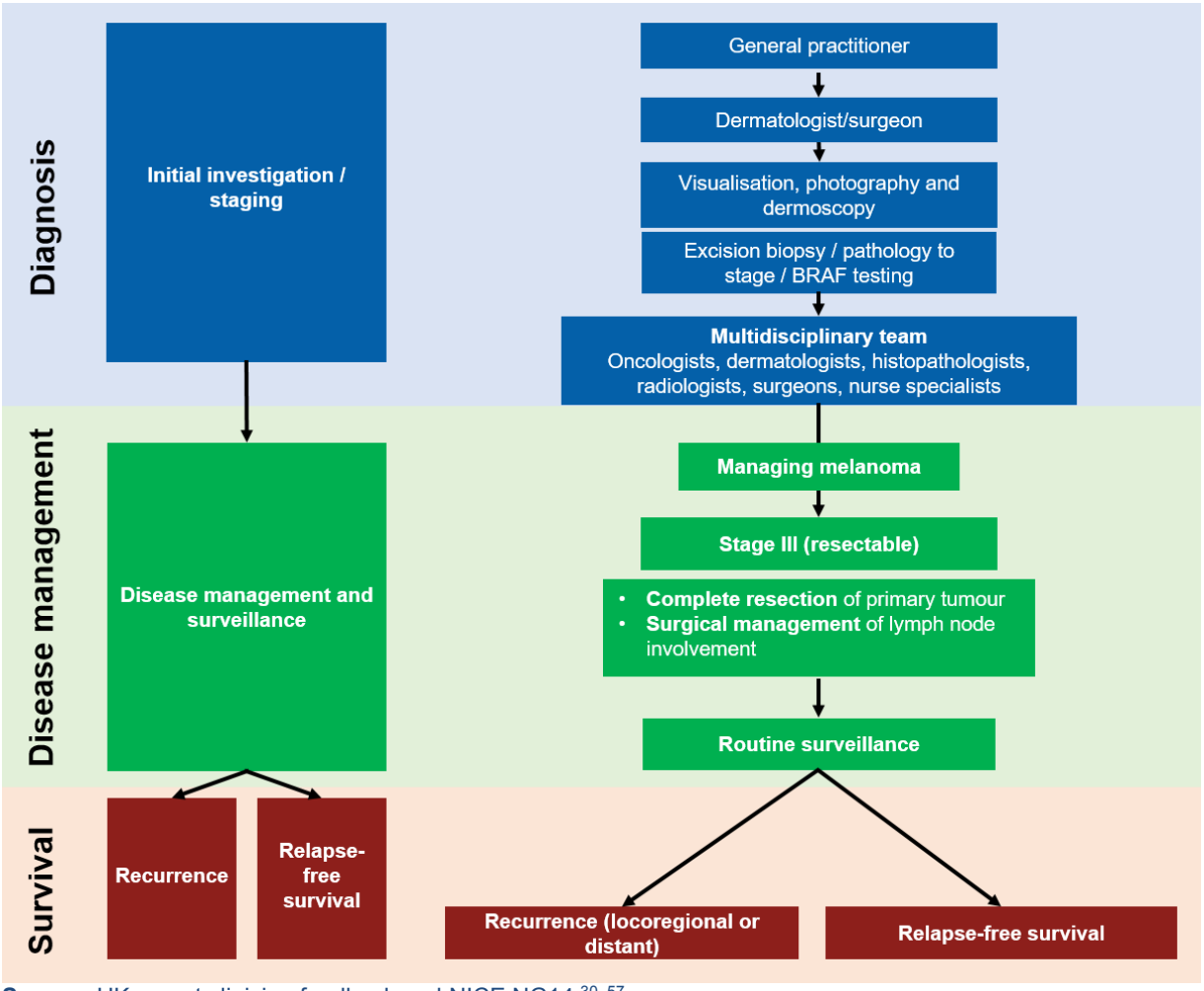
Stage	T	N	M	Description
Stage 0	Tis	N0	M0	Melanoma in situ
Stage IA	T1a	N0	M0	**All** of the following: • The melanoma is less than 1 mm thick • The melanoma is not ulcerated • The melanoma has a mitotic rate of less than 1/mm^2
Stage IB	T1b	N0	M0	**One** of the following: • The melanoma is less than 1 mm thick and is ulcerated • The melanoma has a mitotic rate of at least 1/mm^2 • The melanoma is between 1 and 2 mm and is not ulcerated
	T2a	N0	M0	
Stage IIA	T2b	N0	M0	**One** of the following: • The melanoma is between 1 and 2 mm thick and is ulcerated • The melanoma is between 2 and 4 mm and is not ulcerated
	T3a	N0	M0	
Stage IIB	T3b	N0	M0	**One** of the following: • The melanoma is between 2 and 4 mm thick and is ulcerated • The melanoma is thicker than 4mm and is not ulcerated
	T4a	N0	M0	
Stage IIC	T4b	N0	M0	The melanoma is thicker than 4 mm and is ulcerated
Stage IIIA	T1-4a	N1a	M0	**All** the following: • Up to three nearby lymph nodes contain melanoma cells • The melanoma cell-containing lymph nodes are not enlarged and the cells can only be seen under a microscope • The melanoma is not ulcerated and has not spread to other areas of the body
	T1-4a	N2a	M0	
Stage IIIB	T1-4b	N1a	M0	**One** of the following: • The melanoma is ulcerated and has spread to between one and three nearby lymph nodes, but the lymph nodes are not enlarged and the cells can only be seen under a microscope • The melanoma is not ulcerated and has spread to between one and three nearby lymph nodes, and the lymph nodes are enlarged • The melanoma is not ulcerated and has spread to small areas of skin or lymphatic channels, but nearby lymph nodes do not contain melanoma cells
	T1-4b	N2a	M0	
	T1-4a	N1b	M0	
	T1-4a	N2b	M0	
	T1-4a	N2c	M0	
Stage IIIC	T1-4b	N1b	M0	**One** of the following: • The lymph nodes contain melanoma cells, and there are melanoma cells in the skin or lymph channels close to the main melanoma • The melanoma is ulcerated and has spread to between one and three lymph nodes nearby which are enlarged • The melanoma may or may not be ulcerated and has spread to four or more nearby lymph nodes • The melanoma may or may not be ulcerated and has spread to lymph nodes that have joined together
	T1-4b	N2b	M0	
	T1-4b	N2c	M0	
	Any T	N3	M0	
Stage IV	Any T	Any N	M1	The melanoma is advanced and has metastasised

[a]Although the AJCC eight edition has been released,[63] the seventh edition is still used in clinical practice and was used to stage patients enrolled in COMBI-AD.[55]
Abbreviations: AJCC: American Joint Commission on Cancer; TNM: Tumour, Node, Metastasis.
Source: Balch *et al*. (2009).[41]

Figure 2 describes the patient journey for stage III melanoma patients following diagnosis and staging according to the current clinical pathway in the UK (See Section B.1.3.2). Regarding genetic testing for a BRAF mutation, NICE clinical guidelines for the management of melanoma specify that genetic testing should be offered to all patients if a targeted systemic therapy, such as dabrafenib plus trametinib, is a possible treatment option.[30]

In line with this NICE guidance, all patients considered at high risk of metastatic disease recurrence are currently tested as SoC across the UK,[30] and this would therefore include patients in the proposed new indication. Consequently, there are no additional genetic tests required prior to the initiation of dabrafenib plus trametinib for the new indication of resected BRAF V600 positive stage III melanoma patients.

Figure 2: Simplified patient journey for stage III melanoma in the UK



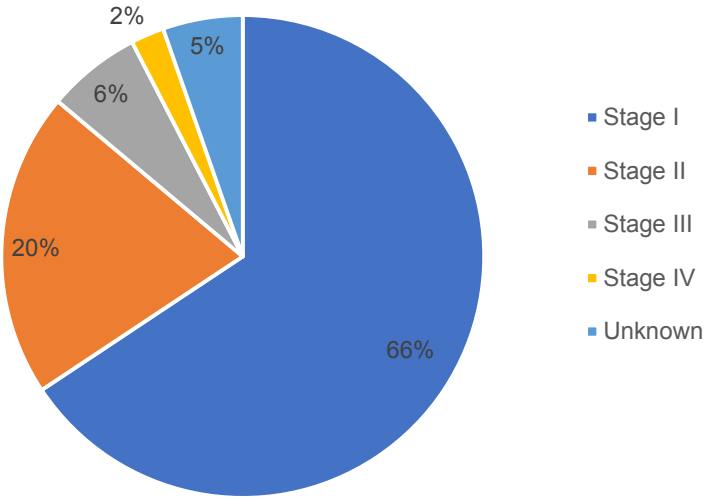
Source: UK expert clinician feedback and NICE NG14.[30, 57]

Epidemiology

In 2015, malignant melanoma was the fifth most common cancer in the UK, accounting for 4% of all newly diagnosed cases of cancer.[43] The incidence of melanoma is related to age, with the highest incidence rates being in older patients (incidence rates in the UK are highest in people aged 85–89).[43] However, in contrast to other cancer types, malignant melanoma disproportionately affects a younger population, with 49% of new cases per year occurring in patients younger than 65. As such melanoma can have a considerable impact on patients, their families and the wider society.[43]

The number of melanoma cancer registrations in England in 2016 was 13,748. Of these, 66% were recorded as stage I, 20% as stage II, 6% as stage III, 2% as stage IV and 5% with the stage recorded as unknown (Figure 3).[42] In 2018, the number of patients eligible for treatment with dabrafenib and trametinib in the proposed adjuvant indication is estimated to be 427 (Table 4).

Figure 3: Melanoma stage recorded at diagnosis in England in 2016



Source: National Cancer Registration.[42]

Table 4: Assumptions and calculation of patient population eligible for treatment with adjuvant dabrafenib and trametinib in 2018

Assumption	Value	Reference
1. Estimated incident number of stage III melanoma patients[a] (2018)	1,157	Kantar Health estimate[64]
2. Percentage of patients with resectable disease (%)	90%	SEER data[65] and expert clinical opinion[57]
3. Patients with resectable stage III melanoma	1,041	Calculation (assumption 1 x assumption 2)
4. Percentage of melanomas that are expected to be BRAF V600 positive	41%	Ackman *et al.* (2015),[4] Barbour *et al.* (2014),[5] Boursault *et al.* (2017),[6] Heppt *et al.* (2017),[7] Johansson *et al.* (2009),[8] Knol *et al.* (2015),[9] Lo *et al.* (2016),[17] Mann *et al.* (2013),[10] Moreau *et al.* (2012),[11] Picard *et al.* (2014),[12] Rutkowski *et al.* (2014),[13] Shinozaki *et al.* (2004),[14] Thomas *et al.* (2015),[15] Weber *et al.* (2017)[16] (Full details of this calculation are reported in Appendix Q)
5. **Patients with resected BRAF V600 positive stage III melanoma**	**427**[b]	Calculation (assumption 3 x assumption 4)

[a]This value includes patients newly diagnosed with stage III melanoma and patients experiencing stage III recurrence; [b]Values have been rounded to the nearest whole number for presentation within this table.
Abbreviations: SEER: Surveillance, Epidemiology, and End Results.

Melanoma incidence rates are expected to increase by 7% between 2014 and 2035.[43] Over the last decade in the UK (between 2003–2005 and 2012–2014), melanoma age-standardised

incidence rates have increased by 45%, with a larger increase for males (56%) than for females (35%), highlighting the urgency for effective therapies for this disease.[43] Reasons for this historical rise in the incidence of melanoma include the changing prevalence of risk factors–for example changes in sun-related behaviour and use of sunbeds, increased accessibility of sunny holidays and also increased public awareness, greater surveillance and early detection, as well as changes in the diagnostic criteria.[36, 66]

Morbidity and mortality

The prognosis of melanoma varies widely depending on the stage of the disease at clinical presentation and HRQoL has shown to deteriorate particularly with later stages of disease.[43, 47, 52]

Early-stage melanoma confined to the skin is potentially curable by complete resection and is associated with an excellent long-term prognosis (five-year OS rates for stage I and II disease are approximately 100% and 78–85%, respectively).[30, 52]

For patients with stage III melanoma, where disease has spread to the lymph nodes, prognosis following complete resection is much poorer. Furthermore, heterogeneity in survival among subgroups of patients with stage III disease has been observed in previous studies, with important differences in prognosis based on underlying melanoma-specific factors (e.g. number of nodal metastases, primary tumour ulceration and micrometastasis versus macrometastasis).[67]

Overall, five-year OS rates for stage III melanoma patients are approximately 50–55%. However, in spite of this, the use of adjuvant therapy following complete resection is currently not SoC in the UK.[30, 43, 44] Patients with lymph node involvement (i.e. stage III melanoma) are by definition at a higher risk of disease recurrence (which can be loco-regional or distant [metastatic]) compared with stage I or stage II patients, and therefore have lower five and ten-year RFS rates (Table 4).[44, 56, 68] Overall, for patients whose disease progresses to a metastatic stage, prognosis is extremely poor, with five-year OS rates ranging from 20% down to just 5%.[46, 49-52]

Table 5: RFS rates in malignant melanoma

Stage	5-year RFS (%)	10-year RFS (%)
Stage I	93.2	89.0
Stage II	65.5	56.9
Stage III	56.9	36.0

Abbreviations: RFS: relapse-free survival. It should be noted that the term 'recurrence-free survival' is interchangeable with 'relapse-free survival' or 'disease-free survival' and that all of these terms appear in related literature.[57]
Source: Leiter *et al*. (2012).[44]

These data therefore demonstrate that disease recurrence reduces life expectancy, and clinical experts agree that there is an OS benefit associated with delayed disease progression.[57] In the last six years, the medical management of metastatic melanoma has been revolutionised with the approval of multiple new drugs as monotherapies[69-73] or combination therapies.[21-25, 74] All of these therapies have demonstrated clear survival benefits in randomised clinical trials (RCTs) and have been adopted into routine clinical practice for the management of metastatic disease.[20-25, 69-78]

In stark contrast, in the adjuvant setting, interferon-α-2b has been the only agent licensed in the EU for the adjuvant treatment of melanoma in the last 30 years, and according to guidelines from the European Society for Medical Oncology (ESMO), patients with microscopic regional nodal involvement and/or ulcerated primary tumours may benefit from treatment with interferon-α-2b .[79]

However, due to uncertainty in the clinical benefit and a high toxicity profile, interferon-α-2b is not currently SoC in UK.[54, 80] More recently, ipilimumab was shown to demonstrate superior efficacy compared to placebo in completely resected stage III and IV melanoma, however, due to significant toxicity and thus an uncertain risk-benefit ratio, it has not been licensed in the EU in this setting.[81]

Although patients with stage III melanoma who are disease free following complete resection may report similar HRQoL compared with the general population, these patients are still at high risk of disease recurrence, and evidence suggests that, after resection, some patients remain fearful about disease recurrence and are concerned about death.[44, 47] Disease recurrence may present as loco-regional (at the same site as the primary tumour) or distant (metastatic) disease, and progression to metastatic disease strongly impacts patient HRQoL, with metastatic disease associated with far worse HRQoL and survival outcomes in comparison to earlier stage disease.[46, 47, 49-52]

Consequently, there is universal agreement on the high unmet medical need for the earlier active treatment of patients with stage III disease following complete resection with clinically effective therapies that have the potential to reduce or prevent progression to metastatic disease, improve OS and potentially alleviate the morbidity and mortality burden associated with metastatic disease.

B.1.3.2 Clinical pathway of care

Current guidelines and treatment pathway

For stage III melanoma, the standard treatment approach is resection including removal of the primary tumour and associated lymph nodes. In approximately 90% of stage III patients, the primary melanoma and involved lymph nodes can be completely removed.[65] However, following complete resection, patients are still at a high risk of disease recurrence, with five- and ten-year RFS rates of 57% and 36%, respectively.[30, 44]

The management of stage III melanoma following resection is described in guidelines published by NICE[30] and associations such as the British Association of Dermatologists (BAD),[54] the European Society Medical Oncology (ESMO)[79] and consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians.[56] The recommendations from these guidelines are described in detail below, and summarised in Table 6. A schematic of the current UK treatment pathway for patients with resected stage III melanoma, with the expected positioning of dabrafenib plus trametinib, is presented in Figure 4.[30]

The BAD guidelines (2010)[54]

Although interferon-α-2b is the only systemic therapy licensed in the adjuvant setting in Europe,[53] clinical guidelines from BAD do not recommend the use of adjuvant interferon-α-2b. This is because its effect on disease free survival is of uncertain clinical relevance and although a meta-analysis of interferon studies showed a significant improvement in OS, the effect was small and associated with significant drug toxicity.[54]

In addition, the BAD guidelines recommend that, from the date of staging, clinical follow-up should be provided by a multi-disciplinary team (MDT) of dermatologists, surgeons and clinical nurse specialists every three months in years 1–3, every six months in years 4–5 and annually in years 6–10. Imaging with computed tomography (CT) should be carried out on the basis of clinical need, if considered appropriate by the MDT and eligible patients should be considered for clinical trials.[54]

Consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK (2013)[56]
This consensus paper represents the views of 49 of the UK's leading melanoma clinicians and provides an update to the BAD guidelines in terms of imaging surveillance (clinical review remains the same as described in the BAD guidelines). Clinical review is recommended every three months in years 1–3, every six months in years 4–5 and annually in years 6–10. Imaging is recommended at baseline, then every six-months in years 1–3 and annually up to year 5, and includes a CT scan of the chest, abdomen and pelvis *or* a positron emission tomography (PET) CT total body scan, and a magnetic resonance imaging (MRI) head scan.[56]

ESMO clinical practice guidelines (2015)[79]
The ESMO clinical practice guidelines were developed in accordance with ESMO standard operating procedures for clinical practice guidelines development and include assessment of relevant literature selected by the expert authors. The guidelines state that there is no consensus on the optimal schedule of frequency of follow-up visits, or on the utility of imaging and blood tests for patients with resected melanoma.[79]

NICE clinical guidelines for the management of melanoma (NG14, 2015)[30]
NICE recommend clinical follow-up with imaging for stage III disease following complete resection, at a schedule of every three months for the first three years post resection, then every six months for the next two years, and discharging them at the end of five years. The guidelines also recommend that adjuvant radiotherapy should *not* be offered in stage IIIA melanoma and should *only* offered in stage IIIB or IIIC melanoma, if a reduction in the risk of local recurrence outweighs the risk of significant adverse events (AEs).[30]

Table 6: Summary of clinical guidelines for management of stage III melanoma

Clinical guideline	Clinical guideline recommendations
BAD, 2010[54]	• Patients with stage IIIA melanoma should be seen 3-monthly for 3 years, then 6-monthly to 5 years (stage IIIA–IIIC), then annually to 10 years (stage IIIB–IIIC) • Imaging as considered appropriate by MDT
ESMO, 2015[79]	• There is no consensus on the optimal schedule or frequency of follow-up visits, or on the utility of imaging and blood tests for patients with resected melanoma
Consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK, 2013[56]	• Clinical review 3-monthly for 3 years, then 6-monthly to 5 years, then annually up to 10 years • Imaging at baseline, then every six-months in years 1–3 and annually up to year 5

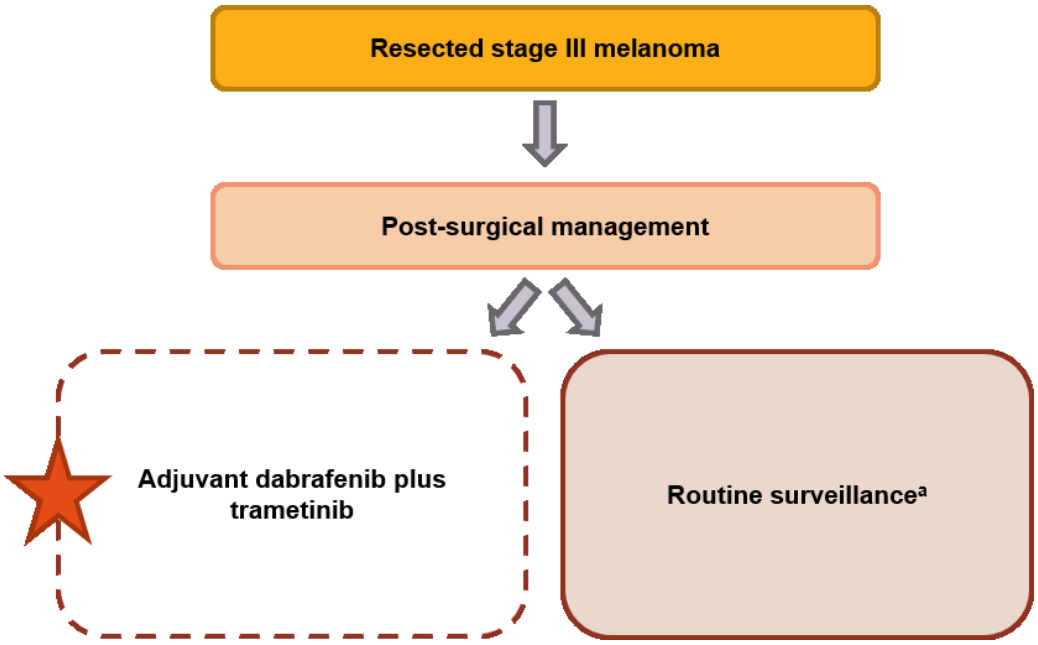
NICE (NG14), 2015[30]	• Clinical follow-up with imaging for stage III disease following complete resection
	• Consider follow-up 3-monthly for 3 years after completion of treatment, then 6-montly to 5 years
	• Consider surveillance imaging for people with stage III melanoma who would become eligible for systemic therapy as a result of early detection of metastatic disease if:
	  ○ There is a clinical trial of the value of regular imaging, or
	  ○ The specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging 6-monthly for 3 years is identified
	• Consider including the brain for people having imaging as part of follow-up; consider CT rather than MRI of the brain for adults having imaging as part of follow-up

Clinical guideline	Clinical guideline recommendations
	• Adjuvant radiotherapy *only* in stage IIIB or IIIC melanoma, if a reduction in the risk of local recurrence outweighs the risk of significant AEs.

Abbreviations: AE: adverse event; BAD: British Association of Dermatologists; CT: computed tomography; ESMO: European Society for Medical Oncology; MDT: multidisciplinary team; MRI: magnetic resonance imaging.
Source: Marsden *et al*. (2010),[54] Dummer *et al*. (2015),[79] Larkin *et al*. (2013),[56] NICE guidelines (NG14)[30]

In line with these guidelines, UK clinical experts agree that radiotherapy and interferon-α-2b are rarely used as adjuvant treatments in UK clinical practice.[57] Since the vast majority of patients receive no systemic adjuvant treatment post resection, UK clinical experts also agree that surveillance (routine clinical review and imaging) represents the SoC in the UK, and is the most relevant comparator for dabrafenib plus trametinib in the context of this appraisal (Figure 4).

Figure 4: Current treatment pathway for resected stage III melanoma in the UK and positioning of dabrafenib plus trametinib in the adjuvant setting



[a]No adjuvant systemic therapies are included in NG14.[30]
Source: Adapted from NICE NG14[30] and expert clinician feedback.[57]

Place of adjuvant therapy in the clinical pathway for melanoma in the UK

As described in Section B.1.3.1, patients with stage III melanoma following complete resection face a high risk of disease recurrence, associated with a reduction in HRQoL and many will ultimately die from metastatic disease.[44, 47] In the UK, there are currently no clinically effective therapies available in the adjuvant setting and the prevention of progression to metastatic disease remains an unmet treatment goal in the management of stage III melanoma patients.[82] A number of systemic adjuvant therapies are currently being investigated in clinical trials, but dabrafenib plus trametinib is the only targeted combination therapy to show a significant reduction in the risk of disease recurrence and a clinically meaningful survival benefit (compared to routine surveillance, the SoC), in patients with resected BRAF V600 positive stage III melanoma (Section B.2.6.2).[55]

Following the recent release of data from the COMBI-AD trial (the pivotal clinical trial for dabrafenib plus trametinib in this indication), the National Clinical Comprehensive Cancer Network (NCCN) guidelines for melanoma in the USA have been updated to include the recommendation for use of

dabrafenib plus trametinib in stage III melanoma with a BRAF V600 mutation, following complete resection.[83]

Although there is expected to be a slight increase in oncology clinic visits whilst patients are on treatment for 12 months with dabrafenib plus trametinib, expert clinician feedback indicates that the resource impact is unlikely to be significant since oncologists already have extensive experience administering this therapy in metastatic melanoma patients.[57] Dabrafenib plus trametinib represents a step change in the management of patients with resected stage III BRAF V600 positive melanoma, providing concomitant inhibition of the MAPK pathway in the adjuvant setting. The proposed licence extension of dabrafenib plus trametinib in the EU therefore offers a clinically effective treatment option with a manageable safety profile for patients with resected BRAF V600 positive stage III melanoma in the UK who are at high risk of disease recurrence and currently have very limited treatment options.[55]

B.1.4 Equality considerations

No equality issues related to the use of dabrafenib plus trametinib are foreseen.

B.2 Clinical effectiveness

Study identification

- A systematic literature review (SLR) identified one clinical trial of dabrafenib plus trametinib (COMBI-AD) relevant to the decision problem in this submission.
- COMBI-AD is an ongoing, randomised controlled trial comparing dabrafenib plus trametinib with two matching placebos in 870 patients with completely resected, histologically confirmed, BRAF V600 mutation-positive, stage III cutaneous melanoma; 86 patients participated in the UK.[55]

Efficacy (COMBI-AD)

- The first data cut was performed for the primary analysis on 30th June 2017 at a median follow-up of 2.8 years. This showed that dabrafenib plus trametinib improved RFS and OS compared to placebo. Investigator-assessed RFS was significantly longer for dabrafenib plus trametinib compared with placebo, representing a 53% lower risk of recurrence (hazard ratio [HR] for recurrence or death: 0.47; 95% confidence interval [CI]: 0.39–0.58; $p=1.53x10^{-14}$ by stratified log-rank test).[55]
    - The estimated HR for OS was 0.57 for dabrafenib plus trametinib versus placebo, representing a 43% reduction in death (95% CI: 0.42–0.79; p=0.0006).[55]
    - Significantly fewer patients had distant metastases or died (distant metastasis-free survival [DMFS]) in the dabrafenib plus trametinib arm than in the placebo arm (110 patients [25%] versus 152 [35%]; HR: 0.51; 95% CI: 0.40–0.65; p<0.001).[55]
    - Significantly fewer patients experienced disease recurrence (freedom from relapse [FFR]) in the dabrafenib plus trametinib arm versus the placebo arm (HR: 0.47; 95% CI: 0.39–0.57; p<0.001).[55]
- A meaningful and consistent improvement in RFS was observed across all stage III subgroups, and regardless of prognostic (e.g. lymph-node involvement or primary tumour ulceration) or demographic factors.[55]
- [redacted].[34]

Safety (COMBI-AD)

- The most frequently reported adverse events (AEs) in the dabrafenib plus trametinib arm were pyrexia (any grade, 63%; grade 3 or 4, 5%), fatigue (any grade, 47%; grade 3 or 4, 4%), and nausea (any grade, 40%; grade 3 or 4, <1%).[55]
- Overall, dabrafenib plus trametinib showed a manageable safety profile for use as an adjuvant therapy, consistent with that observed in patients with metastatic melanoma.[55]

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify relevant clinical evidence for the efficacy and safety of dabrafenib plus trametinib for the adjuvant treatment of stage III melanoma with a BRAF V600 mutation, following complete resection. The review was conducted and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines and full details of the SLR search strategy, study selection process and results are reported in Appendix D.[84]

The searches were conducted on 16–17th October 2017 and 3,054 records were identified and assessed for relevance. A total of two publications were identified as relevant to the decision problem: an abstract by Long *et al*. from the 2017 International Congress of the Society for Melanoma Research and a publication by Long *et al*. in the *New England Journal of Medicine* in 2017, both reporting on one unique clinical trial that investigated dabrafenib plus trametinib in the patient population of interest for this appraisal: COMBI-AD.[55, 85]

B.2.2 List of relevant clinical effectiveness evidence

One clinical trial was identified in the SLR that provides evidence for the efficacy and safety of dabrafenib plus trametinib in patients with resected BRAF V600 positive malignant melanoma.

The COMBI-AD trial is an ongoing randomised, placebo-controlled, double-blind, international, multicentre, phase III clinical trial investigating the efficacy and safety of dabrafenib plus trametinib in patients with resected BRAF V600 positive stage III melanoma.[55] An overview of COMBI-AD is provided in Table 7.

Table 7: Clinical effectiveness evidence

Study	COMBI-AD (NCT01682083)		
Study design	Randomised, placebo-controlled, double-blind, international, multicentre, phase III trial		
Population	Adult patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high risk (defined as stage IIIA [lymph node metastasis >1 mm], IIIB or IIIC) cutaneous melanoma; patients with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were also eligible		
Intervention(s)	Dabrafenib 150 mg BID plus trametinib 2 mg QD for 12 months		
Comparator(s)	Two matched placebos for 12 months		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Reported outcomes specified in the decision problem	• Relapse-free survival • Overall survival • Distant metastasis-free survival • Health-related quality of life (EQ-5D-3L) • Adverse effects of treatment		
All other reported outcomes	• Freedom from relapse		

Abbreviations: BID: twice daily; EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; QD: once-daily.
Source: Long *et al.* (2017).[55]

B.2.3 Summary of methodology of COMBI-AD

B.2.3.1 Trial design

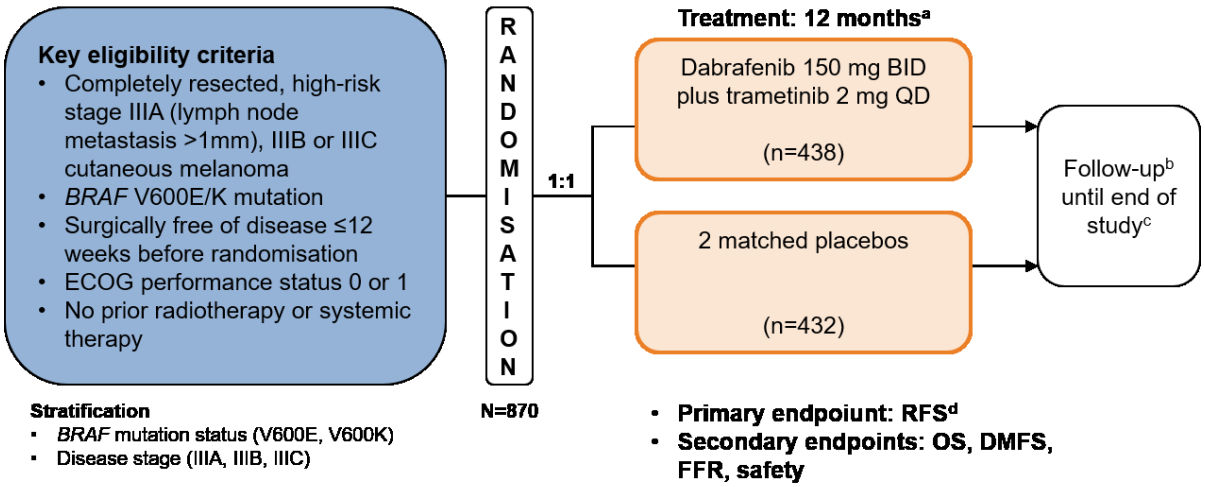
COMBI-AD is an ongoing randomised, placebo-controlled, double-blind, international, multicentre phase III clinical trial evaluating the safety and efficacy of dabrafenib plus trametinib versus two matched placebos as an adjuvant treatment for resected BRAF V600 positive stage III melanoma.

Patients with resected BRAF V600 positive, stage III melanoma were screened for eligibility for inclusion within the trial[55] and staging was completed as per the seventh edition (2009) of the AJCC staging system (the most recent available at the time of the trial).[41]

Between 31-Jan-2013 and 11-Dec-2014, a total of 870 patients were randomised in a 1:1 ratio to the treatment arm dabrafenib 150 mg twice-daily and trametinib 2 mg once-daily or the control arm two matching placebos. Patients in both arms received treatment for up to12 months or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent. Patients were followed for disease recurrence and survival during and after the treatment period.[55]

A schematic of the COMBI-AD study design is presented in Figure 5.

Figure 5: COMBI-AD trial design



[a]Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b]Patients were followed for disease recurrence until the first recurrence and thereafter for survival; [c]The study will be considered complete and final OS analysis will occur when ≈70% of randomised patients have died or are lost to follow-up; [d]New primary melanoma considered as an event.
Abbreviations: BID: twice daily; DMFS: distant metastasis–free survival; ECOG: Eastern Cooperative Oncology Group; FFR: freedom from relapse; OS, overall survival; QD: once daily; RFS: relapse-free survival.
Source: Long *et al*. (2017).[55]

The primary endpoint of COMBI-AD was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause.

Secondary endpoints were:

- Overall survival (OS), defined as the interval from randomisation to the date of death, irrespective of the cause of death;
- Distant metastasis free survival (DMFS), defined as the time from randomisation to the date of first distant metastasis or date of death, whichever occurred first;

- Freedom from relapse (FFR), defined as the time from randomisation to disease recurrence, with censoring of data for patients who had died from causes other than melanoma or treatment-related toxic effects; and safety.[55]

B.2.3.2 Trial methodology

A summary of the methodology and trial design of COMBI-AD is presented in Table 8.[34, 55, 86] Further details of the methodology of COMBI-AD, including the full eligibility criteria are reported in Appendix L.

Table 8: Summary of COMBI-AD study methodology

Trial name	COMBI-AD (NCT01682083)
Location	International: 169 sites in 26 countries in Europe (including 13 sites in the United Kingdom), North and South America, Asia and Oceania
Trial design	Randomised, international, multicentre, placebo-controlled, double-blind, phase III study
Eligibility criteria for participants	**Key inclusion criteria** • At least 18 years of age • Completely resected histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (classified by AJCC staging system, 7th edition [2009]); patients with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were also eligible • Must be surgically rendered free of disease no more than 12 weeks before randomisation • Recovered from definitive surgery • ECOG PS of 0–1 **Key exclusion criteria** • Known mucosal or ocular melanoma or the presence of unresectable in-transit metastases • Evidence of distant metastatic disease • Prior anti-cancer treatment including radiotherapy for melanoma. Prior surgery for melanoma was allowed • Taken an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to randomisation • Current or expected use of a prohibited medication • History of another malignancy, including melanoma or a concurrent malignancy (except if specified to be acceptable) A full list of inclusion and exclusion criteria is presented in Appendix L
Settings and locations where the data were collected	• The study was conducted in a secondary care (hospital) setting at 169 sites across 26 countries worldwide, including 13 sites in the United Kingdom • The study was conducted in accordance with Good Clinical Practice guidelines by qualified investigators
Intervention (n=438) and comparator (n=432)	• A total of 870 patients were randomised in a 1:1 ratio to receive either dabrafenib plus trametinib (n=438), or matched placebos (n=432) • Randomisation was performed centrally using a randomisation schedule • The following information for stratification was entered into the interactive voice response system in order to obtain stratified, random,

	blinded treatment assignment: ○ Mutation type (V600E or V600K) ○ Disease stage (IIIA, IIB, IIIC) • Patients in both arms received treatment for up to 12 months or until disease recurrence, death, unacceptable toxicity or withdrawal of consent occurred.
Method of study drug administration	• Dabrafenib, 150 mg BID plus trametinib, 2 mg QD • The first dose of dabrafenib plus trametinib (or matched placebos) were administered in the morning at approximately the same time every day • The second dose of dabrafenib (or dabrafenib placebo) was administered approximately 12 hours after the morning dose • Study medication was taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal
Permitted and disallowed concomitant medication	The following medications were prohibited during the study: • Other anti-cancer therapies • Other investigational drugs • Antiretroviral drugs • Herbal remedies (e.g. St John's Wort) • Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 were to be used under exception and investigator guidance when the study treatment was interrupted, due to potential for drug-drug interactions between dabrafenib and these drugs The following medications were to be used with caution due to the potential for drug-drug interactions between dabrafenib and these drugs: • Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8. • Drugs that are substrates for CYP3A4, CYP2C9, CYP2B6, CYP2C8, CYP2C19, UDP-glucuronyl transferases and transporters • Warfarin The investigator was to be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment. If required, patients would receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeals, analgesics, and other care as deemed appropriate and in accordance with their institutional guidelines
Primary outcomes	RFS, defined as the time from randomisation to disease recurrence or death from any cause, assessed by clinical examination and imaging by means of computed tomography (CT), magnetic resonance imaging (MRI), or both. Imaging was performed every three months during the first 24 months, then every six months until disease recurrence or the completion of the trial
Secondary and exploratory outcomes	**Secondary outcomes** • OS, DMFS, FFR (as defined in B.2.3.1) • Safety **Exploratory outcomes** • HRQoL • Pharmacokinetics and exploration of exposure-response relationships of dabrafenib, dabrafenib metabolites and trametinib* • Molecular characterisation of relapses, analysis of predictive prognostic

	markers, assessment of immune function, characterisation of mechanisms underlying adverse events of special interest and molecular characterisation of treatment-emergent malignancies* • Analysis of levels of circulating cfDNA as an early predictor of disease recurrence or metastasis* • Relationship between genetic variants in host DNA and the PK, safety, tolerability and efficacy of each therapeutic treatment* *Note these outcomes are not presented within this submission as they are not part of the decision problem
Pre-planned subgroups	The following subgroups were explored in the analysis of RFS: • Mutation status: BRAF V600K-positive, BRAF V600E-positive • Disease stage: IIIA, IIIB, IIIC • Gender: Male, female • Age at screening: <65 years, ≥65 years • Race: White, Asian, Other • Region: North America (USA and Canada), Europe and Israel, Asia, Pacific (excluding Australia and New Zealand), South America, Australia and New Zealand • Nodal metastatic mass: micrometastasis, macrometastasis • Nodal metastatic mass and primary tumour ulceration: micrometastasis and ulceration, micrometastasis and no ulceration, macrometastasis and ulceration, macrometastasis and no ulceration
Discontinuation of study treatment and premature patient withdrawal	• The treatment period was 12 months. Discontinuation of study treatment could occur earlier than 12 months for disease recurrence, death, unacceptable toxicity or withdrawal of consent • Subjects who had not died, but who were no longer being followed for disease recurrence or survival were considered to have discontinued from the study • The study will be considered complete, and the final OS analysis will be conducted when approximately 70% of the total number of randomised subjects have died
Duration of study and follow-up	• Before disease recurrence, subjects were followed for disease recurrence every three months after the end of treatment until Month 24 and every six months after Month 24 • After disease recurrence, subjects remained on study follow-up assessments every three months until Month 24, and then every six months after Month 24,

Abbreviations: BID: twice daily; cfDNA: cell-free DNA; CT: computed tomography; DMFS: distant metastasis-free survival; DNA: deoxyribonucleic acid; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FFR: freedom from relapse; HRQoL: health-related quality of life; MRI: magnetic resonance imaging; OS: overall survival; PK: pharmacokinetics; QD: once daily; RFS: relapse-free survival.
Source: COMBI-AD CSR,[34] Long *et al.* (2017)[55] and ClinicalTrials.gov.[86]

B.2.3.3 Baseline characteristics

Baseline demographics, disease characteristics and a summary of prior therapies of the patients included in the intention-to-treat (ITT) population of COMBI-AD are presented in Table 9.[34, 55]

The baseline demographic characteristics were well-balanced between the two trial arms, including those that may be prognostic indicators for melanoma (e.g. number of nodal metastases, primary tumour ulceration and micrometastasis versus macrometastasis).[67]

[redacted]

Feedback from UK expert clinicians in a recent advisory board meeting was that the interim analysis appears to be robust and that there were no limitations or biases that would be introduced by generalising from COMBI-AD to UK clinical practice.[57] The study included 13 UK centres, and collectively recruited 86 patients in total.[34, 57]

Table 9: Baseline characteristics (ITT population)[a]

Characteristic	Dabrafenib plus trametinib (N=438)	Placebo (N=432)
Demographics		
Age, median years (range)	50 (18–89)	51 (20–85)
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Disease characteristics		
BRAF mutation status, n (%)		
V600E	397 (91)	395 (91)
V600K[b]	41 (9)	37 (9)
ECOG performance status, n (%)		
0	402 (92)	390 (90)
1	33 (8)	41 (9)
Unknown	3 (1)	1 (<1)
Disease stage, n (%)		
IIIA	83 (19)	71 (16)
IIIB	169 (39)	187 (43)
IIIC	181 (41)	166 (38)
III unspecified	5 (1)	8 (2)
Number of positive lymph nodes, n (%)		
1	177 (40)	183 (42)
2 or 3	158 (36)	150 (35)
≥4	73 (17)	72 (17)
Unknown	30 (7)	27 (6)
Type of lymph-node involvement, n (%)		
Microscopic	152 (35)	157 (36)
Macroscopic	158 (36)	161 (37)
Unknown	128 (29)	114 (26)
Primary tumour ulceration, n (%)		
Yes	179 (41)	177 (41)
No	253 (58)	249 (58)
Unknown	6 (1)	6 (1)

Characteristic	Dabrafenib plus trametinib (N=438)	Placebo (N=432)
In-transit metastases, n (%)[c]		
Yes	51 (12)	36 (8)
No	387 (88)	395 (91)
Unknown	0	1 (<1)
Prior therapy		
Sentinel lymphadenectomy, n (%)	[redacted]	[redacted]
Lymph node dissection, n	[redacted]	[redacted]
Median number of lymph node removed	[redacted]	[redacted]

[a]% values may not total 100 due to rounding. [b]One patient who had both a BRAF V600E mutation and a BRAF V600K mutation is included in the V600K subgroup. [c]In-transit metastases are clinically evident cutaneous or subcutaneous metastases identified at a distance of more than 2 cm from the primary melanoma in the region between the primary melanoma and the first echelon of regional lymph nodes.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; ITT: intention-to-treat; TNM: tumour, node, metastasis.
Source: COMBI-AD CSR[34] and Long *et al.* (2017).[55]

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

The definitions of the study populations analysed from COMBI-AD are presented in Table 10 below.[34, 55]

Table 10: Trial populations used for the analysis of outcomes in COMBI-AD

Analysis set	Definition
ITT population (N=870) **Dabrafenib plus trametinib arm (n=438)** **Placebo arm (n=432)**	• Primary population used for efficacy analysis • Describes all randomised patients, regardless of whether they received study drug • Any patient who received a treatment randomisation number was considered to have been randomised
Safety population (N=867) **Dabrafenib plus trametinib arm (n=435)** **Placebo arm (n=432)**	• Population used for clinical safety data and PK analysis, therefore includes all patients who received at least one dose of study drug
Pharmacokinetics population ([redacted])	• All patients from the Safety population for whom a PK sample was obtained and analysed

Abbreviations: ITT: intention-to-treat; PK: pharmacokinetic.
Source: COMBI-AD CSR[34] and Long *et al.* (2017).[55]

The statistical analyses used to calculate the primary endpoint (investigator-assessed RFS), alongside sample size calculations and methods for handling missing data, are presented in Table 11.[34, 55]

Table 11: Statistical methods for the primary analysis of COMBI-AD

Trial	COMBI-AD
Hypothesis objective	The primary objective of this two-arm study is to evaluate the efficacy of dabrafenib plus trametinib compared to placebos with respect to RFS for subjects with stage III, resected BRAF V600E/K mutation-positive melanoma
Statistical analysis	• RFS was summarised using Kaplan-Meier estimates and compared between treatment arms using a stratified log-rank test (using randomisation stratification factors) in the ITT population • The Pike estimator HR was provided, together with a 95% CI. The Pike estimator, which is a nonparametric estimator of the HR, was specifically developed for survival data and is used as a measure of the relative survival experience of two groups. Within the range of values of the ratio of the hazard rates of interest in clinical trials, Pike estimator is more efficient in terms of mean square error than the Cox proportional hazard method • Median times to RFS with first and third quartiles were presented, along with 95% CI, based on the Brookmeyer-Crowley method with linear transformation function • OS analysis used a pre-planned three-look Lan-DeMets group sequential design with an O-Brien-Fleming-type boundary which was used to determine the significance threshold for the first interim OS analysis.
Sample size, power calculation	• The following assumptions were made to estimate the required sample size: ○ Exponential survival distributions ○ An HR of 0.71 (median RFS times of 15 and 21 months in the placebo arm and the dabrafenib plus trametinib arm, respectively) ○ A 1:1 randomisation scheme ○ An overall 5%, two-sided risk of erroneously claiming superiority of dabrafenib plus trametinib in the presence of no true underlying difference (i.e. overall Type I error) ○ A 95% chance of successfully claiming superiority of the dabrafenib plus trametinib in the presence of a true underlying difference (i.e. power or 1-Type II error) ○ An accrual rate of 42 patients per month over 20.3 months ○ A dropout rate of 5% for the placebo arm and 15% for the combination arm • To enable the observation of 467 total events, an estimated total of 852 patients (i.e. approximately 426 patients in each of the arms) would need to be enrolled, leading to implementation of final analyses at approximately 32 months after the start of the study • The final OS analysis is to be performed when approximately 597 deaths are observed which would provide 80% power to detect a HR of 0.793 (corresponding to median OS times of 48 and 60.5 months in the placebo and the combination arm, respectively) • The final primary RFS analysis was to be performed at the pre-defined cut-off date of 30th June 2017, by which time it was expected that approximately 410 RFS events would have accrued, which would provide more than 90% power to detect the targeted HR of 0.71
Data management, patient withdrawals	• Patients with no event by the cut-off date for the primary analysis were censored at the date of the last efficacy assessment (i.e. radiological or non-radiological) prior to the analysis cut-off. Patients lost to follow-up prior to disease recurrence were censored • Patients who started subsequent anti-cancer therapy prior to disease recurrence were censored at the date of last efficacy assessment (either radiological or non-radiological) before the initiation of subsequent anti-cancer therapy. Patients for whom an event occurred after a period of extended lost-to-follow-up were censored

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; RFS: relapse-free survival.
Source: COMBI-AD CSR[34] and Long *et al*. (2017).[55]

If the primary analysis of RFS was found to be significant, statistical analyses of secondary endpoints would be performed to supplement the primary analysis and facilitate the comprehensive description of efficacy results, including an interim analysis of OS.

The two-sided threshold for significance at first interim analysis of OS was set at P=0.000019. If the interim analysis of OS was not significant at this stage, the final OS analysis would be performed when 70% of the total number of randomised subjects had died. If the interim analysis of OS was significant, no further formal analysis would be performed.

B.2.4.1 Participant flow in the relevant randomised controlled trials

In total, 870 patients were randomised between 31st January 2013 and 11th December 2014: 438 patients in the dabrafenib plus trametinib arm and 432 patients in the placebo arm. A total of three patients in the dabrafenib plus trametinib arm were not treated.[55] [redacted] In the UK, 86 patients were included in the ITT analysis: [redacted][34]

The last dose of a study drug was administered in December 2015, and all the patients had completed the trial treatment period at the time of the data cut-off (30th June 2017). At the time of cut-off 272 patients (63%) had completed all scheduled doses of dabrafenib and 163 patients (37%) had discontinued treatment with dabrafenib. Out of the 163 patients who discontinued, 108 were due to AEs, 23 due to disease recurrence and 32 for other reasons.

At the time of cut-off, 277 patients (64%) had completed all scheduled doses with trametinib and 158 patients (36%) had discontinued treatment, due to AEs (n=104), disease recurrence (n=23) or other reasons (n=31). In the placebo arm, 227 patients (53%) completed treatment and 205 (47%) discontinued, due to AEs (n=12), disease recurrence (n=175) or other reasons (n=18).[55]

Full details of the participant flow (CONSORT diagram) for COMBI-AD are reported in Appendix D.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A risk of bias assessment for COMBI-AD was conducted using the CRD cohort study checklist and the NICE risk of bias tool. COMBI-AD scored well across all domains and these tools indicated that randomisation, concealment of treatment allocation and blinding were adequate. Therefore, this assessment indicates that COMBI-AD is a well-conducted, high-quality RCT. Full details of the quality assessment is reported in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Primary endpoint: relapse-free survival (RFS)

Investigator-assessed RFS was chosen as the primary efficacy endpoint for the COMBI-AD study, because RFS is a direct measurement of anti-tumour effect because it will not be subject to confounding from subsequent therapy, as would OS. Since relapses are accompanied by considerable disease- and treatment-related morbidity, RFS is a true measure of patient benefit.[34]

RFS was defined as the time from randomisation to disease recurrence or death from any cause (note that the term 'recurrence-free survival' is interchangeable with 'relapse-free survival' or 'disease-free survival', and they all appear in related literature).[57] The analysis of RFS was based on the ITT population (Table 10).[55]

RFS events were defined as:

- Occurrence of loco-regional or distant metastases,
- Identification of a new primary melanoma,
- Occurrence of death without prior documentation of tumour recurrence (and not censored in the statistical analysis)[55]

As of the data cut-off for the primary analysis (30th June 2017), median follow-up time was [redacted] in the dabrafenib plus trametinib arm and [redacted] in the placebo arm.[34]

RFS events (disease recurrence or death) had occurred in 166 (38%) of 438 patients in the dabrafenib plus trametinib arm and in 248 (57%) of 432 patients in the placebo arm.

The RFS analysis only included the first recurrence event and as such, if a patient experienced a loco-regional recurrence first followed by a distant recurrence at a later time point, only the former one was counted as an event. In addition, patients who experienced several types of recurrence on the same day were counted in several categories of recurrence subtypes.[34] At the time of first recurrence, 54 patients (12%) in the dabrafenib plus trametinib arm had experienced loco-regional recurrence, 7 (2%) had both local and distant recurrence and 96 (22%) had a distant recurrence, as compared with 107 (25%), 7 (2%) and 126 (29%), respectively, in the placebo group.[55] Full results of the RFS analysis are summarised in Table 12.

RFS was significantly longer in the dabrafenib plus trametinib arm than in the placebo arm, representing a 53% lower risk of relapse (HR for relapse or death: 0.47; 95% CI: 0.39–0.58; p<0.001 by stratified log-rank test). Median RFS in the dabrafenib plus trametinib arm had not yet been reached due to the low event rate (95% CI: 44.5–not reached) and median RFS in the placebo arm was reached at 16.6 months (95% CI: 12.7–22.1 months).[55]

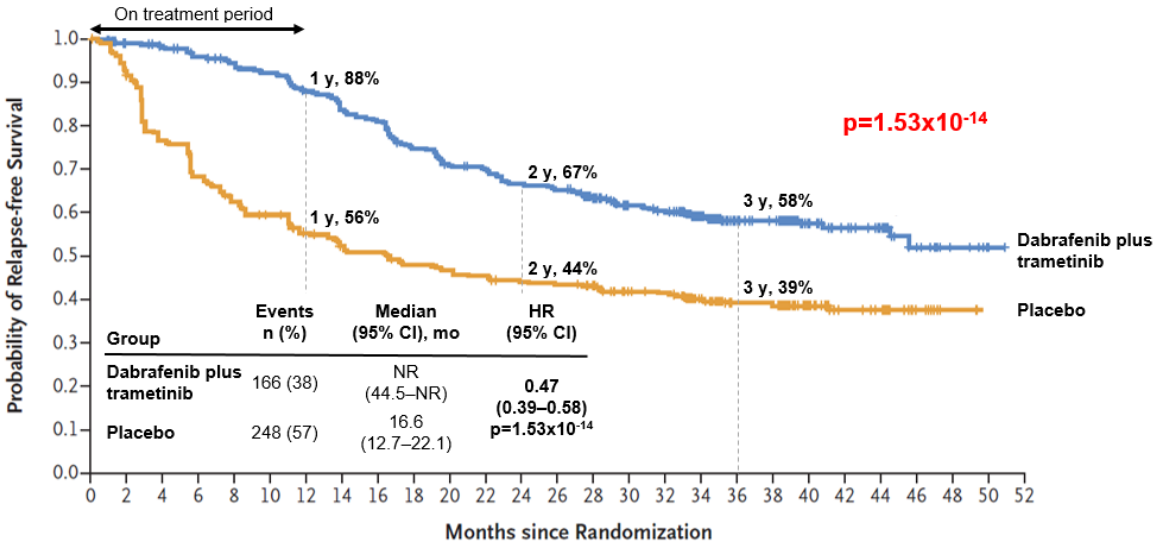
The Kaplan-Meier plot for RFS is presented in Figure 6 and shows a clear separation of the respective curves for dabrafenib plus trametinib and placebo from approximately three months onwards, corresponding to the first tumour assessment in the study. The RFS curve remains consistently higher for the dabrafenib plus trametinib treatment arm relative to placebo at all subsequent time points, thereby indicating an early and also sustained advantage with dabrafenib plus trametinib versus placebo.[34, 55] The estimated RFS rates at 1, 2, and 3 years in the dabrafenib plus were 88% at 1 year, 67% at 2 years, and 58% at 3 years in the compared with rates of 56%, 44%, and 39%, respectively, in the placebo arm.[55]

Table 12: Summary of investigator-assessed RFS in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population)

	Dabrafenib plus trametinib (N=438)	Placebo (N=432)
Number of Investigator-assessed RFS events recorded, n (%)	166 (38)	248 (57)
Recurrence (event)[a], n (%)	163 (37)	247 (57)
Loco-regional recurrence only	54 (12)	107 (25)
Local and distant recurrence	7 (2)	7 (2)
Distant recurrence only	96 (22)	126 (29)
Death without prior tumour recurrence n (%)	3 (<1)	1 (<1)
Censored, follow-up ended[b], n (%)	[redacted]	[redacted]
Censored, follow-up ongoing[b], n (%)	[redacted]	[redacted]
HR (95% CI) vs placebo	0.47 (0.39–0.58)	
P-value	1.53×10^{-14}	
Kaplan-Meier estimate, (95% CI)		
1-year RFS rate	0.88 [redacted]	0.56 [redacted]
2-year RFS rate	0.67 [redacted]	0.44 [redacted]
3-year RFS rate	0.58 [redacted]	0.39 [redacted]

[a]Relapsed event subtypes (local recurrence, distant recurrence) are not mutually exclusive. [b]Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from the study by the data cut-off for the primary analysis (30th June 2017). Patients censored with follow-up ended are the remaining censored patients.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; RFS: relapse-free survival.
Source: COMBI-AD CSR,[34] Long *et al.* (2017).[55]

Figure 6: Kaplan-Meier plot for investigator-assessed RFS (primary analysis; ITT population)[a]



No. at Risk

Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

[a]As of data cut-off for the primary analysis (30th June 2017).
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reached; RFS: relapse-free survival.
Source: COMBI-AD CSR,[34] Long *et al.* (2017).[55]

B.2.6.2 Secondary endpoints

Overall survival (OS)

As the primary endpoint of the study was met and was statistically significant ($p=1.53x10^{-14}$) the key secondary endpoint of OS was formally tested. OS was defined as the time interval from randomisation to the date of death, irrespective of the cause of death.[55]

At the time of the data cut-off for the primary analysis (30th June 2017), 153 deaths had occurred; 60 (14%) in the dabrafenib plus trametinib arm and 93 (22%) in the placebo arm, representing 26% of the total targeted 597 deaths required for the final OS analysis.[55] The most common cause of death was melanoma, which occurred in 54 patients (12%) in the dabrafenib plus trametinib arm and 77 patients (18%) in the placebo arm. For all other deaths, 6 in the dabrafenib plus trametinib arm and 16 in the placebo arm, the cause of death was listed as "other", which includes pneumonia, haemorrhage, trauma, suicide, other cancer and heart failure, or unknown.[55] The results of the OS analysis are summarised in Table 13.

Median OS was not reached in either arm since the OS data are still immature due to the low number of events observed. 331 (76%) patients in the dabrafenib plus trametinib arm and 277 (64%) patients in the placebo arm were censored and are still being followed for OS events.[55] Censoring was performed using the date of the last known contact for those who were alive at the time of analysis. Follow-up for the remaining 47 patients (11%) and 62 patients (14%) in the dabrafenib plus trametinib arm and placebo arms, respectively, has ended.

The estimated rate of OS was 97% at 1 year, 91% at 2 years, and 86% at 3 years in the dabrafenib plus trametinib arm, compared with rates of 94%, 83%, and 77%, respectively, in the placebo arm.

The estimated HR for OS was 0.57 (95% CI: 0.42–0.79; p=0.0006). Despite this low p-value, the between-arm difference was not statistically significant because it did not cross the pre-specified conservative interim boundary of p=0.000019. Nevertheless, this result shows a clinically meaningful improvement in OS, which is considered promising given the proven statistically and clinically significant OS benefit observed with dabrafenib plus trametinib in metastatic disease.[21-26]

As per the study's statistical analysis plan (see Section B.2.4), the final OS analysis will be performed when 70% of the total number of randomised subjects have died (i.e. approximately 597 deaths).[55] [redacted].[34]

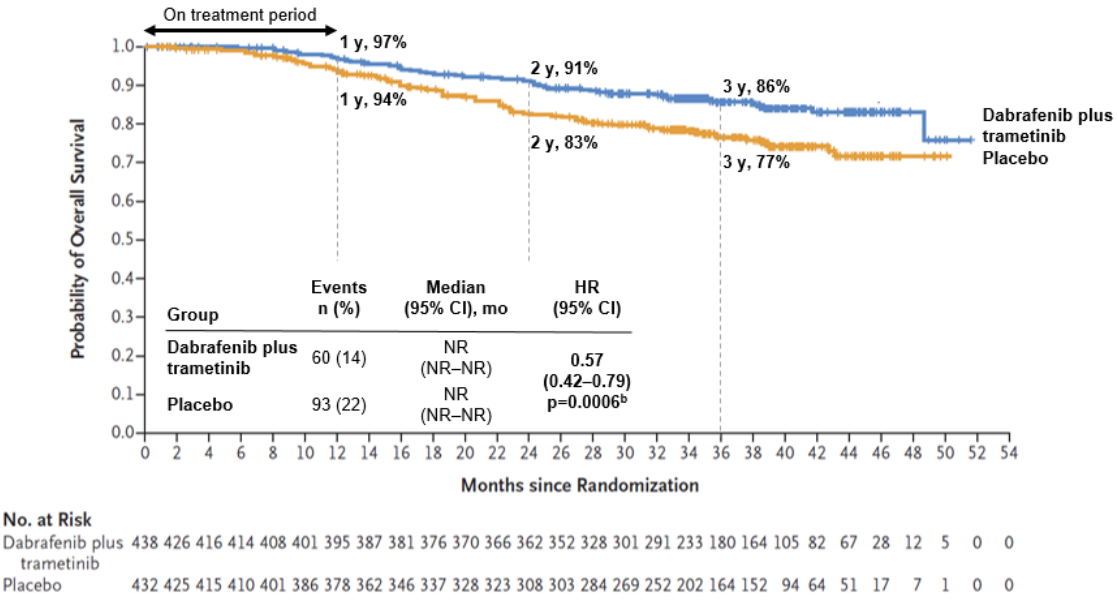
The Kaplan-Meier plot for the first interim analysis of OS is presented in Figure 7 and shows a separation of the respective curves for dabrafenib plus trametinib and placebo from approximately ten months onwards. The OS curve remains consistently higher for the dabrafenib plus trametinib treatment arm relative to placebo at all subsequent time points, thereby indicating a sustained OS advantage with dabrafenib plus trametinib versus placebo.[34, 55]

Table 13: Summary of OS in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population)

	Dabrafenib plus trametinib (N=438)	Placebo (N=432)
Died (event), n (%)	60 (14)	93 (22)
Censored, follow-up ended[a], n (%)	47 (11)	62 (14)
Censored, follow-up ongoing[a], n (%)	331 (76)	277 (64)
HR (95% CI) vs placebo	0.57 (0.42–0.79)	
P-value	$6x10^{-4}$	
Kaplan-Meier estimate, (95% CI)		
1-year OS rate	0.97 [redacted]	0.94 [redacted]
2-year OS rate	0.91 [redacted]	0.83 [redacted]
3-year OS rate	0.86 [redacted]	0.77 [redacted]

[a]Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from the study by the data cut-off for the primary analysis (30th June 2017). Patients censored with follow-up ended are the remaining censored patients.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival.
Source: COMBI-AD CSR[34] and Long *et al.* (2017).[55]

Figure 7: Kaplan-Meier plot for OS (primary analysis; ITT population)[a]



[a]As of data cut-off for the primary analysis (30th June 2017). [b]Prespecified significant boundary p=0.000019.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; NR: not reached; OS: overall survival.
Source: COMBI-AD CSR,[34] Long *et al.* (2017).[55]

Distant metastasis-free survival (DMFS)

DMFS was defined as the interval from randomisation to the date of first distant metastasis or date of death, whichever occurred first. As of the data cut-off for the primary analysis (30th June 2017), [redacted][34] Significantly fewer patients had distant metastases or died in the dabrafenib plus trametinib arm than in the placebo arm (110 patients [25%] versus 152 [35%]; HR: 0.51; 95% CI: 0.40–0.65; p<0.001). The median DMFS was not reached in either treatment arm due to the low event rates.[55] The results of the DMFS analysis are summarised in Table 14. [redacted].[34]

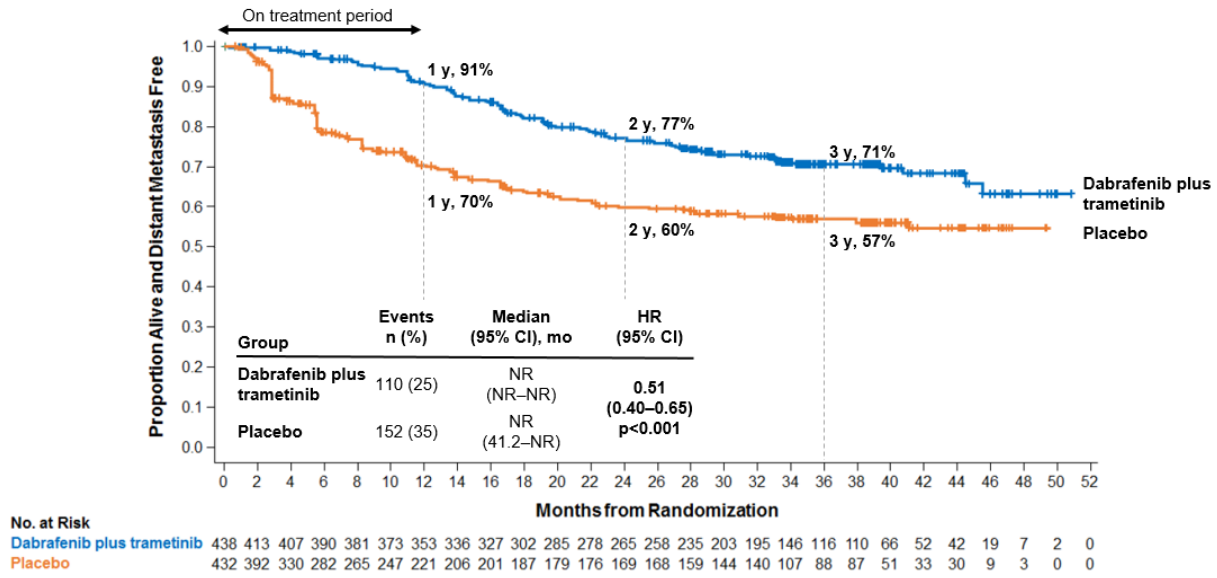
The Kaplan-Meier plot for DMFS is presented in Figure 8 and, as for the Kaplan-Meier plot for RFS, shows a clear separation of the respective curves for dabrafenib plus trametinib and placebo early on in the study. The DMFS curve remains consistently higher for the dabrafenib plus trametinib arm relative to placebo at all subsequent time points, thereby indicating an early and sustained advantage with dabrafenib plus trametinib versus placebo.[34, 55]

Table 14: Summary of DMFS in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population)

	Dabrafenib plus trametinib (N=438)	Placebo (N=432)
DMFS (event), n (%)	110 (25)	152 (35)
Relapsed (event)	[redacted]	[redacted]
Died (event)	[redacted]	[redacted]
Censored, follow-up ended[a], n (%)	[redacted]	[redacted]
Censored, follow-up ongoing[a], n (%)	[redacted]	[redacted]
HR (95% CI) vs placebo	0.51 (0.40–0.65)	
P-value	<0.001	

[a]Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from the study by the data cut-off for the primary analysis (30th June 2017). Patients censored with follow-up ended are the remaining censored patients.
Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival; HR: hazard ratio; ITT: intention-to-treat.
Source: COMBI-AD CSR[34] and Long *et al.* (2017).[55]

Figure 8: Kaplan-Meier plot for investigator-assessed DMFS (ITT population)[a]



[a]As of data cut-off for the primary analysis (30th June 2017).
Abbreviations: CI: confidence interval; DMFS: distant metastasis-free survival; HR: hazard ratio; ITT: intention-to-treat.
Source: COMBI-AD CSR,[34] Long *et al.* (2017).[55]

Freedom from relapse (FFR)

FFR was defined as the interval from randomisation to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death. As of the data cut-off for the primary analysis (30th June 2017), the FFR event analysis included a total of 412 disease- or treatment-related relapses or deaths. Among these, 163 (37%) events of relapse and [redacted] occurred in the dabrafenib plus trametinib arm, and 247 (57%) events of relapse and [redacted] occurred in the placebo arm. Significantly fewer patients relapsed in the dabrafenib plus trametinib arm in comparison with the placebo arm (HR: 0.47; 95% CI: 0.39–0.57; p<0.001).[55] The results of the FFR analysis are summarised in Table 15.

Median FFR was 16.6 months in the placebo arm and was not reached in the dabrafenib plus trametinib arm.[55] [redacted][34]

The FFR results are closely correlated to those of RFS, as both analyses included similar numbers of relapse or death as events (one death in each arm counted as events for RFS was censored for FFR analysis as the deaths occurred due to reasons other than melanoma).[55]

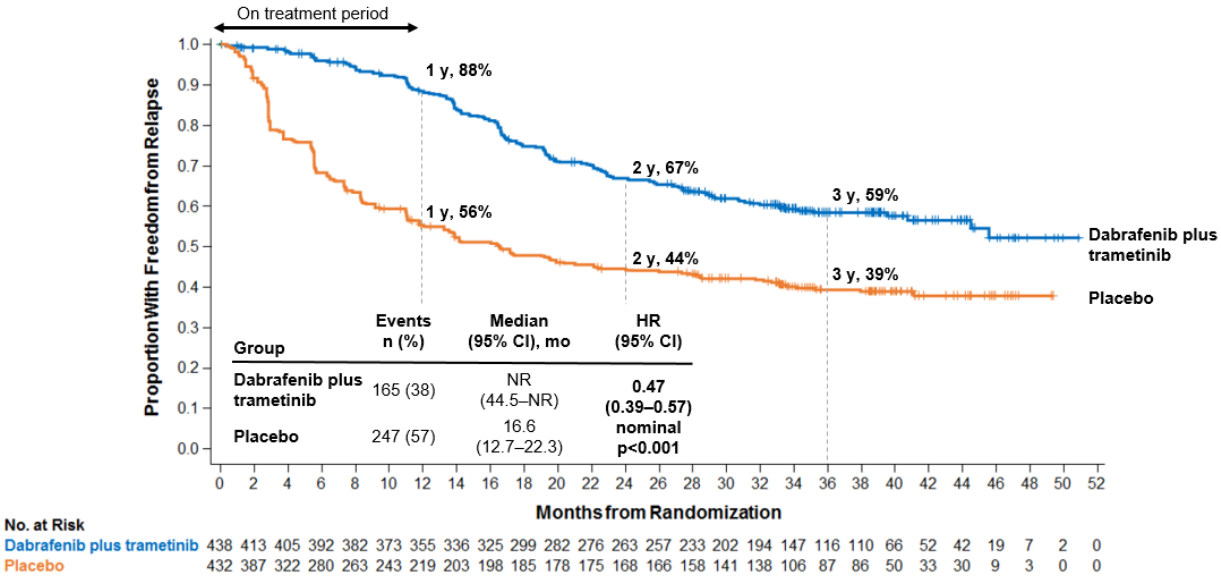
The Kaplan-Meier plot for FFR is presented in Figure 9 and, similarly to the Kaplan-Meier plot for RFS and DMFS, shows a clear separation of the respective curves for dabrafenib plus trametinib and placebo very early on in the study. The probability of FFR remains consistently higher for the dabrafenib plus trametinib arm relative to placebo at all subsequent time points, thereby indicating an early and sustained advantage with dabrafenib plus trametinib versus placebo.[34, 55]

Table 15: Summary of FFR in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis (ITT population)

	Dabrafenib plus trametinib (N=438)	Placebo (N=432)
FFR (event), n (%)	165 (38)	247 (57)
Relapsed (event)	163 (37)	247 (57)
Died (event)	2 (<1)	0 (0)
Censored, follow-up ended[a], n (%)	[redacted]	[redacted]
Censored, follow-up ongoing[a], n (%)	[redacted]	[redacted]
HR (95% CI) vs placebo	0.47 (0.39–0.57)	
P-value	<0.001	

[a]Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from the study by the data cut-off for the primary analysis (30th June 2017). Patients censored with follow-up ended are the remaining censored patients.
Abbreviations: CI: confidence interval; FFR: freedom from relapse; HR: hazard ratio; ITT: intention-to-treat.
Source: COMBI-AD CSR[34] and Long *et al.* (2017).[55]

Figure 9: Kaplan-Meier plot for investigator-assessed FFR (ITT population)[a]



[a]As of data cut-off for the primary analysis (30th June 2017).
Abbreviations: CI: confidence interval; FFR: freedom from relapse; HR: hazard ratio; ITT: intention-to-treat; NR: not reached.
Source: COMBI-AD CSR,[34] Long *et al.* (2017).[55]

B.2.6.3 Patient-reported outcomes

HRQoL within the COMBI-AD trial was assessed via the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire.[34] Although no disease-related symptoms are expected to occur following complete resection in the adjuvant setting, the assessment of HRQoL using the EQ-5D-3L provides a comprehensive assessment of patient wellbeing throughout the treatment period, particularly in relation to any potential negative effects that treatment may have on HRQoL .[34]

As of the data cut-off for the primary analysis (30th June 2017), EQ-5D-3L questionnaire completion rates, as a percentage of available patients at the time of assessment, [redacted] between the two arms at the Month 12 assessment ([redacted] in the dabrafenib plus trametinib arm and [redacted] in the placebo arm).

[redacted] and throughout the treatment period, [redacted]

When assessed for differences between treatment arms using mixed-model repeated measures analyses, [redacted]
However, it should be noted that the study was not powered to observe a difference in HRQoL.[34]

[redacted][34]

Figure 10: Summary of EQ-5D-3L utility scores in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

Patient numbers for each data point are reported in Table 16.
Abbreviations: EQ-5D-3L: EuroQol 5-Dimensions 3-Levels.
Source: COMBI-AD CSR.[34]

Table 16: Summary of EQ-5D-3L utility scores in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

Abbreviations: EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; HRQoL: health-related quality of life.
Source: COMBI-AD CSR.[34]

B.2.6.4 Concomitant medications

The majority of patients received at least one concomitant medication during the study treatment and follow-up, with similar frequencies in each arm [redacted]; Table 17).[34]

[redacted] These results show that the majority of patients did not receive prophylactic treatment for these two commonly observed AEs.[34]

[redacted]

Table 17: Summary of concomitant medications received by ≥5% patients during COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

	Dabrafenib plus trametinib (N=435)	Placebo (N=432)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: COMBI-AD CSR.[34]

B.2.6.5 Post-recurrence therapies

As of the primary data analysis cut (30th June 2017), a lower proportion of patients in the dabrafenib plus trametinib arm (28%) compared to the placebo arm (42%) received any systemic anti-cancer therapy post-recurrence, which is primarily due to a higher number of disease relapses in the placebo arm. A summary of the therapies received post-disease recurrence in all patients who received at least one dose of either dabrafenib plus trametinib or matched placebos (safety population) is presented in Appendix M.

Within the patients who experienced disease recurrence (Table 18), a similar proportion of patients in the dabrafenib plus trametinib arm received any anti-cancer therapy post-recurrence compared to the placebo arm ([redacted] versus [redacted], respectively),). The percentage of patients who received any systemic anti-cancer therapy post-recurrence was also similar across both arms: [redacted] ([redacted]) and [redacted] ([redacted]) in the dabrafenib plus trametinib arm versus the placebo arm, respectively. [redacted] patients in the dabrafenib plus trametinib arm received immunotherapy compared to the placebo arm ([redacted] versus [redacted]); chemotherapy was administered to [redacted] patients in the dabrafenib plus trametinib arm and [redacted] ([redacted]) patients in the placebo arm. [redacted] were the most commonly used targeted agents[34]

Given the markedly prolonged time to disease recurrence in the dabrafenib plus trametinib arm, and the fact that immunotherapies and BRAF and MEK inhibitors (single agent or combination) have proven to be effective treatments in metastatic melanoma, these data suggest that the higher survival rate in the dabrafenib plus trametinib arm resulted from the trial drugs and not from post-recurrence therapies.[55] Median time from disease recurrence to the start of subsequent anti-cancer therapy was similar between the two arms (7.1 weeks for dabrafenib plus trametinib and 7.3 weeks for placebo).[55]

Table 18: Summary of post-treatment anti-cancer therapy in subjects with disease recurrence in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

	Dabrafenib plus trametinib (N=163)	Placebo (N=247)
Any anti-cancer therapy, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Any systemic anti-cancer therapy, n (%)	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Small molecule targeted therapy	[redacted]	[redacted]
Any BRAF inhibitor	[redacted]	[redacted]
Any MEK inhibitor	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Biologic therapy	[redacted]	[redacted]
Investigational treatment	[redacted]	[redacted]
Other therapy	[redacted]	[redacted]

Source: COMBI-AD CSR.[34]

B.2.7 Subgroup analysis

Heterogeneity in survival among subgroups of patients with stage III disease has been observed in previous studies, with important differences in prognosis based on underlying melanoma-specific factors (e.g. number of nodal metastases, primary tumour ulceration and micrometastasis versus macrometastasis).[67]

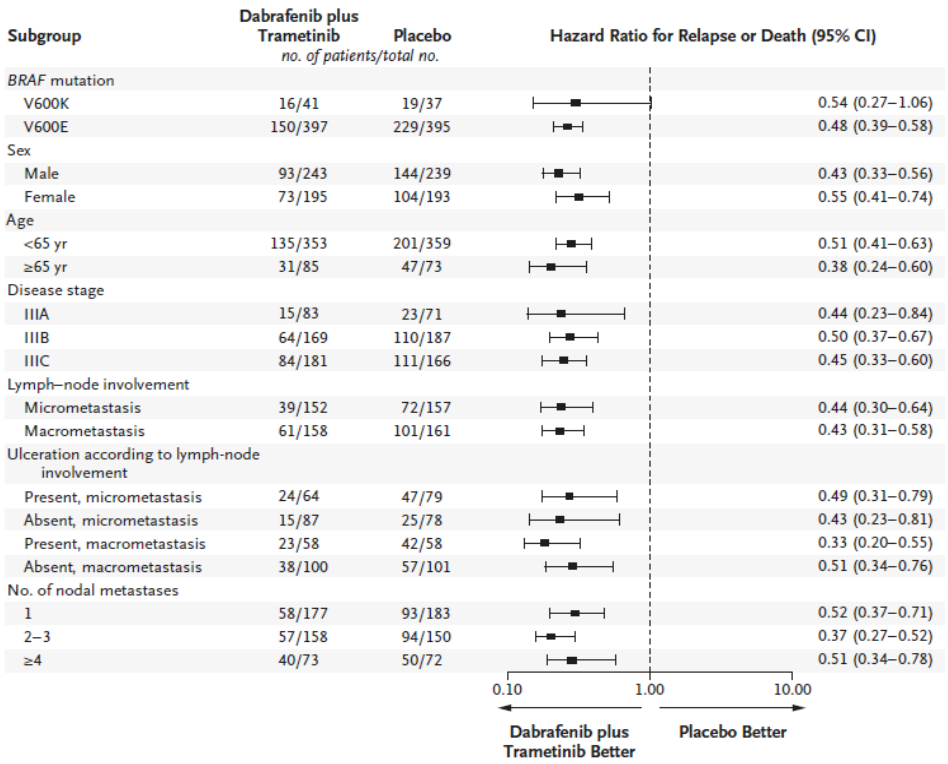
To assess the homogeneity and consistency of treatment effect with dabrafenib plus trametinib, pre-planned subgroup analyses of RFS were performed according to the following classification factors:[34, 55]

- Mutation status (BRAF V600K/E positive)
- Gender (Male/Female)
- Age at screening (<65 years/≥65 years)
- Disease stage (IIIA/IIIB/IIIC)
- Lymph-node involvement (micrometastasis/macrometastasis)
- Tumour ulceration (micrometastasis and ulceration/micrometastasis and no ulceration/macrometastasis and ulceration/macrometastasis and no ulceration)
- Number of nodal metastases

Pike hazard ratios with corresponding 95% CIs were calculated within each of the defined subgroups and results were presented in a forest plot (Figure 11). The analyses performed within subgroups were non-stratified, and in addition, the RFS analysis for the stage IIIB/IIIC subgroup included the Pike estimator as well as a multivariate Cox regression analysis to adjust for important prognostic factors.

The results of the subgroup analyses demonstrate that the treatment effect estimates observed in all subgroups were consistent with those observed in the overall population. (the V600K subgroup had a broad confidence interval due to the low sample size within this subgroup).

Figure 11: Hazard ratios and 95% confidence intervals for relapse or death, according to subgroup (ITT population)[a, b]



[a]As of data cut-off for the primary analysis (30th June 2017). [b]Wider hazard ratio CIs were observed in some subgroups; however, this was often a consequence of few patients included in particular subgroups and fewer RFS events observed.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat.
Source: Long *et al.* (2017).[55]

A meaningful and consistent RFS benefit was observed across all pre-planned subgroups. Notably, this benefit was observed even in subgroups with the poorest prognostic factors, such as lymph node involvement or primary tumour ulceration, and across all subgroups of stage III disease.

This provides a strong rationale for treatment of all patients with resected BRAF V600 positive stage III melanoma with adjuvant dabrafenib plus trametinib to mitigate the risk of disease recurrence.

B.2.8 Meta-analysis

The SLR identified only one RCT (COMBI-AD) relevant to the decision problem and a meta-analysis was not conducted as part of this appraisal.

B.2.9 Indirect and mixed treatment comparisons

As defined by the decision problem (Table 1), routine surveillance (i.e. no active treatment) represents the only relevant comparator in this appraisal. Since the COMBI-AD trial provides direct comparative evidence of dabrafenib plus trametinib versus placebo in a phase III, randomised controlled trial, no indirect or mixed treatment comparisons were conducted as part of this submission.

B.2.10 Adverse reactions

Summary of COMBI-AD safety analysis

- A total of 435 patients in the dabrafenib plus trametinib arm and 432 patients in the placebo arm were included in the safety analysis.[55]
- The mean daily dose and cumulative dose of each of the treatments received within the trial were close to the targeted dose. Median duration of exposure was 11.0 months for both dabrafenib and trametinib, and 10.0 months for the placebo arm.[55]
- In the adjuvant treatment setting, patients are disease free and therefore potentially working or otherwise pursuing normal activities; it is therefore important that such treatments show a tolerable safety profile given the patient demographic is relatively healthy.
- Dabrafenib plus trametinib showed a manageable safety profile for use as an adjuvant therapy which was consistent with that observed in patients with metastatic melanoma, with no new safety signals identified.[55] Specifically:
    - As of this primary data cut-off (30th June 2017), at least one AE was reported in 422 patients (97%) in the dabrafenib plus trametinib arm and 380 patients (88%) in the placebo arm.[55]
    - The most frequently reported AEs in the dabrafenib plus trametinib arm were pyrexia (63% of patients), fatigue (47%), and nausea (40%). In the placebo arm, the most frequently reported AEs were fatigue (28%), headache (24%), and nausea (20%).[55]
    - [redacted].[34]
    - Serious adverse events (SAEs) occurred in 155 patients (36%) in the dabrafenib plus trametinib arm and in 44 patients (10%) in the placebo arm. One fatal SAE (pneumonia) was reported in the dabrafenib plus trametinib arm.[55]
    - [redacted] (see Section B.2.6.3), indicating that the AEs associated with dabrafenib plus trametinib do not incur any additional burden to the HRQoL of patients with this disease.[34]
- As of the primary data cut-off (30th June 2017), a total of 153 deaths had occurred; 60 (14%) in the dabrafenib plus trametinib arm and 93 (22%) in the placebo arm. In both trial arms, the most common cause of death was melanoma (54 patients [12%] in the dabrafenib plus trametinib group and 77 patients [18%] in the placebo group).[55]

The safety and tolerability of dabrafenib plus trametinib in resected BRAF V600 positive stage III melanoma patients was evaluated as a secondary endpoint in the COMBI-AD trial.[55] As described previously (Table 10), the safety population included all patients who received at least one dose of

randomised treatment and was based on the actual treatment received, therefore 435 patients in the combination arm and 432 patients in the placebo arm were included in the safety analysis.

Safety was assessed by monitoring and recording potential adverse effects of the treatment using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, including the relationship to the study treatment, at each study visit. Clinical examination and radiological assessments were performed every three months during the first 24 months, then every six months until disease recurrence or the completion of the trial. Clinical assessments included vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), eye examinations, chemistry and haematology laboratory values, and adverse events (AEs) to detect potential toxicities from the treatment. AEs and laboratory values were assessed at screening, on the date of randomisation, at least once per month through month 12, and at every visit for disease-recurrence assessment after month 12.[55]

B.2.10.1 Treatment duration, dose interruptions and dose modifications

As of the data cut-off for the primary analysis (30th June 2017), the median duration of treatment exposure was 11.0 months for both dabrafenib and trametinib, and 10.0 months for the placebo arm. The median daily dose of dabrafenib and trametinib received by the patients was 283.9 mg (range, 88.5 mg to 300.0 mg) and 1.97 mg (range, 0.6 mg to 2.0 mg) respectively, which is similar to the planned daily dose (300 mg/day for dabrafenib and 2 mg/day for trametinib).[34, 55]

Patients in the dabrafenib plus trametinib arm had more dose interruptions ([redacted]) compared to those who received placebo ([redacted]). The median duration of dose interruptions was [redacted] in the dabrafenib plus trametinib arm ([redacted], respectively) than in the placebo arm ([redacted]). The most common reason for dose interruption was [redacted] in the dabrafenib plus trametinib arm ([redacted]), and [redacted] in the placebo arm ([redacted]). A [redacted] percentage of patients in the dabrafenib plus trametinib arm had three or more dose interruptions ([redacted]) compared to placebo ([redacted]).[34]

Dose reductions were [redacted] in the dabrafenib plus trametinib arm [redacted] compared to the placebo arm ([redacted]).[34] The most common reasons for dose reductions were [redacted]. In the dabrafenib plus trametinib arm, two or more dabrafenib dose reductions were required in [redacted] and two or more trametinib reductions were reported in [redacted].[34]

The proportion of patients with dose escalations was [redacted] in the dabrafenib plus trametinib arm ([redacted]) and in the placebo arm ([redacted]). The most common reason for dose escalation was [redacted].[34]

A summary of the exposure to study treatment and dose interruptions in COMBI-AD is presented in Table 19.

Table 19: Summary of treatment duration and dose interruptions in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

	Dabrafenib plus trametinib		Placebo	
	Dabrafenib (N=435)	Trametinib (N=435)	Placebo for dabrafenib (N=432)	Placebo for trametinib (N=432)
Duration of exposure, months				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	11.0 [redacted]	11.0 [redacted]	10.0 [redacted]	10.0 [redacted]
Average daily dose, mg				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	283.85 (88.5–300.0)	1.97 (0.6–2.0)	[redacted]	[redacted]
Cumulative dose, mg				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruptions				
Patients with any dose interruptions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of dose interruptions, n	[redacted]	[redacted]	[redacted]	[redacted]
Number of dose interruptions, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable[a]	[redacted]	[redacted]	[redacted]	[redacted]
Interruption duration (days), n (%)				
≤7	[redacted]	[redacted]	[redacted]	[redacted]
8 to 14	[redacted]	[redacted]	[redacted]	[redacted]
>14	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for interruption[b], n (%)				
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Patient non-compliance	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions				

	Dabrafenib plus trametinib		Placebo	
	Dabrafenib (N=435)	**Trametinib (N=435)**	**Placebo for dabrafenib (N=432)**	**Placebo for trametinib (N=432)**
Patients with any dose reduction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of dose reductions, n	[redacted]	[redacted]	[redacted]	[redacted]
Number of dose reductions, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable[a]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for reduction[b], n (%)				
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Patient non-compliance	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Dose escalations				
Patients with any dose escalation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of dose escalations, n	[redacted]	[redacted]	[redacted]	[redacted]
Number of dose escalations, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable[a]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for escalation[b], n (%)				
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Patient non-compliance	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

[a]Not evaluable means the patient did not receive any drug in any succeeding time period after the first dose. [b]Patients may be counted multiple times in the same 'reason' row if the patient had multiple interruptions for the same reason
Abbreviations: SD : standard deviation.
Source: COMBI-AD CSR.[34]

B.2.10.2 Safety analysis in COMBI-AD

As per the COMBI-AD study protocol, AEs were recorded from the first dose of study treatment until 30 days after discontinuation of study treatment (with the exceptions of treatment emergent malignancies and SAEs related to study treatments). A summary of the safety results from COMBI-AD is presented in Table 20.

As of the data cut-off for the primary analysis (30th June 2017), 153 patients had died; 60 (14%) in the dabrafenib plus trametinib arm and 93 (22%) in the placebo arm. In both treatment arms, the most common cause of death was melanoma (54 patients [12%] in the dabrafenib plus trametinib arm and 77 patients [18%] in the placebo arm). For all other deaths (six in the dabrafenib plus trametinib arm and 16 in the placebo arm), the cause of death was listed as "other" or unknown, and amongst these patients, 5 in the combination arm and 15 in the placebo arm experienced disease recurrence before death.[55] [redacted].[34]

At least one AE was reported in 97% of patients in the dabrafenib plus trametinib arm and 88% of patients in the placebo arm, with serious adverse events (SAEs) occurring in 36% and 10% of the combination therapy and placebo arms respectively.[55] In the dabrafenib plus trametinib arm, 114 patients (26%) experienced AEs leading to permanent discontinuation of a trial drug, 167 (38%) had AEs leading to a dose reduction, and 289 (66%) had AEs leading to a dose interruption, compared with 12 (3%), 11 (3%), and 65 (15%), in the placebo arm, respectively.[55]

Although the type of AEs observed in the COMBI-AD trial were consistent with the known and manageable safety profile of combination treatment, the rate of treatment discontinuation in this study was higher than that observed in metastatic disease.[20] The reasons for the high discontinuation rate remain unclear, however it has been suggested that since these patients are generally in better health than metastatic patients, a perceived lack of urgency for adjuvant therapy in stage III melanoma may be a reason why patients may opt out of systemic therapy. Patients may also be less likely to persevere with treatment and the management of toxicities than in the metastatic setting.[87]

Table 20: Summary of safety analysis in COMBI-AD (30th June 2017 data cut-off)

AEs, n (%)	Dabrafenib plus trametinib (N=435)	Placebo (N=432)
Deaths	60 (14)	93 (22)
Deaths due to study drug toxicity	[redacted]	[redacted]
All causality AEs (any grade)	422 (97)	380 (88)
Grade 3 or 4 AEs	180 (41)	61 (14)
AEs related to study treatment	[redacted]	[redacted]
AEs leading to treatment discontinuation	114 (26)	12 (3)
AEs leading to dose reduction	167 (38)	11 (3)

AEs, n (%)	Dabrafenib plus trametinib (N=435)	Placebo (N=432)
AEs leading to dose interruption	289 (66)	65 (15)
All-causality SAEs	155 (36)	44 (10)
SAEs related to study treatment	[redacted]	[redacted]
Fatal SAEs	1 (<1)	0
Fatal SAEs related to study treatment	[redacted]	[redacted]

Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: COMBI-AD CSR[34] and Long *et al*. (2017).[55]

All-cause and drug-related adverse events

AEs of any cause that occurred in at least 10% of patients are presented in Table 21, with the most frequently reported AEs in the combination arm reported as pyrexia (63%), fatigue (47%), and nausea (40%). In the placebo arm, the most frequently reported AEs were fatigue (28%), headache (24%) and nausea (20%). Events were primarily grade 1 or 2 in severity and grade 3/4 AEs were reported in 41% patients in the dabrafenib plus trametinib treatment arm compared to 14% in placebo arm.[55]

Table 21: Summary of most frequent AEs in ≥10% patients in a treatment arm in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

	Dabrafenib plus trametinib (N=435)		Placebo (N=432)	
AEs, n (%)	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any adverse event	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (<1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (<1)
Nausea	172 (40)	4 (<1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhoea	144 (33)	4 (<1)	65 (15)	1 (<1)
Vomiting	122 (28)	4 (<1)	43 (10)	0
Arthralgia	120 (28)	4 (<1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (<1)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (<1)	40 (9)	0
Elevated alanine aminotransferase	67 (15)	16 (4)	6 (1)	1 (<1)
Influenza-like illness	67 (15)	2 (<1)	29 (7)	0
Elevated aspartate aminotransferase	63 (14)	16 (4)	7 (2)	1 (<1)
Pain in extremity	60 (14)	2 (<1)	38 (9)	0
Asthenia	58 (13)	2 (<1)	42 (10)	1 (<1)

	Dabrafenib plus trametinib (N=435)		Placebo (N=432)	
AEs, n (%)	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Peripheral oedema	58 (13)	1 (<1)	19 (4)	0
Dry skin	55 (13)	0	32 (7)	0
Dermatitis acneiform	54 (12)	2 (<1)	10 (2)	0
Constipation	51 (12)	0	27 (6)	0
Hypertension	49 (11)	25 (6)	35 (8)	8 (2)
Decreased appetite	48 (11)	2 (<1)	25 (6)	0
Erythema	48 (11)	0	14 (3)	0

Abbreviations: AE: adverse event; PT: preferred term.
Source: Long *et al.* (2017).[55]

A summary of treatment-related AEs occurring in at least 10% of patients is presented in Table 20. [redacted] (Table 22).[34]

Table 22: Summary of most frequent treatment-related AEs in ≥10% patients in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

AEs, n (%)	Dabrafenib plus trametinib (N=435)	Placebo (N=432)
[redacted]		

AEs, n (%)	Dabrafenib plus trametinib (N=435)	Placebo (N=432)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event.
Source: COMBI-AD CSR.[34]

Serious adverse events

SAEs occurred in 155 patients (36%) in the dabrafenib plus trametinib arm and in 44 patients (10%) in the placebo arm, as summarised in Table 23. One fatal SAE (pneumonia) was reported in the dabrafenib plus trametinib arm. A new primary melanoma was reported in 11 patients (3%) in the dabrafenib plus trametinib arm and in 10 (2%) in the placebo arm.[55] This safety profile was consistent with that observed in patients with metastatic melanoma, with no new safety signals identified.[55]

Table 23: Summary of most frequent SAEs in ≥1% patients in a treatment arm in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

AEs, n (%)	Dabrafenib plus trametinib (N=435)	Placebo (N=432)
Any event, n (%)	155 (36)	44 (10)
Pyrexia	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Chorioretinopathy	[redacted]	[redacted]

Abbreviations: SAE: serious adverse event.
Source: Long *et al.* (2017)[55] and COMBI-AD CSR.[34]

Adverse events of special interest

An adverse event of special interest (AESI) is a grouping of AEs that are of scientific and medical concern specific to trametinib and dabrafenib. AESIs include events that are either known class effects, were identified in pre-clinical or prior clinical studies, or are potentially life-threatening. A comprehensive list of MedDRA terms based on clinical review was used to identify each type of event. For some of the AESI categories several AE preferred terms were identified and combined.[34]

[redacted]
24[redacted]

Table 24: Summary of AESIs in COMBI-AD as of 30th June 2017 data cut-off for the primary analysis

AEs, n (%)	Dabrafenib plus trametinib (N=435)				Placebo (N=432)			
Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
AESIs, n (%)								
Pyrexia	[redacted]							
Skin related toxicities	[redacted]							
Diarrhoea	[redacted]							
Hepatic disorders	[redacted]							
Hypersensitivity	[redacted]							
Oedema	[redacted]							
Hyperglycaemia	[redacted]							
Ocular Events	[redacted]							
Uveitis	[redacted]							
Bleeding events	[redacted]							
Hypertension	[redacted]							
Neutropenia	[redacted]							
Cardiac related event	[redacted]							
Pre-renal and intrinsic renal failure	[redacted]							
Deep vein thrombosis/Pulmonary embolism	[redacted]							
Pancreatitis	[redacted]							
Cutaneous small cell carcinoma (including keratoacanthoma)	[redacted]							
Non-cutaneous secondary/recurrent malignancies	[redacted]							
New primary melanoma	[redacted]							
Pneumonitis/Interstitial lung disease	[redacted]							

Abbreviations: AE: adverse event; AESI: adverse event of special interest.
Source: COMBI-AD CSR.[34]

In summary, dabrafenib plus trametinib showed a manageable safety profile for use as an adjuvant therapy which was consistent with that observed in patients with metastatic melanoma, with no new safety signals identified.[55]

B.2.11 Ongoing studies

Additional evidence from COMBI-AD to support the use of dabrafenib plus trametinib for the new indication is likely to become available in the next six months, as summarised in Table 25.

Table 25: Summary of planned additional analyses of COMBI-AD data

Additional evidence	Type of analysis	Expected date of publication
Reclassification of COMBI-AD staging from AJCC seventh edition to eighth edition	Post-hoc clinical results	ASCO 2018
HRQoL	First Interpretable Results	ASCO 2018
Biomarker profiling	First Interpretable Results	ASCO 2018

Abbreviations: AJCC: American Joint Commission on Cancer; ASCO: American Society of Clinical Oncology; HRQoL: health-related quality of life.

B.2.12 Innovation

The last two decades have seen very few advances in the development of new therapies in the adjuvant setting for melanoma.[88] COMBI-AD is the first clinical trial to show that the established clinical benefit of dabrafenib plus trametinib in metastatic melanoma is also translated to the adjuvant setting in a patient population that is at high risk of recurence.[55]

If approved by the EMA, dabrafenib plus trametinib will be the first targeted combination therapy to receive a marketing authorisation for resected BRAF V600 positive stage III melanoma, and will be the first active treatment option available for patients who are currently managed through routine surveillance. The oral route of administration for dabrafenib plus trametinib offers a convenient route of drug administration where there is already increased demands on burdened melanoma clinics within the NHS.

The clinical benefit of dabrafenib plus trametinib on RFS is demonstrated very early on after initiating treatment; there is a clear separation of the Kaplan-Meier curves visible from approximately three months ($p=1.53x10^{-14}$),[55, 81] and the continued benefit of treatment is still apparent even after discontinuing treatment at 12 months. The results of COMBI-AD clearly show that dabrafenib plus trametinib can be considered an effective adjuvant treatment for resected BRAF V600 positive stage III melanoma patients, with consistent results across all pre-specified sub-groups. This is particularly important because melanoma disproportionately affects a younger population, who are of working age and may have young families. As melanoma can have a significant impact on patients, their carers and wider society including the loss of economic productivity,[89] this highlights the magnitude of the positive impact an effective adjuvant treatment may have on patients (which may not be captured in the QALY calculation in the subsequent cost-effectiveness section).

The introduction of dabrafenib plus trametinib in this indication will change the way in which treatment decisions are made in clinical practice, representing a step change in the management of resected BRAF V600 positive stage III melanoma by providing a favourable risk-benefit ratio with manageable transient toxicities and no long-term AEs.

In recognition of the above, on 23rd October 2017, the Food and Drug Administration (FDA) in the United States granted Breakthrough Therapy Designation of dabrafenib plus trametinib for the adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation following complete resection.[28] Treatments that receive Breakthrough Therapy Designation are those that treat a serious or life-threatening disease or condition and demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints based on preliminary clinical evidence.[29]

Moreover, this new indication for dabrafenib plus trametinib has already been included in the 2018 update of the National Clinical Comprehensive Cancer Network Guidelines for melanoma,[83] indicating that dabrafenib plus trametinib is already changing the treatment landscape for melanoma outside the UK.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence base

Dabrafenib plus trametinib is the first and only targeted combination therapy to demonstrate a statistically significant and clinically meaningful improvement in RFS in patients with BRAF V600 mutated stage III melanoma following complete resection, with a 53% lower risk of relapse ($p=1.53x10^{-14}$) compared to placebo as of the data cut-off for the primary analysis (30th June 2017).[55]

Dabrafenib plus trametinib also resulted in higher rates of OS, with an estimated three-year OS rate of 86% compared to 77% in the placebo arm (p=0.0006). Although the OS benefit was not statistically significant as per the stringent pre-specified conservative interim boundary of p=0.000019, this result shows a clinically meaningful improvement in OS.[55]

Dabrafenib plus trametinib also resulted in a significant improvement in DMFS and FFR versus placebo (49% and 53%, respectively, both p<0.001), which is consistent with the RFS improvement observed. Notably, a meaningful and consistent clinical benefit was observed across all stage III subgroups and regardless of prognostic factors such as of lymph-node involvement or primary tumour ulceration.[55] Overall, the results of COMBI-AD show that dabrafenib plus trametinib represents a step change in the management of stage III melanoma following complete resection, offering a clinically effective treatment option that mitigates the risk of disease recurrence and alleviates the morbidity and mortality burden associated with progression to metastatic disease.[47]

In addition, the majority of patients on dabrafenib plus trametinib in COMBI-AD completed the scheduled 12 months of therapy with a median dose close to the scheduled dose for each drug, highlighting the manageable safety profile of the combination therapy. The safety profile of dabrafenib plus trametinib was consistent with the known profile of these therapies and no new safety signals were raised.[55] Although the rate of treatment discontinuation in COMBI-AD was higher (37% for dabrafenib and 36% for trametinib) than that observed metastatic disease (9%),[25] this could be because the patient population included in COMBI-AD was, in general, healthier than the patients included in the metastatic clinical trials and therefore were more inclined to discontinue treatment if they did not tolerate it well.

B.2.13.2 Strengths and limitations of the clinical evidence base

Head to head trial provides comparative evidence to current standard of care

COMBI-AD provides direct RCT evidence of combined BRAF and MEK inhibition compared with placebo in the adjuvant setting for resected BRAF V600 positive stage III melanoma patients. Routine surveillance is current standard of care in UK clinical practice for this group of patients post-resection and is represented by the placebo arm.

COMBI-AD is well designed with clinically relevant study endpoints

COMBI-AD was designed to capture the endpoints most relevant to adjuvant melanoma patients and clinicians alike, as well as to healthcare providers. It therefore not only included clinical efficacy and safety endpoints consistent with other studies of therapeutic agents in adjuvant melanoma, but also relevant assessments such as HRQoL. The primary endpoint RFS is a true measure of patient benefit since unlike OS, it is not confounded by subsequent therapy, and relapses are accompanied by considerable disease and treatment related morbidity. The study completed recruitment to the target of 870 patients and was analysed according to the original statistical plan.

The patient cohort is reflective of patient profiles in UK clinical practice

Although an international and multicentre study, the trial included 86 patients from 13 UK sites and is representative of the population seen in UK clinical practice.[39] Importantly, consistently superior clinical benefit was observed across all pre-determined subgroups including those based on treatment history and prognostic factors such as ulceration, staging and lymph node involvement.[55]

Estimates of long-term benefit are clinically valid despite immaturity of survival data

Even though median OS has not yet been reached, the evidence to date demonstrate a maintenance of benefit even after the drugs are stopped. This benefit shows a clinically significant improvement in outcomes, with a three-year OS rate of 86% (active arm) versus 77% (placebo arm) (HR 0.57; 95% CI, 0.42–0.79, p=0.0006).[55] Whilst there is an immaturity of data for dabrafenib plus trametinib that adds uncertainty to estimates of its long-term benefit, the high degree of improved clinical benefit observed in clinical trial data available to date can only support the introduction of this combination into the clinical pathway of care for adjuvant melanoma.

Estimates of long-term benefit did not cross an ambitious pre-specified statistical boundary

The estimated HR for OS was 0.57 (95% CI: 0.42–0.79; p=0.0006). Despite this low p-value, the between-arm difference was not statistically significant because it did not cross the pre-specified conservative interim boundary of p=0.000019.[55]

Dabrafenib plus trametinib was well tolerated treatment with no new safety signals observed

Adjuvant use of dabrafenib plus trametinib was shown to significantly lower risk of disease recurrence in resected BRAF V600 positive stage III melanoma patients, resulting in a reduction in receipt of subsequent systemic anti-cancer therapies. The safety profile was consistent with that observed with the combination in patients with metastatic disease, without any indication of new toxic effects.[55]

In conclusion, despite the recent evolution of the treatment pathway for metastatic melanoma, there remains an unmet need for clinically effective and well tolerated therapies in the adjuvant setting to reduce the risk of disease recurrence in patients with resected disease. Dabrafenib plus trametinib is the first effective and well tolerated combination targeted therapy to demonstrate efficacy in the adjuvant setting for BRAF positive resected stage III melanoma patients, and the COMBI-AD trial showed a clinically meaningful and consistent RFS and OS benefit across all assessed prognostic factors. It is therefore reasonable to assume that the responses seen in the study would also be seen in clinical practice.

B.3 Cost-effectiveness

Summary of the cost-effectiveness analysis

- A *de novo* cost-utility model was developed for the economic evaluation in accordance with the NICE reference case. A lifetime analysis was performed, with costs and outcomes discounted at 3.5% per annum.
- Efficacy data were derived from the COMBI-AD trial,[55] supplemented by evidence from the literature to estimate long-term OS during the post-trial period.
- Health-state utilities for the relapse-free and post-recurrence health states were derived from the COMBI-AD trial;[55] QALYs and costs accrued after distant recurrence were applied as a one-off value and were estimated from previous NICE appraisals in metastatic disease (TA366[90] and TA396[20]).

Base case cost-effectiveness results

- Base case deterministic results show that dabrafenib plus trametinib is associated with higher costs but also higher QALYs than routine surveillance (placebo), with an incremental cost per QALY gained of £20,039 with the existing confidential PAS. This incremental cost-effectiveness ratio (ICER) is well within acceptable limits of cost-effectiveness.

Sensitivity analyses

- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess uncertainty and the cost-effectiveness results were robust to an extensive number of scenario analyses.
- The PSA ICER was estimated to be £20,037 per QALY gained with the existing confidential PAS, with an [redacted] probability of dabrafenib plus trametinib being a cost-effective treatment option at £30,000/QALY threshold.
- The DSA shows that the parameters varied have a limited impact on the base case results and the cost-effectiveness results remain well within the acceptable limits of cost-effectiveness.
- Fourteen scenario analyses were conducted varying the model time horizon, clinical inputs informing efficacy values, costs and outcomes associated with DR, utility values, routine surveillance (placebo) resource use and monitoring costs. Overall, the results were robust to most parameters and structural assumptions, with the ICERs across the majority of the analyses performed with the existing confidential PAS remaining below the cost-effectiveness threshold of £30,000 per QALY gained.

Summary

- The economic analysis presents a robust evaluation demonstrating that adjuvant dabrafenib plus trametinib represents a cost-effective option compared to routine surveillance (placebo).

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify any relevant cost-effectiveness studies previously published in patients with stage III melanoma following complete resection in the adjuvant setting. Searches were performed in November 2017 and full details of the SLR search strategy, study selection process and results are reported in Appendix G.

No previous cost-effectiveness studies of the technology, dabrafenib plus trametinib, compared to routine surveillance (placebo) in the patient population and setting of interest were identified hence a *de novo* cost-effectiveness model was constructed for the purposes of this appraisal.

B.3.2 Economic analysis

The objective of the economic evaluation was to assess the cost-effectiveness of dabrafenib plus trametinib compared to routine surveillance (placebo) for the [redacted]. In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) and included direct medical costs only.

B.3.2.1 Patient population

The patient population in the economic analysis reflects the patient population in the COMBI-AD trial: patients with completely resected, histologically-confirmed, BRAF V600E/K mutation-positive stage III melanoma.[55] This is consistent with the population defined in the NICE final scope,[1] the decision problem for this appraisal and the expected European marketing authorisation for this new indication.

The baseline characteristics of the patients in the COMBI-AD trial, and hence the economic analysis, have been described previously in Section B.2.3.3.

B.3.2.2 Model structure

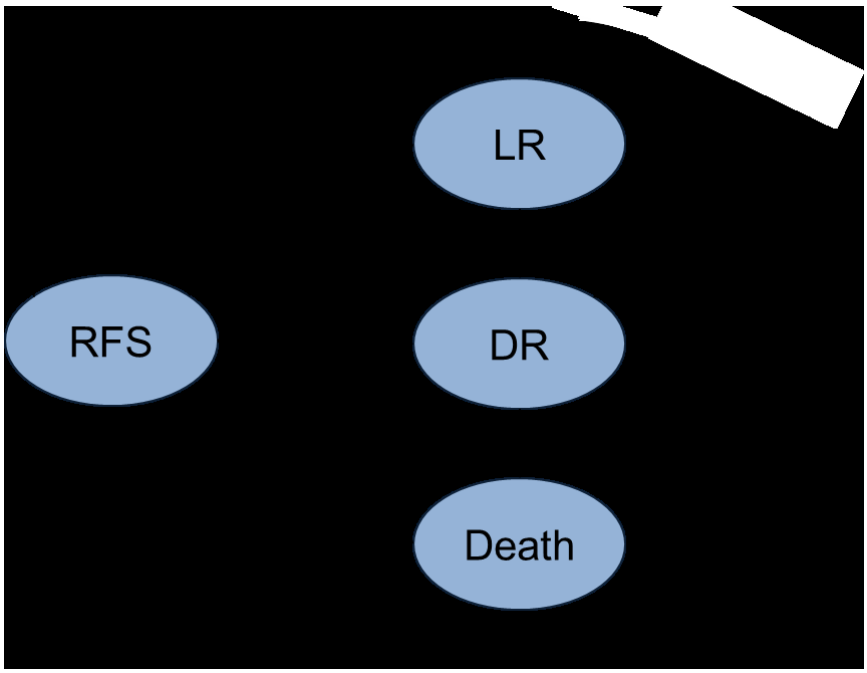
A cohort state-transition model was developed in Microsoft Excel® to reflect the natural history of disease for melanoma and the current UK clinical pathway by:

- Incorporating the outcomes of the COMBI-AD trial, providing direct evidence of dabrafenib plus trametinib with the appropriate comparator: routine surveillance (placebo)
- Making the best use of the available evidence in the metastatic setting, by incorporating the treatment mix of therapies currently used in the management of metastatic disease

The model structure was validated by clinical experts[57] and consisted of four mutually exclusive health states: relapse-free survival (RFS), loco-regional recurrence (LR), distant recurrence (DR) and death (separated into death from melanoma and death from other causes), appropriately capturing the patient journey and the clinical pathway of care described in Section B.1.3.2.

The structure of the model is shown in Figure 12, and a complete description of the health states and the associated transitions are described in further detail below.

Figure 12: *De novo* model structure



Notes: The death health state is represented in the model diagram for the sake of simplicity as one health state. The model includes two death states: one for death due to melanoma, and another for death due to other causes.
Abbreviations: DR: distant recurrence; LR: loco-regional recurrence; RFS: relapse-free survival.

Relapse-free survival health state (RFS)

Following complete resection, all patients enter the model in the RFS health state where they receive either:

- Adjuvant treatment with dabrafenib plus trametinib for a period of 12 months (unless there is disease recurrence, unacceptable toxicity or death), followed by routine surveillance after completion of treatment, or
- Routine surveillance (represented by the placebo arm of COMBI-AD).

As described previously in Section B.1.3.2, the management of stage III melanoma following resection is described in guidelines published by NICE (NG14)[30] and associations such as the BAD,[54] consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians,[56] and the European Society Medical Oncology (ESMO).[79]

Following clinical expert advice,[57] base case estimates of the costs and resource use associated with routine surveillance were derived from the consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians (see Section B.3.5.1).[56]

Patients in the RFS health state are at risk of experiencing a recurrence event and can either:

- Remain in this health state in the absence of a recurrence event,
- Develop a loco-regional recurrence and transition to the LR health state,
- Develop a distant recurrence and transition to the DR health state, or

- Die from melanoma or other causes.

Since patients receiving adjuvant therapy in the COMBI-AD trial received dabrafenib plus trametinib for a maximum duration of 12 months, the RFS health state is sub-divided into on-treatment and off-treatment phases to reflect the treatment duration, drug acquisition costs and differences in HRQoL associated with being on or off treatment (Section B.3.5.1 and Section B.3.4.5).

After completing adjuvant treatment with dabrafenib plus trametinib, patients were assumed to undergo the same schedule of routine surveillance as those receiving routine surveillance (placebo) only.

Loco-regional recurrence health state (LR)

Patients experiencing a loco-regional recurrence entered the LR health state. Upon entry into the LR health state, a one-off cost was applied for treatment of LR, assuming a proportion of patients receive surgery (if resectable) or systemic therapy (assumed to be immunotherapy or targeted therapy) if unresectable (Section B.3.5.2).

Patients in the LR health state were at further risk of experiencing a subsequent recurrence event and could either:

- Remain in this health state until death and experience a small reduction in QoL compared with RFS,
- Develop a new LR,
- Develop a DR,
- Die from melanoma or other causes.

Distant recurrence health state (DR)

Patients entered the DR health state upon experiencing a distant recurrence, and remained in this health state until death. Following DR, patients were assumed to receive a mix of treatments for the management of metastatic disease in line with UK clinical practice. Upon entry into this health state, a one-off cost and QALY was applied, derived from the total discounted costs and QALYs reported in previous NICE appraisals of first-line metastatic disease[20, 90] (Section B.3.5.2) based on the mix of treatments patients were likely to receive following a recurrence. This one-off cost captured all costs associated with the DR health state, including costs for subsequent treatment associated resource use and terminal care.

Death state

The model includes two death states: one for death due to melanoma, and another for death due to other causes.

Justification of model structure

There are three key characteristics of this model that support the model structure and approach to modelling the outcomes:

1. **The model uses a cohort state-transition approach to model different recurrence events and to facilitate the modelling of OS through the use of these intermediate events (LR and DR)**

   The state-transition approach is one commonly used in the assessment of interventions in the adjuvant setting including interventions for the treatment of breast cancer, gastrointestinal stromal tumours and colon cancer.[91-96] Furthermore, a state-transition approach was also used for the assessment of different strategies for disease staging in the NICE clinical guidelines for the management of melanoma.[97]

   The partitioned-survival model approach commonly seen in appraisals of oncology interventions was not considered appropriate for this appraisal given the difficulty in (a) extrapolating OS with a low number of events (despite evidence of a survival advantage in the COMBI-AD trial) and (b) appropriately assigning costs and utility values (for different events such as LR and DR) when transitions are not modelled explicitly.

2. **The outcomes for post-recurrence therapies are not explicitly modeled for distant recurrences, with the total discounted costs and QALYs associated with DR applied as a one-off cost and QALY at the point of entry into the DR health state.**

   In order to simplify the model and avoid recreating a series of metastatic models, the outcomes following a distant recurrence were applied as one-off total costs and QALYs at the point of recurrence. This approach was chosen and considered appropriate given that the outcomes associated with DR were the downstream effect related to the efficacy of metastatic treatments, which are not the subject of this appraisal. The total costs and QALYs were derived from a review of previous NICE appraisals in the first-line treatment of metastatic disease,[20, 90] similar to the approach that was used in the NICE clinical guideline for the management of melanoma.[97] However, it should be noted that in the NICE clinical guidelines, only total costs were applied as a one-off cost at the point of recurrence and the QALYs were estimated from the life years (LY) and utility value.[97]

   Models for metastatic melanoma are often complicated and rely on a large number of assumptions, particularly with respect to extrapolations of long term survival.[75, 76, 90, 98] This is demonstrated by the wide variations in the clinical and economic outcomes between the different appraisals and the underlying assumptions used in these appraisals.[75, 76, 90, 98] Furthermore, although some data on post-recurrence therapies were collected in the COMBI-AD trial, these data were incomplete and insufficient to explicitly and robustly model the outcomes (costs and QALYs) following a DR with each potential treatment, without relying on a series of assumptions based on a limited clinical evidence.

   In recent years, the rapid evolution of the treatment pathway for metastatic disease has resulted in several treatment options including targeted therapies indicated for BRAF V600 positive melanoma and immunotherapies independent of BRAF V600 mutation status. However, despite these recent developments, the optimal sequencing of these treatments in UK clinical practice remains unknown and given these uncertainties, explicitly modelling the treatment pathway in the DR health state would increase the complexity of the model and potentially introduce further unecessary uncertainty.

It should be noted that the difficulty in modelling treatment sequence was acknowledged by the committee in the review of TA319, where the manufacturer explicitly tried to model treatment sequencing post-progression.[98] Moreover, since modelling lines of treatment and determining the optimum sequence of treatments in metastatic disease is outside the scope of this appraisal, only an *approximation* of the costs and benefits associated with this health state is required. Consequently, the approach used here in this appraisal and in the NICE clinical guideline is pragmatic and avoids introducing 'false accuracy' into the model.[97] Our approach however, for consistency, further simplifies the approach used in the NICE clinical guideline by extending the approach taken for total costs in DR to QALYs as well, so that the total discounted costs and QALYs were derived from the same source with the same underlying assumptions. In addition, using estimates from previous appraisals is also consistent with previous decisions made and accepted by NICE.

Although the outcomes following a DR were derived from previous NICE appraisals (Section B.3.5.2), there remain some uncertainties, particularly with respect to the methods used for the estimation of long-term survival, the type of treatments received post-recurrence and the availability of newer therapies for metastatic disease since these appraisals were conducted. Given these uncertainties, scenario analyses were conducted varying the total discounted costs and QALYs to explore the impact of these outcomes in the model. Despite some of the uncertainty in the estimate for the total costs and QALYs, scenario analyses show that the results were not very sensitive to these assumptions (Section B.3.8.3) and that the ICER for adjuvant dabrafenib plus trametinib remains within acceptable range for decision making.

3. **Post-DR overall survival is disconnected from the model outcomes**

Given the approach described above, it was not necessary to model OS post-DR since costs and QALYs post-DR were applied as a one-off. However, since OS is not directly estimated in the state-transition model, but life years are estimated as a function of the time spent in previous health states, the time in post-DR OS was incorporated into the model purely for the purposes of assessing the validity of the model predictions for OS compared to those observed in COMBI-AD. To be more explicit, since OS is disconnected from the model outcomes (costs and QALYs) it has no impact on the model results. This modelling approach was discussed with several clinical experts and health economic experts who considered the approach reasonable.

Features of the economic analysis

The economic analysis was conducted in accordance with the NICE reference case,[99] employing a patient lifetime horizon (assumed to be a maximum of 50 years) and the perspective of direct NHS and PSS (2016/2017 price year). The lifetime horizon and monthly cycle length were selected to reflect the chronic nature of the disease and to fully capture the costs and benefits of adjuvant treatment with dabrafenib plus trametinib. Costs and benefits were discounted at 3.5% per annum, however given the uncertainty in the long-term extrapolations, different time horizons and discount rates were explored in the scenario analyses (Section B.3.8.3).

The key features of the economic analysis are described in Table 26, noting that there have been no previous appraisals conducted by NICE for this patient population in this setting.

Table 26: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
		Chosen values	**Justification**
Time horizon	N/A (no previous appraisals for the use of adjuvant treatment in melanoma)	Lifetime (assumed to be 50 years)	In line with NICE reference case[99] Sufficient to capture all meaningful differences in technologies compared
Discount of 3.5% for utilities and costs		3.5% discounting per annum applied for both costs and benefits	In line with the NICE reference case[99]
Cycle length		One month	To capture costs and benefits associated with recurrence
Perspective (NHS/PSS)		NHS/PSS	In line with the NICE reference case[99]
Treatment waning effect?		RFS by treatment arm was used directly from the COMBI-AD trial during the observed period (observed period defined as maximum censoring time in placebo arm: 50 months) The hazard of recurrence (time varying) beyond the observed trial period (after month 50) was derived from the placebo arm of the EORTC 18071 trial.[81] The hazard is time-varying and was assumed to be the same between treatment arms following the end of the observed period (Section B.3.3.1) After the treatment period, patients in the dabrafenib plus trametinib arm underwent the same schedule of routine surveillance as the patients in the routine surveillance (placebo) arm	To incorporate external evidence on the long-term hazard of recurrence since data from COMBI-AD are relatively immature Since the risk of disease recurrence diminishes with time (Section B.3.3.1) there is no evidence to suggest that after the trial period the: a) hazard for recurrence would increase and b) the hazard for recurrence in patients treated with adjuvant therapy would be greater than those receiving routine surveillance (placebo)

Source of utilities		Age-adjusted utility values from the COMBI-AD trial were used for RFS and LR health states (Section B.3.4.5) For the DR health state, the total QALYs derived from previous NICE appraisals were applied as a one-off QALY at the point of distant metastasis (Section B.3.5.2)	Utility values (using EQ-5D-3L) were directly collected in the COMBI-AD trial in line with NICE reference case[99] As a simplifying assumption, QALYs in DR were derived from TA366[90] and TA396[20] (Section B.3.5.2)
Source of costs		BNF for drug costs[33] An existing confidential PAS is included for dabrafenib plus trametinib For the DR health state, costs derived from previous NICE appraisals were applied as one-off costs at the point of distant metastasis (Section B.3.5.2)	In line with the NICE reference case[99] As a simplifying assumption, costs in DR were derived from TA366[90] and TA396[20] and include PAS associated with the respective therapies (Section B.3.5.2)

Abbreviations: BNF: British National Formulary; DR: distant recurrence; EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; LR: loco-regional recurrence; N/A: not applicable; NHS: National Health Service; PAS: patient access scheme; PSS: Personal Social Services; QALY: quality-adjusted life years; RFS: relapse-free survival.

B.3.3 Clinical parameters and variables

The majority of clinical parameters used to populate the model were derived from the COMBI-AD trial[55] and for the estimation of long-term survival after the observed period of the trial, the trial data was supplemented with evidence from external data sources as follows:

Clinical data from the COMBI-AD trial:

- Patient baseline characteristics (Section B.2.3.3)
- RFS during the observed period of the trial (Section B.3.3.1)
    - Probability of RFS during the observed period of the COMBI-AD trial
    - Proportion of LR, DR and death events in RFS
- LR (Section B.3.3.2)
    - Probability of recurrence (LR or DR) or death following a LR
- Cumulative dose for drug costs (Section B.3.5.1)

Clinical data from other sources:

- RFS after the observed period of the COMBI-AD trial (Section B.3.3.1)
    - Probability of RFS after the observed period of the COMBI-AD trial

    - Proportion of LR, DR and death events in RFS after the observed period of the COMBI-AD trial
- LR (Section B.3.3.2)
    - Proportion of LR, DR and death events following a LR
- Time to death following a distant metastasis (e.g. overall survival following a DR) (Section B.3.3.3)

The key sources of clinical evidence are summarised in Table 27 and the key parameters are discussed in turn in subsequent sections below.

Table 27: Key sources of clinical evidence used to populate the model

Parameter	Brief description of use in model	Source
Patient characteristics	Section B.2.3.3	COMBI-AD[55] Pivotal phase III trial in completely resected stage III melanoma, investigating the safety and efficacy of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (n=438) for 12 months compared with placebo (n=432)
Cumulative dose of dabrafenib and trametinib	The calculation of number of packs of medication and hence drug costs (Section B.3.5.1)	
EQ-5D-3L	Trial-based utility analysis of dabrafenib plus trametinib (Section B.3.4.1)	
Incidence of AEs	The estimation of costs and management of specific AEs whilst on treatment with dabrafenib plus trametinib (Section B.3.5.4)	
RFS health state transitions **during** the observed period of the COMBI-AD trial	Direct data on the probability of RFS during the observed period of the COMBI-AD trial (Section B.3.3.1)	
	Direct data on the distribution of RFS events (LR, DR and death events) during the observed period of the COMBI-AD trial (Section B.3.3.1)	
LR health state transitions **during** the observed period of the COMBI-AD trial	The estimation of transitions from LR health state during observed period of COMBI-AD by calibration of RFS curve by applying a HR so that model predicted post-LR OS matched the observed post-LR OS (Section B.3.3.2)	
	Derivations of the proportions of LR, DR and death events in the LR health state during the observed period[a] (Section B.3.3.2)	**White *et al*. (2002)[100]** Long-term survival in melanoma patients with regional lymph node metastasis
RFS health state transitions **after** the observed period of the COMBI-AD trial	The estimation of the probability of RFS after the observed period of the COMBI-AD trial by using the hazard (time varying) from placebo	**EORTC 18071[81]** Phase III trial in completely resected stage III melanoma,

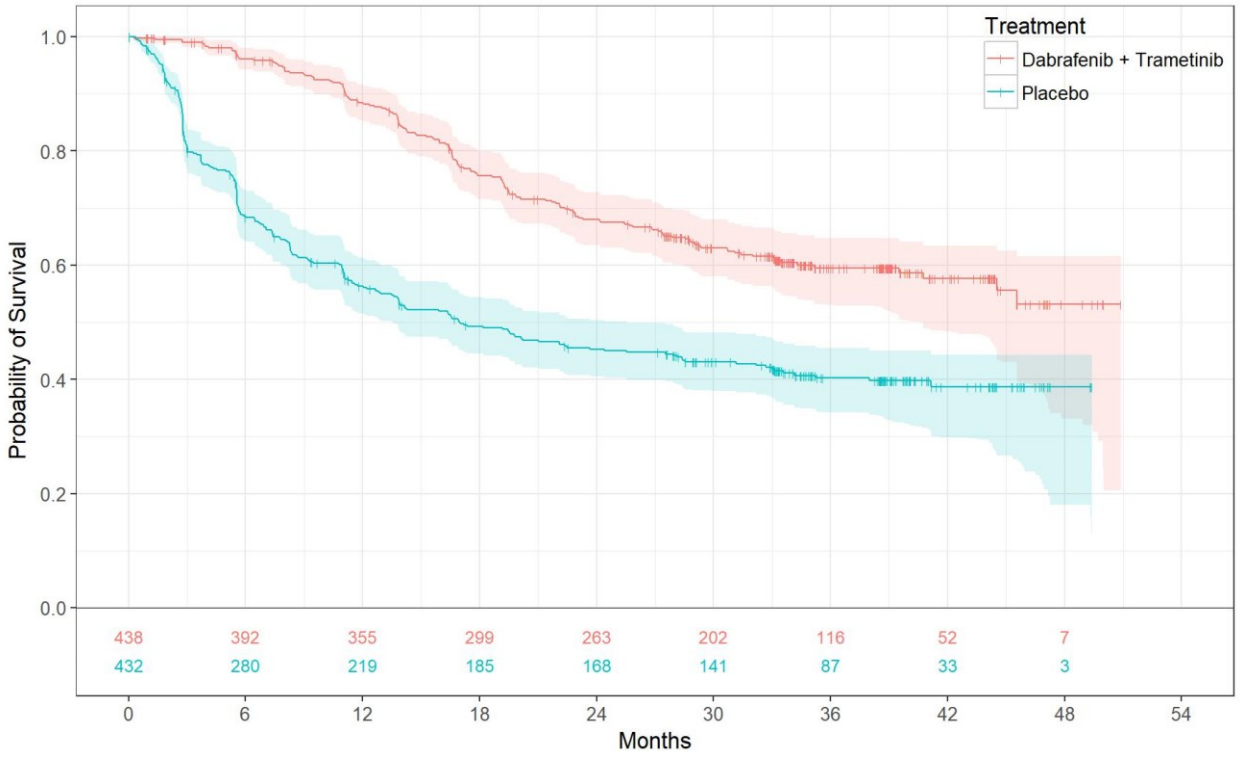
Parameter	Brief description of use in model	Source
	arm of the EORTC18071 trial (Section B.3.3.1)	investigating the safety and efficacy of adjuvant ipilimumab, 10 mg/kg every three weeks for four doses, then every three months for up to three years or until disease recurrence or unacceptable level of toxicity (n=475) compared with placebo (n=476)
	Derivation of the proportions of RFS events (LR, DR and death events) after the observed period of the COMBI-AD (Section B.3.3.1)	
Costs and QALYs for DR, and hence metastatic disease	Post-DR survival is the downstream effect of the efficacy of post recurrence therapies, and since metastatic treatments, are not the subject of this appraisal, data from TA396[20] and TA366[90] was used to represent the outcomes of targeted therapies and immunotherapies respectively (Section B.3.5.2)	**COMBI-v and COMBI-d[21, 101]** Phase III trials in unresectable or metastatic melanoma, investigating the safety and efficacy of dabrafenib (150 mg twice-daily) plus trametinib (2 mg once-daily) (COMBI-v n=352, COMBI-d n=212) compared with vemurafenib monotherapy (960 mg twice-daily) (COMBI-v n=352) or dabrafenib monotherapy (COMBI-d n=212) **KEYNOTE-006[21, 102]** Phase III trial in unresectable stage III or IV melanoma, investigating the safety and efficacy of pembrolizumab 10 mg/kg every 2 weeks (n=279) or every 3 weeks (n=277) compared with ipilimumab 3 mg/kg every 3 weeks for four doses (n=278)
England general population mortality by single year of age	Supplementation of long-term RFS from EORTC 18071 trial with general mortality data Determination of the minimum threshold of age-matching mortality rates for modelled patients in all treatment arms (Section B.3.3.1)	**General population mortality from Office for National Statistics[103]** England general population mortality by single year of age

[a]Distribution of events following an LR was assumed the same during the observed period and after the observed period.
Abbreviations: AEs: adverse events; AJCC: American Joint Committee on Cancer; DR: distant recurrence; EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; HR: hazard ratio; LR: loco-regional recurrence; OS: overall survival; QALY: quality-adjusted life year; RFS: relapse-free survival; TA: technology appraisal.

B.3.3.1 Relapse-free survival

At the time of the primary analysis data cut of the COMBI-AD trial (30th June 2017), approximately 38% of patients in the dabrafenib plus trametinib arm and 57% of patients in the placebo arm had experienced an RFS event (LR, DR or death) (Figure 13).[55] Consultation with clinical experts indicated that secondary primary melanoma (SPM) should not be considered an RFS event, and as such patients who experienced a SPM without concurrent LR or DR events (n=7 for dabrafenib and trametinib and n=6 for placebo) were censored for RFS in these analyses.

Figure 13: Kaplan-Meier curve for relapse-free survival from COMBI-AD



Source: Analysis of COMBI-AD individual patient-level data.[34]

The extrapolation of clinical trial data beyond the observed period is often challenging and, although the fit during the observed period is important, the use of clinical trial data to estimate long-term survival is often limited, and should where possible account for other longer-term evidence.

In line with the NICE DSU Technical Support Document 14,[104] a number of options to extrapolate RFS from the COMBI-AD trial were explored using a combination of mixture cure and non-mixture cure models (described in detail in Appendix N).

The parametric functions considered were exponential, Weibull, Gompertz, lognormal, log-logistic, gamma, generalised-F and restricted cubic spline (RCS). Non-mixture cure and mixture cure versions of these models were also explored.

Two approaches for estimating RFS were employed:

- Using survival distributions from the COMBI-AD data during the observed period (approximately 50 months) and extrapolated for the whole duration of the model (50 years), or
- Using survival distributions from the COMBI-AD trial during the observed period then supplemented with long-term survival data from external sources to predict survival after the trial.

The base case uses parametric functions fitted to the COMBI-AD data during the observed period, followed by data from external sources for the estimation of RFS in the long-term. This approach was taken because of the challenges of extrapolating data from the trial only, for which only a limited number of parametric functions provided clinically plausible extrapolations (Section B.3.8.3).

Scenario analyses were conducted using non-parametric survival distributions (i.e. Kaplan-Meier curves) (Section B.3.8.3). The estimation of RFS during the trial period and after the trial is described in further detail below.

RFS during the observed period of the COMBI-AD trial

Individual patient-level data (IPD) based on a median follow-up of 2.8 years from the COMBI-AD trial was used to estimate RFS during the observed period of the trial. In the base case, data from the COMBI-AD trial were used to last censoring time (approximately 50 months) for both treatment arms, and the most appropriate parametric distribution was selected. The curve fitting process involved: (a) assessment of the visual fit to the observed Kaplan-Meier curve and (b) assessment of the statistical goodness-of-fit using Akaike information criterion (AIC) and Bayesian information criterion (BIC) data (c) clinical expert validation.

Models for RFS were estimated using 2 approaches: “restricted” models and “unrestricted” models, and for both approaches, the distributions of survival for the treatment and control group are assumed to be of the same class (e.g. both are Weibull).

Restricted models include a single indicator variable for the treatment group in the model formulation (e.g. the treatment effect is restricted to a single distributional parameter, for example the scale parameter of the Weibull distribution). Unrestricted models include treatment-group interaction terms for every distributional parameter and place no such restrictions on the distributional parameters or the assumed nature of treatment effect within the class of distributions.

Mixture cure models were fit with an additional parameter to allow for the possibility that a fraction of patients is “cured” (“cure fraction” or “cure probability”). For these so-called “mixture” models, distributions were estimated using 3 alternative approaches:

- Including a single indicator variable for treatment group which varied the cure fraction in the model formulation (“mixture”),
- Including treatment group interaction terms which varied the cure fraction and a single parameter of the baseline distribution (“restricted mixture”), and
- Including treatment-group interaction terms for every distributional parameter (“unrestricted mixture”).

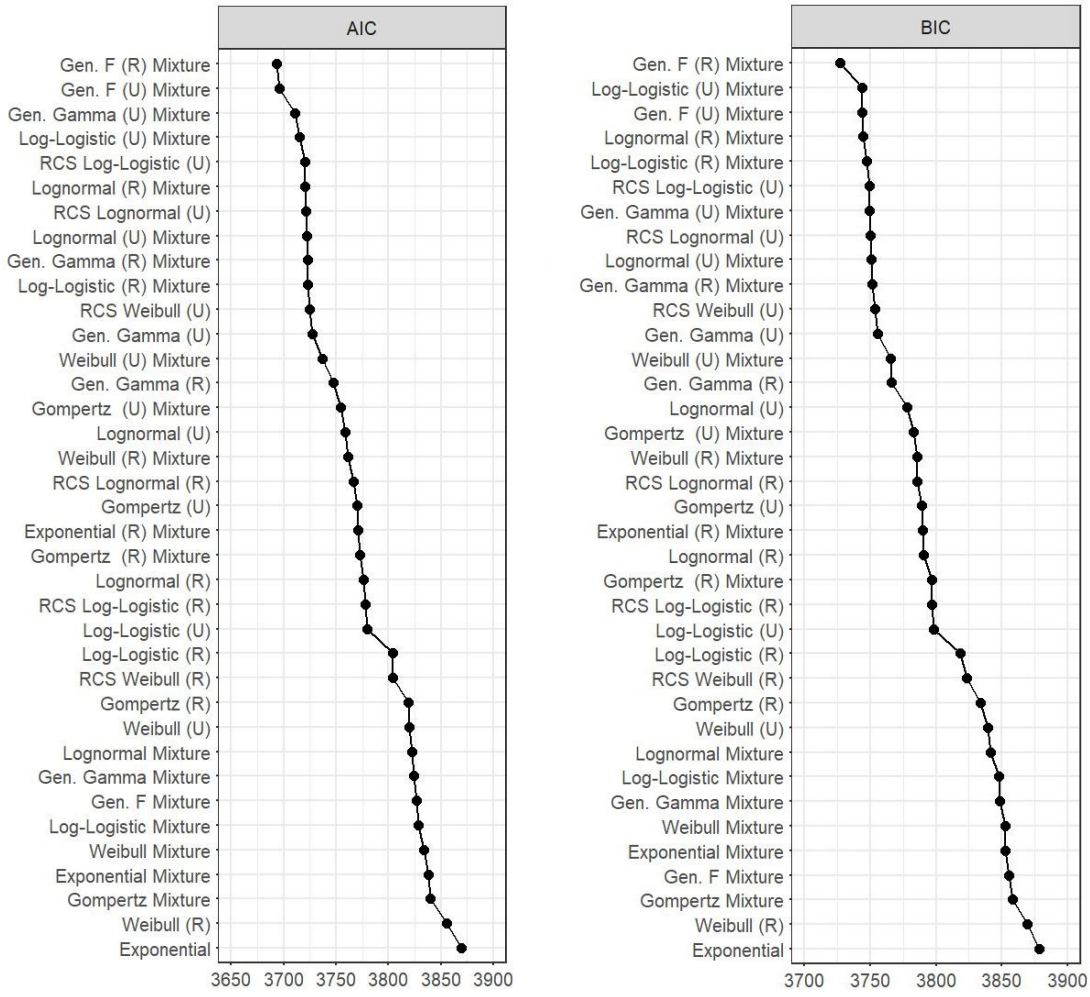
For example, with a “Weibull mixture” model, the cure probability is allowed to differ for the two treatment arms but both the scale and shape parameters of the Weibull distribution for the “uncured

patients" are assumed to be the same for the two arms. With a "Weibull restricted mixture" model, the cure probability is allowed to vary between arms, as is the scale parameter. With a "Weibull unrestricted mixture" model, all parameters of the models are allowed to differ across arms, including the cure probability, the scale parameter and the shape parameter. Thus, with the "Weibull mixture" model, the hazards among the uncured are the same in the two arms. With the "Weibull restricted mixture" model, the hazards among the uncured are proportional. With the "Weibull unrestricted mixture" model, the hazards among the uncured are not necessarily the same or proportional hazards.

It is important to note that the "restricted mixture" model is actually less "restrictive" than the "mixture" model, as the former will have more parameters than the latter. The parameters of each survival distribution and the associated cure fraction is described in Appendix N)

Figure 14 shows the AIC and BIC statistics for each parametric distribution, ranked in order of the best statistical fit. It should be noted that relative to the AIC, the BIC penalises distributions with more parameters.

Figure 14: AIC and BIC for parametric distributions fit to RFS from COMBI-AD



Note: Smaller values indicate a better fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Gen.: generalised; R: restricted; RCS: restricted cubic splines; RFS: relapse-free survival; U: unrestricted.
Source: Analysis of COMBI-AD individual patient-level data.[34]

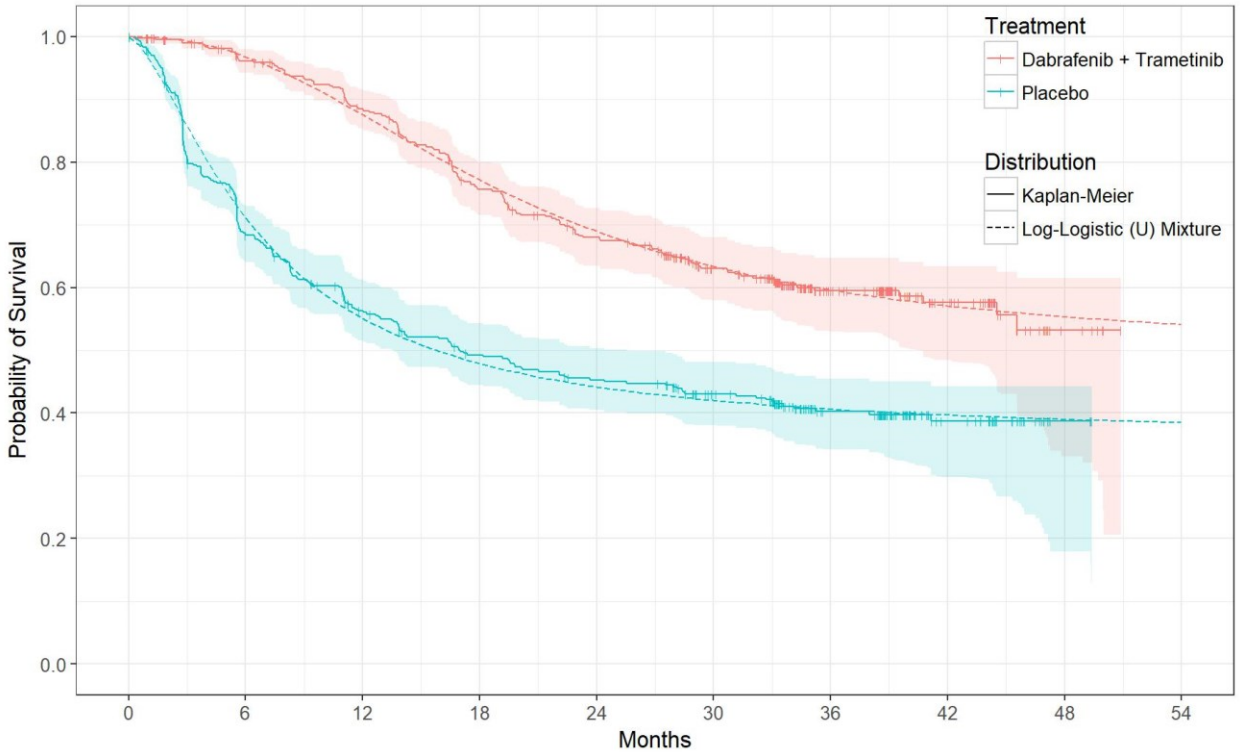
Based on the AIC and BIC, the generalised-F provided the best (statistical) fit to the data for both arms, followed by the generalised gamma unrestricted mixture, log-logistic unrestricted mixture and lognormal restricted mixture. However, goodness-of-fit criteria only provide an indication of the goodness-of-fit to the observed period, and do not categorically indicate that one distribution should be preferred over the remaining distributions.

The fit of each distribution relative to the Kaplan-Meier curve is shown in Appendix N (Figure N.2.9), and it can be seen that although the generalised-F models provided the best statistical fit (in terms of AIC and BIC), these models did not provide a good visual fit at the beginning of the curve. The log-logistic unrestricted mixture model (Figure 15), in contrast, provided the best visual fit to both treatment arms throughout the trial follow-up and also provided a good statistical fit (in terms of AIC and BIC).

Clinical experts also considered that the log-logistic unrestricted mixture-cure model provided a more accurate prediction of the RFS observed in the trial.[57]

Consequently, the log-logistic unrestricted mixture-cure model was selected for use in base case analysis (Figure 15), in which the parametric function was fitted for the first 50 months of the trial to reflect the last censoring point (51 months in adjuvant dabrafenib plus trametinib arm and 50 months in the placebo arm). In scenario analysis, the exploration of different cut-off points in the Kaplan-Meier curve and the use of the direct Kaplan-Meier curve (non-parametric extrapolation) (Section B.3.8.3) was explored. A parametric function (log-logistic unrestricted mixture-cure model) was used in the base case instead of the non-parametric direct Kaplan-Meier curve to (a) facilitate the probabilistic sensitivity analyses (PSA) and (b) because the use of parametric functions is less influenced by events at the tail of the distribution.

Figure 15: Log-logistic unrestricted mixture model fit to RFS in COMBI-AD to the end of trial follow-up



Abbreviations: RFS: relapse-free survival; U: unrestricted.
Source: Analysis of COMBI-AD individual patient-level data.[34]

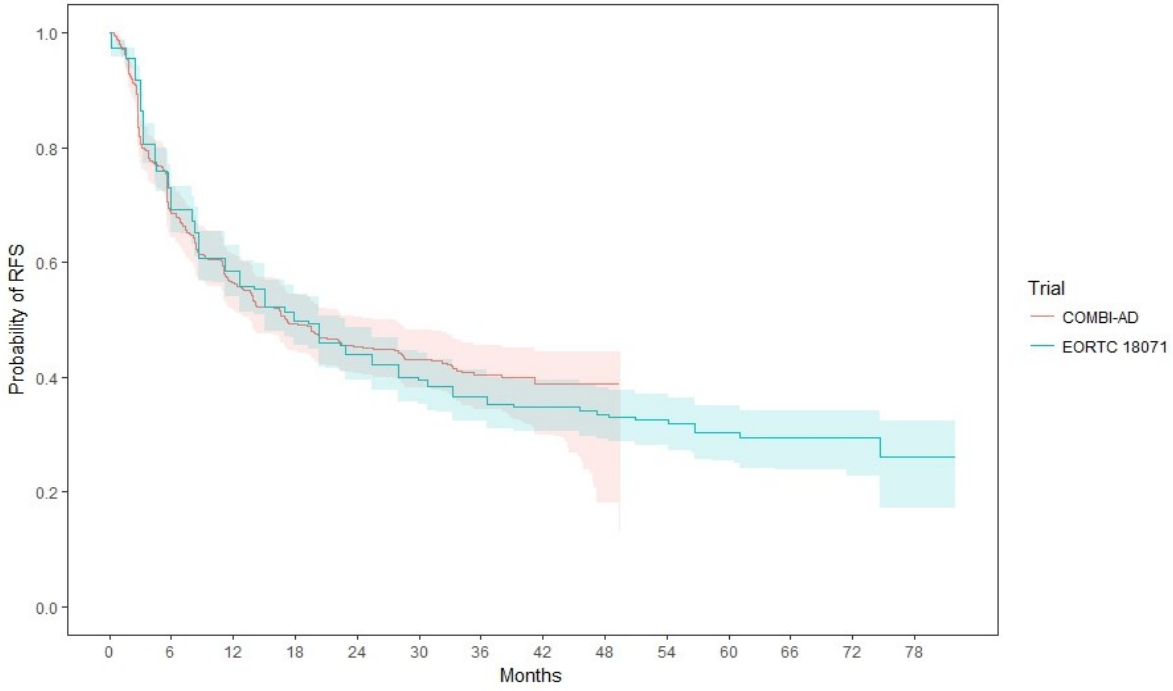
RFS after the observed period of the COMBI-AD trial

For the estimation of long-term RFS for all patients (those who received adjuvant dabrafenib plus trametinib and those who underwent routine surveillance [received placebo] only), clinical experts recommended the use of data from the EORTC 18071 trial: a phase III RCT comparing adjuvant ipilimumab to placebo in completely resected stage III melanoma.[57, 81]

Clinical experts considered the baseline characteristics of the patient population to be generally similar to that of the COMBI-AD trial (Appendix O).[81] Similarly, although data on BRAF status was not reported in the EORTC 18071 trial, the exact prognostic role of BRAF V600 mutations in melanoma remains uncertain. Data on the efficacy of immunotherapies in the metastatic setting have provided little evidence of a difference in outcomes for BRAF positive and BRAF wild-type patients, with the results observed in the trial populations assumed to be applicable to both sub-populations.[71, 90] As such, and in the absence of evidence to suggest that there would be a difference in outcomes for patients in the adjuvant setting, it is assumed that outcomes in the EORTC 18071 trial would be similar irrespective of BRAF status.

This assumption is further supported when comparing RFS for the placebo arms of the EORTC 18071 and COMBI-AD trials (Figure 16). The Kaplan-Meier curves were relatively similar up to month 24–30, after which a large number of patients were censored in COMBI-AD. Despite the visual separation after month 24–30, the confidence intervals overlap, indicating that the separation may be attributable to the number of patients at risk and censoring in the COMBI-AD trial.

Figure 16: COMBI-AD placebo and EORTC 18071 placebo RFS



Abbreviations: RFS: relapse-free survival.
Source: Analysis of COMBI-AD individual patient-level data[34] and EORTC 18071 data.[81]

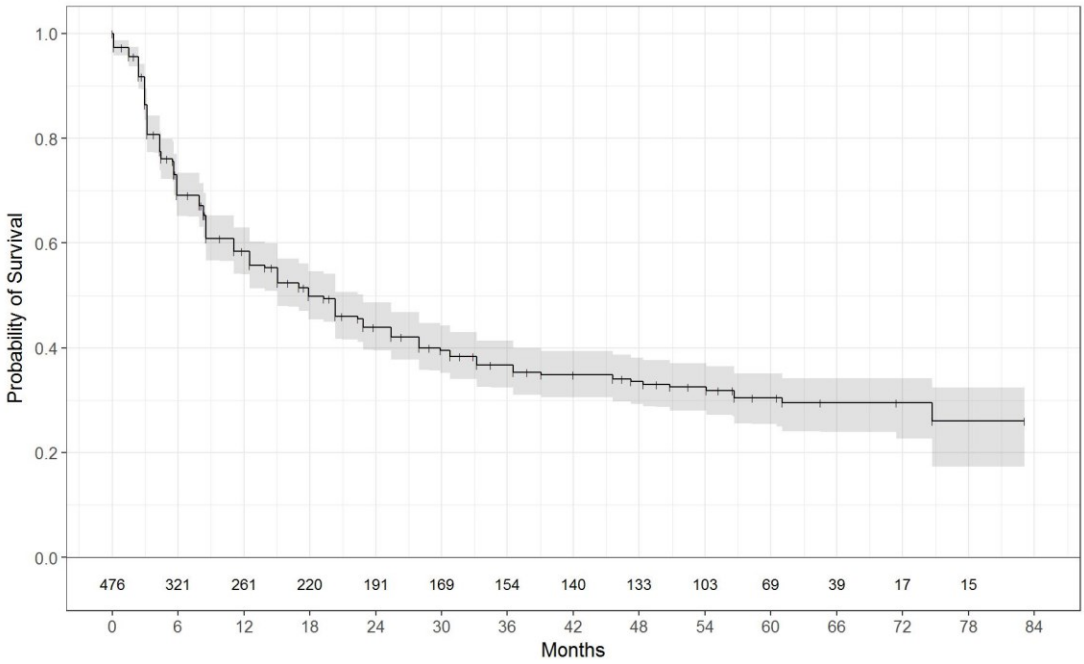
Data for RFS from the placebo arm of the EORTC 18071[81] were available for up to 7 years (using January 31st 2017 data cut-off) and were included in the model by digitising the Kaplan-Meier curve and recreating individual patient-level data using an adaptation of the Guyot algorithm (Figure 17).[81] Whilst the EORTC 18071 trial provided longer follow-up (5.3 year median follow-up[81]) than the COMBI-AD trial (2.8 year median follow-up[55]), it was still necessary to further extrapolate RFS from the placebo arm of the EORTC 18071 trial over the lifetime of the model.

In order to estimate the hazard of recurrence over time, parametric functions were fitted to the placebo arm of the EORTC 18071 RFS data from randomisation until the end of the observed period. The estimated hazard (time varying) was then applied to the COMBI-AD RFS data from the end of the observed period in the COMBI-AD (approximately 50 months), and the same hazard was applied to both the placebo and adjuvant dabrafenib plus trametinib treatment arms. This approach was considered reasonable in the absence of evidence that would suggest the hazard would be different between the two treatment arms following the observed period in the trial. Furthermore, clinical experts considered that there is no reason to believe that the hazard of recurrence in people who received adjuvant treatment would be greater than that observed in the placebo arm.[57]

Clinical experts also noted that adjuvant dabrafenib plus trametinib treatment was for a maximum duration of 12 months in the trial, and that there was no catch-up in the risk of recurrence after the end of the treatment. The experts also indicated that without adjuvant treatment the risk of recurrence is reduced with time (e.g. the hazard of recurrence reduces with time), and that this is independent of receipt of adjuvant treatment,[57] consequently, there were no reason to believe that the hazard of recurrence in the adjuvant arm would suddenly increase. This is supported by the literature that

suggests patients with stage III disease have a very high risk of recurrence for the first three years, with at least 80% of all recurrences occurring within this period. The risk of recurrence reduces significantly thereafter.[56]

Figure 17: EORTC 18071 placebo pseudo IPD Kaplan-Meier curve for RFS



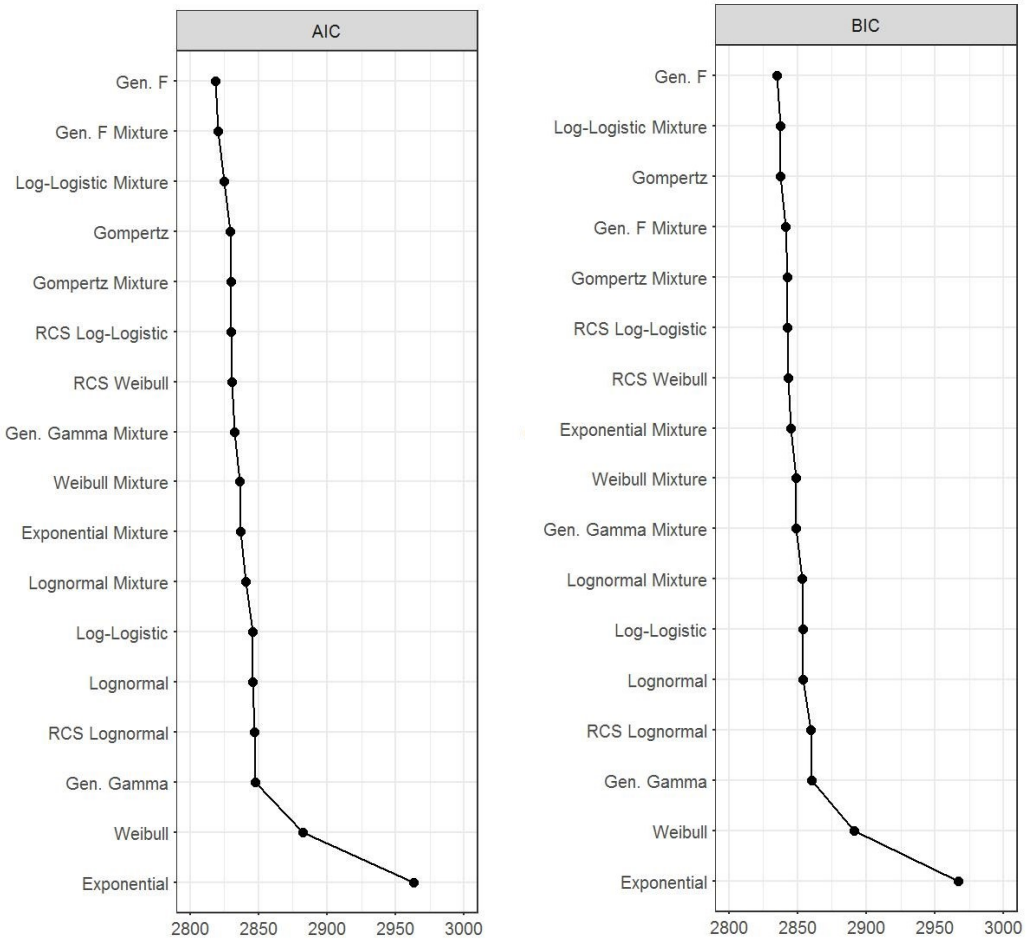
Abbreviations: IPD: individual patient-level data.
Source: Analysis of EORTC 18071 data.[81]

A range of parametric functions (exponential, Weibull, Gompertz, lognormal, log-logistic, gamma, generalised-F, RCS) were explored and fitted to RFS from the placebo arm of the EORTC 18071. These distributions were separated into two broad families (a) mixture-cure models and (b) non-mixture models.

The most appropriate distribution was selected by assessment of the visual fit to the Kaplan–Meier curve, assessment of the statistical goodness-of-fit using the AIC and BIC data and assessment of the clinical plausibility of the long-term extrapolation by clinical validation.

Figure 18 shows the statistical goodness-of-fit measured by the AIC and BIC and ranked in order of the best statistical fit. The generalised-F provided the best statistical fit the data (in terms of both AIC and BIC), followed by the generalised-F mixture-cure, the log-logistic mixture-cure and the Gompertz.

Figure 18: AIC and BIC for parametric distributions fit to RFS from EORTC 18071 placebo arm

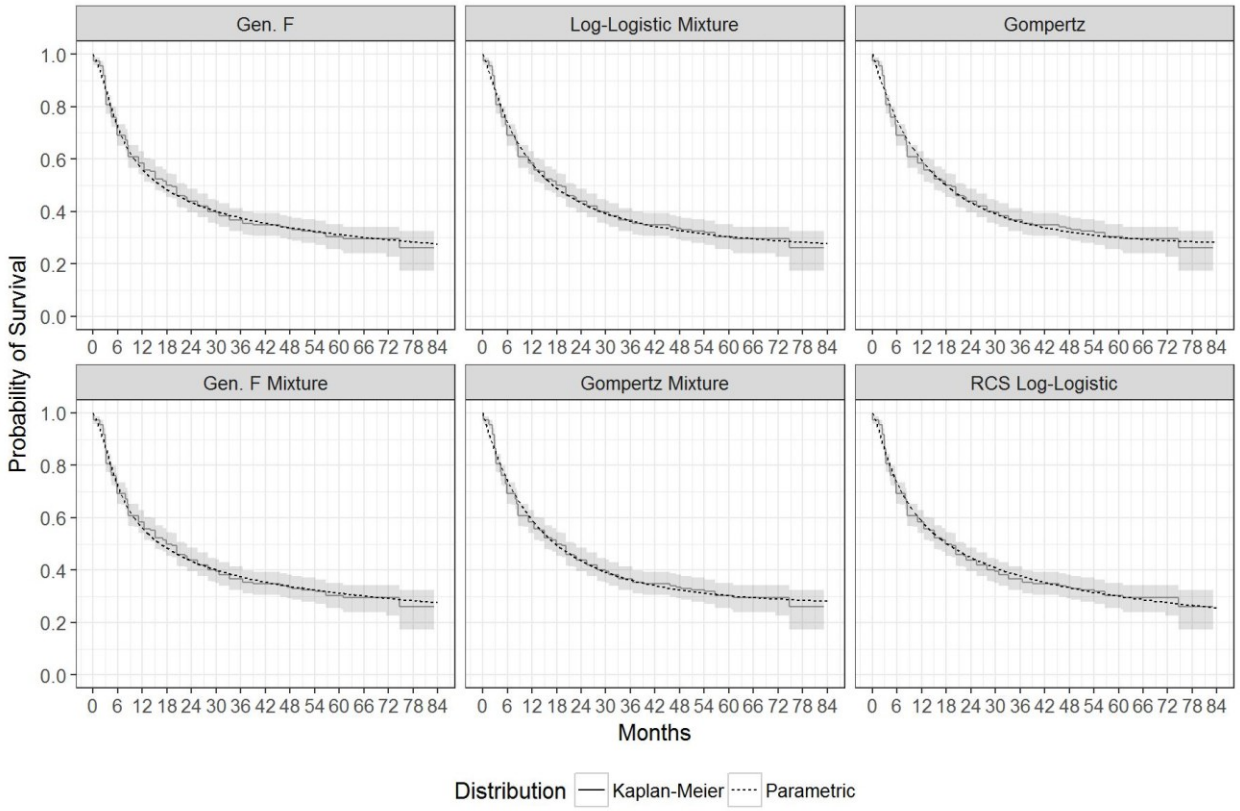


Note: Smaller values indicate a better fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Gen.: generalised; R: restricted; RCS: restricted cubic splines; RFS: relapse-free survival; U: unrestricted.
Source: Analysis of EORTC 18071 placebo arm patient-level data.[81]

However, as previously described, goodness-of-fit criteria only provide an indication of the goodness-of-fit to the observed period and do not categorically indicate that one distribution should be preferred over the remaining distributions.

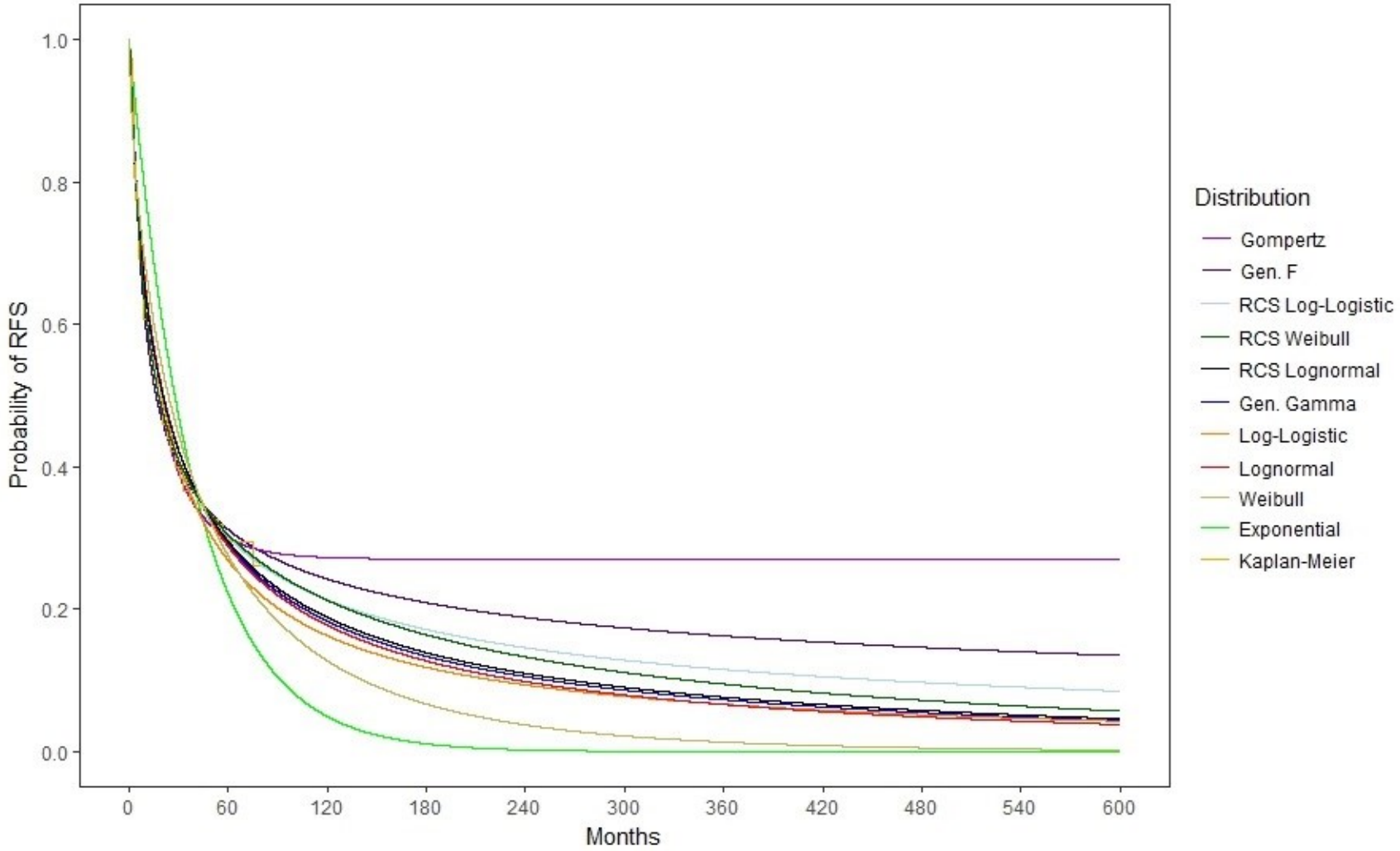
The distributions with the best AIC and BIC also provided a good visual fit to the observed period as shown in Figure 19. The full curve fitting report for all distributions can be found in Appendix N (Figure N.4.4).

Figure 19: Comparison of parametric distribution fits to RFS for the placebo arm of EORTC 18071 trial to the end of follow-up



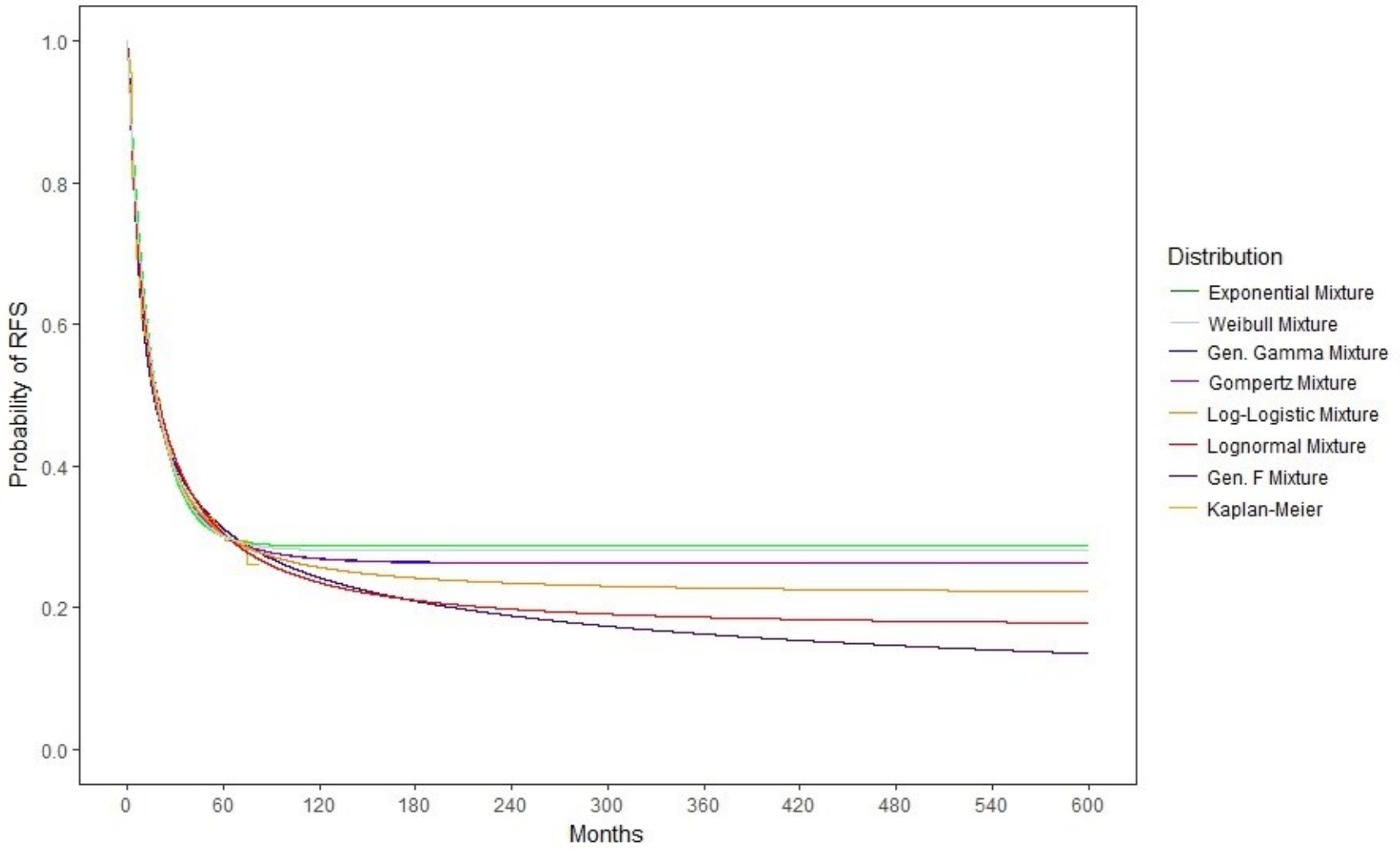
Abbreviations: Gen.: generalised; RCS: restricted cubic splines; RFS: relapse-free survival.
Source: Analysis of EORTC 18071 placebo arm patient-level data.[81]

Figure 20: Long-term RFS predictions for EORTC 18071 placebo arm (non-mixture models)



Abbreviations: Gen: generalised; RCS: restricted cubic splines; RFS: relapse-free survival.
Source: Analysis of EORTC 18071 placebo arm patient-level data.[81]

Figure 21: Long-term RFS predictions for EORTC 18071 placebo arm (mixture models)



Abbreviations: Gen: generalised; RFS: relapse-free survival.
Source: Analysis of EORTC 18071 placebo arm patient-level data.[81]

Whilst the statistical and visual fit should be considered, assessing the plausibility of the long-term extrapolation is crucial. UK clinical experts considered that the risk of recurrence after the end of the EORTC 18071 trial was expected to be low, with a low rate of recurrence after 10 years.[57] This assumption was supported by the latest data from the AJCC registry which showed a plateauing of the melanoma-specific survival after 10 years,[41] suggesting a low likelihood of recurrence after this point.

Although the generalised-F was considered the best fit statistically using the BIC (Figure 18), and was a good visual fit to the data (Figure 19) clinical experts considered the most clinically plausible curve for the EORTC 18071 placebo data in the non-mixture model family was likely to be in between the Gompertz and generalised-F distributions (Figure 20). To be more specific, the clinical experts considered the Gompertz estimates higher than expected and generalised-F estimates lower than expected.[57]

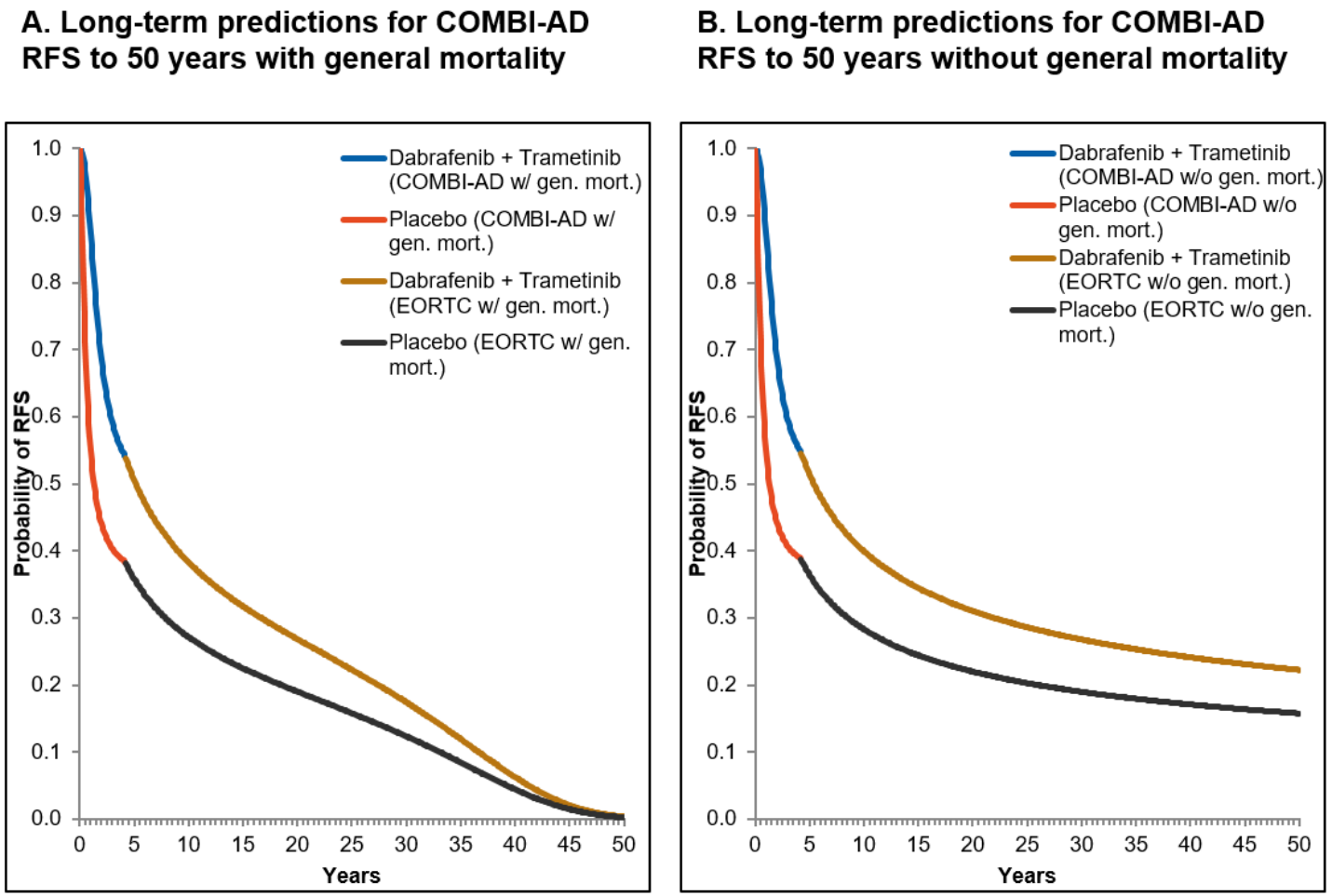
Within the mixture model family (Figure 21), the clinical experts also considered that the generalised-F distribution provided a lower bound estimate for long-term RFS, with the remaining mixture models considered to be more plausible.[57] Consequently, as a conservative measure, the base case for long-term extrapolation of the COMBI-AD trial used the hazard for recurrence from the generalised-F non-mixture model from the end of the COMBI-AD trial (approximately 50 months) out to the lifetime of the model. In order to assess the impact of the choice of parametric fit to the EORTC 18071 data, a range of scenario analyses were conducted assuming alternative clinically plausible distributions (Section B.3.8.3). A description of the cure fraction for the different mixture models assessed is reported in Appendix N, Table N.1.3.

Final estimate of RFS with and without adjustment for age-related mortality

Although the risk of disease recurrence was considered to be low after 10 years, patients are at an increased risk of dying from non-melanoma causes. Consequently, the base case analysis incorporated age-specific mortality data from UK specific lifetables[103] to account for the increased risk of dying due to older age (Figure 22).

To summarise, the final base case estimates for RFS over the lifetime horizon assumed the COMBI-AD trial data (log-logistic mixture model) up to month 50 for dabrafenib plus trametinib and placebo, followed by the hazard of recurrence from the generalised-F non-mixture distribution fit to the placebo arm of the EORTC 18071 trial. The results of the long-term RFS predictions with and without general mortality are shown in Figure 22A and B, respectively.

Figure 22: Long-term predictions for COMBI-AD RFS to 50 years



Abbreviations: RFS: relapse-free survival.
Source: Analysis of COMBI-AD individual patient-level data[34] and EORTC 18071 placebo arm patient-level data[81] incorporated age-specific mortality data from UK specific lifetables.[103]

Proportion of LR, DR and death events in RFS

The distribution of RFS events (LR, DR or death) during the trial period was assumed to be different to the distribution beyond the trial period, consistent with the data used for RFS.

RFS events within the observed period

The distribution of RFS events during the trial period was derived directly from COMBI-AD data: 166 out of 438 (38%) patients experienced an RFS event in the adjuvant dabrafenib plus trametinib arm of which: 3 (2%) patients died, 54 (33%) had a LR, 96 (58%) had DR, and 7 (4%) had LR and DR.[55]

In the placebo arm of the COMBI-AD trial, 248 out of 435 (57%) patients experienced an RFS event, of which: 1 (<1%) patient died, 107 (43%) had a LR, 126 (51%) had DR, and 7 (3%) had LR and DR.[55]

For the purposes of the economic model, patients who experienced both LR and DR were considered to have experienced a DR, and SPM were excluded from the economic analysis. The distribution of RFS events used in the model is summarised in Table 28 (the denominator is the number of patients in each arm that experienced an RFS event).

RFS beyond the observed period

In the absence of direct evidence, the distribution of events beyond the observed period of the COMBI-AD trial (50 months) was derived from the placebo arm of the EORTC 18071 trial. In this trial, 323 out of 476 (68%) patients in the placebo arm experienced an RFS event, of which: local or regional recurrence was reported in 114 patients (35%), distant metastasis in 199 (62%), and death in 10 (3%).[81] Given the assumption of the same hazard beyond the observed period for both treatment arms in the COMBI-AD trial, the same distribution of events from the placebo arm of the EORTC 1807 trial was applied to both treatment groups in the model (Table 28).

Table 28: Distribution of RFS events during the trial period and post-trial period used in the model[a]

RFS event category	COMBI-AD observed period		After COMBI-AD observed period (estimated from EORTC 18071)	
	Dabrafenib plus trametinib N (%)	Placebo N (%)	Dabrafenib plus trametinib N (%)	Placebo N (%)
LR	54 (33.8)	107 (44.4)	114 (35.3)	114 (35.3)
DR	103 (64.4)	133 (55.2)	199 (61.6)	199 (61.6)
Death	3 (1.9)	1 (0.4)	10 (3.1)	10 (3.1)
Total	160 (100)	241 (100)	323 (100)	323 (100)

[a]Excludes SPM and patients with both LR and DR events were considered as DR events for purposes of economic modelling.
Abbreviations: DR: distant recurrence; LR: loco-regional recurrence; RFS: relapse-free survival; SPM: second primary melanoma.
Source: Long *et al.* (2017)[55] and Eggermont *et al.* (2016).[81]

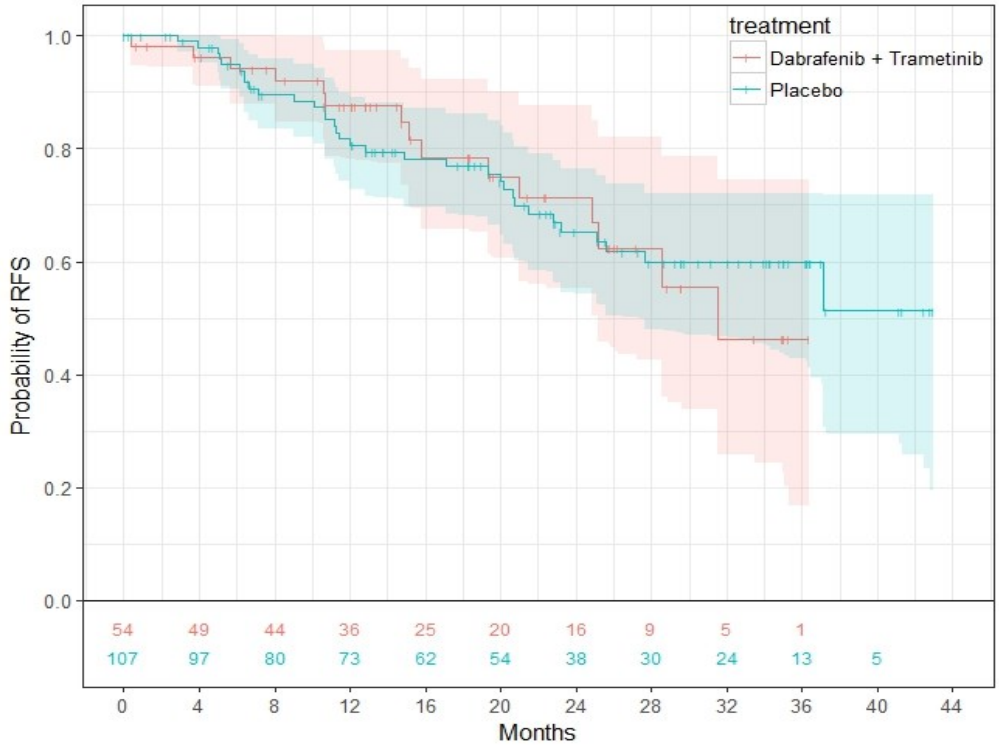
B.3.3.2 Loco-regional recurrence

In the economic model, patients in the LR health state could experience a subsequent LR, DR or death. Since follow-up for disease recurrence in COMBI-AD only continued until the first recurrence (and thereafter, patients were followed for survival), the transitions from the LR health state to the DR health state or subsequent LR were not directly available from the trial.

There are limited data on the risk of subsequent LR or DR following a previous LR in a population similar to the one included in the COMBI-AD trial. Clinical opinion suggested that the shape of the survival distribution is likely to follow the same pattern as RFS (e.g. high hazard initially which decreases with time).[57] This was supported by a study conducted by Salama *et al*. (2017)[105] that analysed the timing and patterns of recurrence in early stage melanoma. The study showed that the hazard of recurrence following a previous LR was higher compared with the hazard of recurrence in patients without a previous LR up to month 40, after which the hazard was broadly similar.[105]

Since data were available on post-LR survival in COMBI-AD (Figure 23), it was possible to approximate the transitions from the LR health state by calibrating RFS using a HR so that the model prediction for OS post-LR matches what was observed in the trial. This was achieved by adjusting the placebo arm of the RFS curve by a HR that yielded a model prediction for post-LR OS similar to that observed in the COMBI-AD trial. The HR was only applied to the RFS curve during the observed period (up to month 50), after which the hazard of recurrence for LR was assumed to be the same as for RFS. Figure 13 shows that the post-LR OS curves for the two treatment arms cross at approximately 24 months, which is possibly due to the lower number of patients at risk in the dabrafenib plus trametinib arm.

Figure 23: OS after LR in COMBI-AD



Abbreviations: LR: loco-regional recurrence; OS: overall survival.
Source: Analysis of COMBI-AD individual patient-level data.[34]

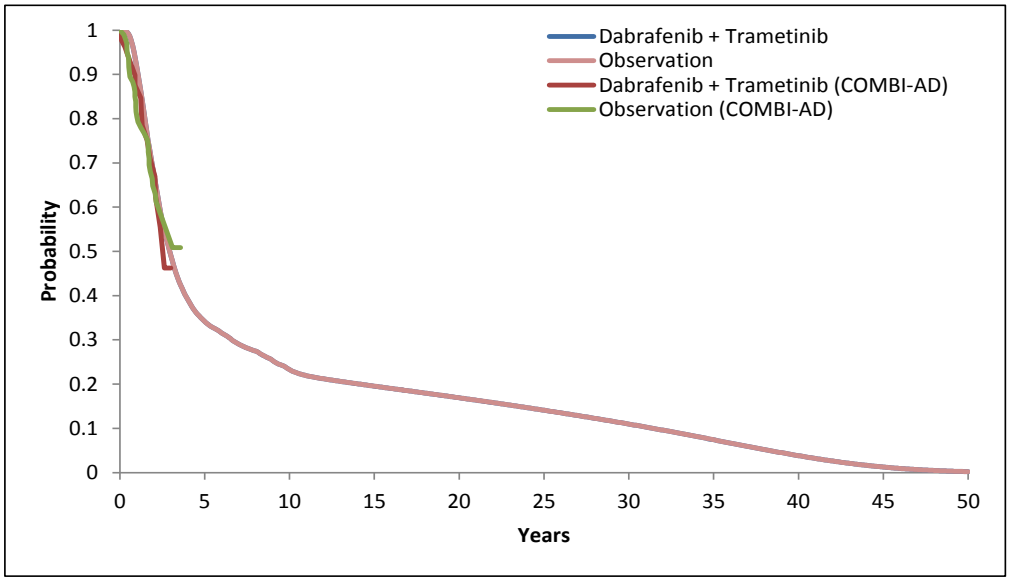
An option has been included in the model to calibrate the transition from LR to a subsequent LR, DR or death. The model calibration employs an iterative process as described by the following steps:

1. All patients were assumed to start in the LR health state.
2. The RFS curve for placebo from the COMBI-AD trial was used initially to model the probability of recurrence events,
3. A HR was applied to the RFS curve (during the observed period only),
4. The sum of the squared differences between the model prediction and observed survival was calculated,
5. The HR applied to the RFS curve was then varied (iteratively) until the model prediction for OS (post-LR) was close to the observed post-LR OS (e.g. until the sum of the squared error was minimised). The linear programming solver engine provided within Microsoft Excel (Excel Solver) was used to calibrate the HR applied to the RFS curve.

The calibration process estimated a HR of 2.53, suggesting that the risk of recurrence following a LR was approximately 2.5 times higher in patients who had experienced a LR compared with those who had not experienced a LR during the first 50 months. Clinical experts considered this estimate to be plausible[57] and it is broadly in line with HR for the second recurrence versus first recurrence in the study performed by Salama *et al*. (2017),[105] where from figure 2 in this publication, the 40-month average HR for the second recurrence versus first recurrence was calculated to be around 2.68. A comparison of the baseline characteristics of the patient population in the COMBI-AD trial versus Salama *et al*. (2017) can be found in Appendix O.

The results of the calibrated post-LR OS compared to the COMBI-AD observed post-LR OS are shown in Figure 24, and the risk of recurrence following a LR was explored in the sensitivity analyses by varying the HR. Despite the uncertainty in the risk of recurrence following an initial recurrence, varying the HR had no material impact on the ICER (Section B.3.8.3).

Figure 24: Calibrated post LR OS vs observed post-LR OS



Abbreviations: LR: loco-regional recurrence; OS: overall survival.
Source: Analysis of COMBI-AD individual patient-level data.[34]

Proportion of LR, DR and death events following a LR

There is limited evidence on the distribution of recurrence events following a LR. Clinical expert advice suggested that patients who had experienced a LR event were more likely to experience a DR compared with patients with no previous LR.[57] As such, clinical experts expected the proportion of patients in the LR health state that experienced a DR to be greater compared with the proportion of patients in RFS that experienced a DR.[57]

In the absence of direct evidence, the distribution of events following a LR was derived from a study conducted in 2,505 melanoma patients with regional lymph node metastasis (White *et al.* [2002]).[100] In this study, 814 did not have a recurrence and 1,608 developed a recurrence, of which 245 were local/in-transit, 296 regional and 1,067 distant. Based on the total number of patients (n=2,505) and number of patients who did not have a recurrence (n=814) or experienced a recurrence (n=1,608), it was possible to derive the number of patients who died prior to a recurrence (n=83).[100] Although the population included in this study may not reflect the patient population in the COMBI-AD trial, the uncertainty in these parameters was explored in the scenario analyses (Section B.3.8.3). The distribution of events following a LR used in the base case is presented in Table 29, and whilst the distribution was assumed to be constant, it should be noted that age-related mortality was included separately. A comparison of the baseline characteristics of the patient population in the COMBI-AD trial versus White *et al.* (2002) can be found in Appendix O.

Table 29: Distribution of events following a LR in base case

Event	Number of Events	Distribution
Local/in-transit/regional	541	32.0%
Distant	1,067	63.1%
Death	83	4.9%
Total	**1,691**	**100%**

Abbreviations: LR: loco-regional recurrence.
Source: White *et al.* (2002).[100]

B.3.3.3 Overall survival following distant recurrence

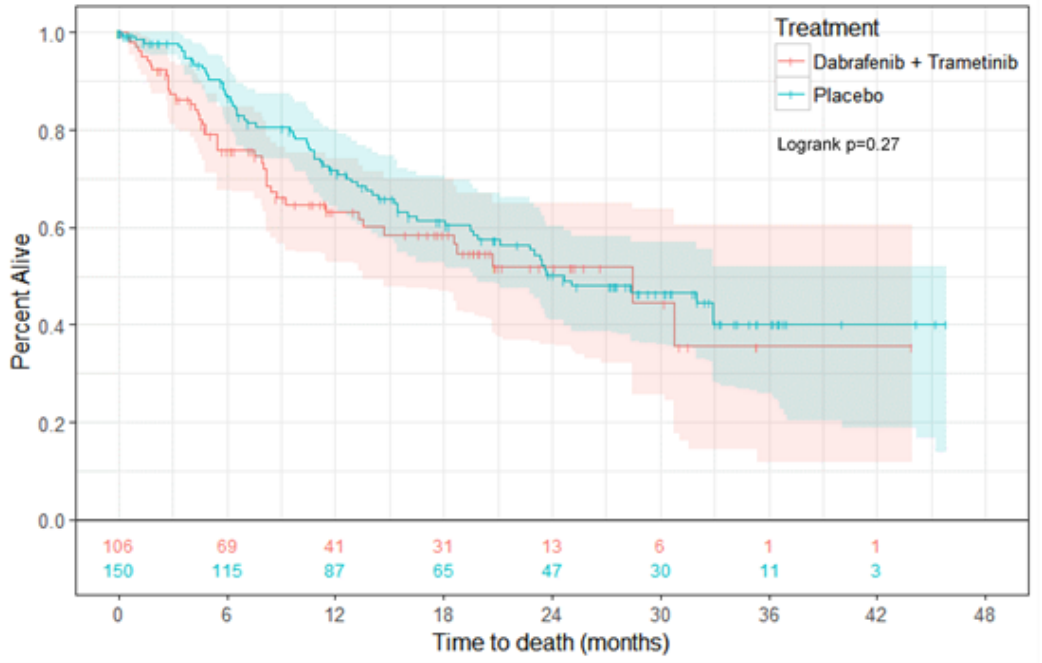
As highlighted in Section B.3.2.2, post-DR OS was not explicitly used in the model, but for validation purposes was included to estimate OS, since OS is a function of the time spent in previous health states.

As described in Section B.2.6.5, amongst those patients who experienced a recurrence event (excluding death), similar proportions of patients in both treatment arms of the COMBI-AD trial received any type of systemic anti-cancer therapy post-recurrence, but more patients in the dabrafenib plus trametinib arm received immunotherapy compared to placebo [34] Figure 25 shows the post-DR OS from the COMBI-AD trial during the observed period, and shows there was no statistically significant differences (p=0.27) in post-DR OS in patients receiving adjuvant dabrafenib plus trametinib or placebo (confidence intervals overlapping). Clinical experts suggested that the visual difference could be explained by the different mix of treatments (e.g. immunotherapies or targeted therapies) received at the point of recurrence, but that they expected the long-term to be similar irrespective of the starting treatment.[57]

A log-logistic function was fitted to the data from COMBI-AD up to month 30, after which it assumed the weighted hazard reported in TA366 for pembrolizumab[90] and TA396 for dabrafenib plus

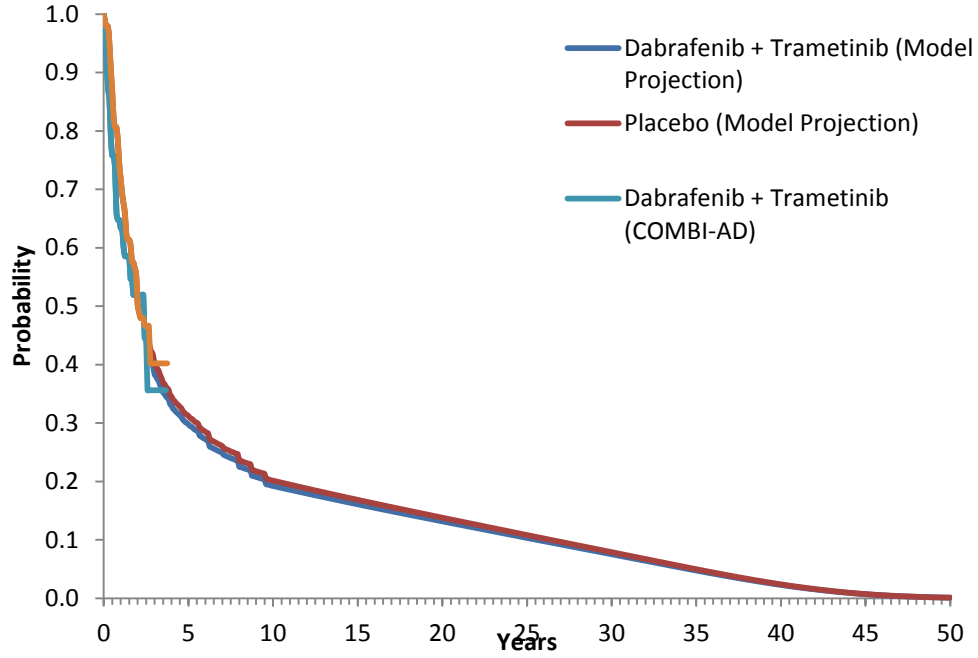
trametinib.[20] The proportions of patients receiving immunotherapy and targeted therapy were taken from the COMBI-AD trial and were used to calculate the one-off cost and QALYs for immunotherapy and targeted therapy at the point of recurrence (Table 38 in Section B.3.5.2). It should be noted that although a number of alternative assumptions or extrapolations could be used following the observed period, post-DR OS has no impact on incremental costs and QALY and hence, the ICER and the simplified approach was considered reasonable by clinical experts.[57] The post-DR OS assumed in the model is shown below in Figure 26.

Figure 25: COMBI-AD post-DR OS



Abbreviations: DR: distant recurrence; OS: overall survival.
Source: Analysis of COMBI-AD individual patient-level data.[34]

Figure 26: Post-DR OS estimated in the model



Abbreviations: DR: distant recurrence; OS: overall survival.
Source: Analysis of COMBI-AD patient-level data[34] and data from TA366[90] and TA396[20]

B.3.4 Measurement and valuation of health effects

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

As described in Section B.2.6.3, HRQoL was assessed in COMBI-AD using the EQ-5D-3L, which is consistent with the NICE reference case.[99] Per study protocol, assessments were scheduled to occur at baseline and then every 3 months up until month 24. After month 24, assessments were scheduled every 6 months, and although the number of patients available for assessment declined during the study (primarily due to consent withdrawal, missed scheduled visits, and deaths), completion rates amongst available patients were high [redacted].[34]

Differences in mean EQ-5D-3L scores from baseline was assessed between the treatment arms using mixed-model repeated measures analyses and [redacted] (Section B.2.6.3).[34] As reported in Table 14 in in Section B.2.6.3, baseline utility scores were [redacted] and [redacted] for the dabrafenib plus trametinib arm and the placebo arm, respectively. Over the 12 month treatment period, utility scores ranged from [redacted] and [redacted] in the dabrafenib plus trametinib arm and the placebo arm, respectively.[34]

B.3.4.2 Mapping

Mapping was not applicable since utility values were evaluated using EQ-5D-3L data directly from the COMBI-AD trial.

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

An SLR was conducted to identify relevant HRQoL data in patients with stage III melanoma, following complete resection. Studies conducted in patients with advanced (metastatic) resectable melanoma were also considered for inclusion. Searches were performed on 2nd November 2017. The full texts of 202 records were retrieved and following assessment for relevance, only one study was eligible for inclusion within the SLR. The study was reported in two records: an abstract by Middleton *et al.* in *Value in Health*, and a 2017 publication by Middleton *et al.* in *BMC Cancer.*[106, 107] Full details of the SLR search strategy, study selection process and results are reported in Appendix H.

B.3.4.4 Adverse reactions

The results of the COMBI-AD trial demonstrated that adjuvant dabrafenib plus trametinib is generally well tolerated, with the majority of AEs mostly grade 1 or 2 and were consistent with the known safety profile of dabrafenib plus trametinib (Section B.2.10.2).

Since the HRQoL was directly measured in the COMBI-AD trial,[34] the decrements in HRQoL associated with AEs is already implicitly included in the economic analysis.

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

Utility values for the RFS and LR health states were taken directly from COMBI-AD trial using the EQ-5D-3L.[34]

To adjust for the baseline utility, utility values were estimated using a generalised estimation model (GEE) with an identity link function, normal error term distribution, and exchangeable correlation structure with model covariates for baseline EQ-5D utility index value and health state at assessment. The latter included RFS on treatment, RFS off treatment, LR, and DR. RFS off treatment included both patients randomised to placebo and those randomised to dabrafenib plus trametinib who had discontinued treatment. The number of patients contributing the GEE regression model is shown in Table 30.

Table 30: Numbers of patients and EQ-5D-3L assessments contributing to GEE regression analyses of EQ-5D-3L assessments in COMBI-AD

	Dabrafenib plus trametinib	Placebo	Total
Number of patients			
Baseline	394	370	764
RFS on treatment	355	0	355
RFS off treatment	362	332	694
On or after loco-regional recurrence	36	52	88
On or after distant recurrence	54	78	132
Number of assessments			
Baseline	394	370	764
RFS on treatment	941	0	941
RFS off treatment	2,039	2,140	4,179

On or after loco-regional recurrence	47	67	114
On or after distant recurrence	57	83	140

Abbreviations: EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; GEE: generalised estimating equation.
Source: Analysis of COMBI-AD patient-level data.[34]

Results of the GEE regression on EQ-5D utility index values are shown in Table 31. Baseline EQ-5D-3L utility index values were significant predictors of follow-up utility values, with higher baseline scores associated with higher EQ-5D-3L scores at follow-up assessments. Utility values for RFS on and off treatment, and for LR were significantly higher than for patients in DR

Table 31: Results of GEE regression model predicting EQ-5D-3L at follow-up assessments in COMBI-AD

Variable	Parameter Estimate	95% Confidence Interval	P-value
Intercept	0.3729	0.3097–0.4360	<0.0001
Baseline EQ-5D	0.5753	0.5070–0.6436	<0.0001
RFS on treatment	-0.0154	-0.0266– -0.0042	0.007
LR	-0.0336	-0.0588– -0.0084	0.009
DR	-0.0773	-0.1096– -0.0451	<0.0001
RFS off treatment	0.0000	-	-

Abbreviations: DR: distant recurrence; EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; GEE: generalised linear model/generalised estimating equation; LR: loco-regional recurrence; RFS: relapse-free survival.

The utility values estimated from the GEE regression analyses of COMBI-AD EQ-5D assessments used in the economic model for RFS and LR are shown in Table 32. It is noted that utility value for the LR health state is relatively high (0.836) and may be due to the small numbers of patients and assessments contributing to the analysis (table 30). Additionally, the timing of the EQ-5D assessment in relation to the documentation of disease recurrence may also have also had an impact on the observed value.

Table 32: Utilities used in the model

State	Utility value: mean (SE)	95% confidence interval	Justification
RFS on treatment	0.854 (0.006)	0.8426–0.8653	Based on statistical models fitted to EQ-5D-3L data collected in COMBI-AD
RFS off treatment[a]	0.869 (0.005)	0.8601–0.8786	Based on statistical models fitted to EQ-5D-3L data collected in COMBI-AD
LR	0.836 (0.013)	0.8100–0.8616	Based on statistical models fitted to EQ-5D-3L data collected in COMBI-AD

[a]RFS off treatment includes post-treatment dabrafenib plus trametinib and all placebo.
Abbreviations: DR: distant recurrence; EQ-50-3LD: EuroQol 5-Dimensions 3-Levels; RFS: relapse-free survival; SE: standard error.

As previously described in Section B.3.2.2, the discounted QALYs (and costs) associated with distant recurrence were applied as one-off costs and QALYs at the point of entry into the DR health state. As such the utility value for DR derived from the EQ-5D in COMBI-AD was not used in the

economic model, and further details of the QALYs (and costs) in the DR health state are provided in Section B.3.5.2.

The utility values were adjusted for age-related declines in HRQoL by using age- and gender-matched general population utilities based on published UK population norms for the EQ-5D-3L.[108]

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

An SLR was conducted to identify any relevant cost or resource use data associated with the treatment of with stage III melanoma, following complete resection. Searches were performed in November 2017 and full details of the SLR search strategy, study selection process and results are reported in Appendix I. The full texts for 152 records were retrieved and three eligible studies, reported in six publications, were deemed eligible for inclusion.

The three studies identified are detailed below:

- One decision model and micro-costing study, reporting Australian healthcare costs of melanoma diagnosis and treatment (Elliot *et al.* [2017a] and Elliot *et al.* [2017b])[109, 110]
- One retrospective routine surveillance study estimating the cost of illness associated with stage IIIB/IIIC melanoma in France, Germany and the UK (Grange *et al.* [2017], Harries *et al.* [2017] and Kontoudis *et al.* [2014])[111-113]
- One study reporting the cost-effectiveness of complete lymph node dissection in a German hospital (Stoffels *et al.* [2012]).[114]

Despite the identification of one study that provided resource use data from the UK, resource use estimates within the economic model were derived from consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by leading UK melanoma clinicians. These estimates were further validated by UK clinical experts as appropriate for use in the economic model and thus the study by Grange *et al.* (2017), Harries *et al.* (2017) and Kontoudis *et al.* (2014) was not considered in the model.

Costs informing the economic model were sourced from 2016/2017 NHS reference costs, the Personal Social Services Research Unit (PSSRU) and the British National Formulary (BNF) where possible.

B.3.5.1 Intervention and comparators' costs and resource use

BRAF V600 mutation testing

NICE clinical guidelines for the management of melanoma specify that genetic testing should be offered to all patients if a targeted systemic therapy, such as dabrafenib plus trametinib, is a possible treatment option.[20, 30] As such, the costs of BRAF testing were excluded from the model since the cost of BRAF testing would be the same in both the dabrafenib plus trametinib and routine surveillance (placebo) arms.

Intervention (adjuvant treatment with dabrafenib plus trametinib)

The costs associated with the treatment of dabrafenib plus trametinib included drug acquisition and administration costs as well as follow-up and monitoring costs.

Drug acquisition costs

A confidential simple PAS exists for dabrafenib plus trametinib for unresectable or metastatic melanoma, in which the NHS will be able to procure both dabrafenib and trametinib at net prices lower than the current list prices. Should the list prices of either dabrafenib or trametinib change, the percentage discount will change accordingly to maintain a confidential fixed net price.

Dabrafenib is provided to the NHS with a [redacted] discount off the current NHS list price and trametinib is provided with a [redacted] discount off the current NHS list price. The unit costs of both are presented in Table 33.

Table 33: Unit costs of dabrafenib and trametinib

Drug	Form	Strength	Pack size	Cost per pack (£)		Total number of mg in a pack	Cost per unit (mg), £		Source
				List price	PAS price		List price	PAS price	
Dabrafenib (Tafinlar)	Capsule	75 mg	28	1,400.00	[redacted]	2,100	0.67	[redacted]	BNF[33]
Trametinib (Mekinist)	Tablet	2 mg	30	4,800.00	[redacted]	60	80	[redacted]	BNF[33]

Abbreviations: BNF: British National Formulary; PAS: patient access scheme.

Drug acquisition costs were applied in the on-treatment phase of the RFS health state only. In line with the proposed marketing authorisation and dosing schedule followed in the COMBI-AD trial, adjuvant treatment with dabrafenib plus trametinib was assumed to continue for a maximum duration of 12 months.

The dosing for dabrafenib plus trametinib is as follows:

- Dabrafenib 150 mg twice daily
- Trametinib 2 mg once daily.

Time-on-treatment data were complete in the COMBI-AD trial, in that there were no censored patients.[34] Consequently, data on the cumulative dose (Figure 27a, Figure 27b) was used to calculate drug costs as the cumulative dose provides a more accurate reflection of the dose received, taking into account both dose interruptions and dose reductions.

In order to estimate the total number of packs of dabrafenib and trametinib per patient, the cumulative dose for each patient was divided by the total number of mg in a pack (based on 28 x 75 mg for dabrafenib and 30 x 2 mg for trametinib) rounding up to the nearest whole number (Figure 27c, Figure 27d). Based on these data, the average number of packs required per patient was estimated to be [redacted] packs of dabrafenib plus [redacted] packs of trametinib. This approach assumes that open packs of medication are costed in full (i.e. assuming wastage) and any packs that are not open would be returned. Scenario analyses were conducted using drug costs based on mean cumulative dose (i.e. assuming no wastage).

No administration costs were applied in the economic model because dabrafenib plus trametinib is an oral therapy. However, a monthly pharmacy cost was applied, based on the mean duration of treatment in the COMBI-AD trial and a monthly dispensing cost of £13.90, based on the cost of 12 minutes of time for a hospital pharmacist (hourly rate of a hospital pharmacist £69.51/ 5 =

£13.90), inflated to 2015/2016 price [20, 115, 116]. This cost was applied in the on-treatment phase of the RFS health state only.

The number of prescriptions for each patient was estimated by dividing cumulative dose of each medication by the dosage in a 28-day supply of dabrafenib and a 30-day supply of trametinib. This yielded an average of [redacted] prescriptions of dabrafenib and [redacted] prescriptions of trametinib and the cost of dispensing dabrafenib was therefore estimated to be [redacted] (£13.90 x [redacted]) and trametinib [redacted] (£13.90 x [redacted]).

[redacted]

Source: Analysis of COMBI-AD patient-level data.[34]

Comparator (routine surveillance)

No drug acquisition costs were applied for routine surveillance (placebo) since no active treatment is given. Routine surveillance (placebo) instead comprises clinical follow-up and imaging surveillance (see Monitoring and follow-up costs below).

Monitoring and follow-up costs

Following UK clinical expert advice,[57] base case estimates of the costs and resource use associated with routine surveillance (placebo) were derived from consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians.[56] As described in Section B.1.3.2, clinical review is recommended every 3 months for 3 years, then every 6 months up to 5 years, and then annually up to 10 years. In addition, imaging (CT chest, abdomen and pelvis *or* PET-CT total body scan, plus MRI head scan) is recommended at baseline and then every 6 months through year 3, and annually up to year 5 (Table 34).[56]

Clinical experts also indicated that patients who receive dabrafenib and trametinib in the adjuvant setting would be monitored more closely than those on routine surveillance, with monthly clinical review during the first year (during the 12-month treatment period), a CT or PET body scan every 6 months, and an echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) every 3 months.[57] After completion of treatment, resource utilisation for patients receiving dabrafenib plus trametinib was assumed to be the same as patients receiving routine surveillance (placebo); patients who discontinue treatment early were assumed to have follow-up and monitoring equal to routine surveillance (placebo) for the remainder of the first year.

The one-month resource use estimates inputs used in the model are reported in Table 35 with the unit costs for follow-up and monitoring reported in Table 34. In clinical practice, while on treatment with dabrafenib plus trametinib, patients would be seen by an oncologist, whilst those who have completed treatment and/or undergoing routine surveillance could be seen by a combination of oncologists, surgeons, and dermatologists. A simplifying assumption of an outpatient visit to a medical oncologist was used in the model base case as the medical resource associated with the management of these patients, and the costs of monitoring were explored in the scenario analyses.

Table 34: Routine surveillance as described by consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians as used in the model base case

Clinical review	Full examination of the skin and regional lymph nodes: • Through Year 3 (after staging): 3-monthly • Years 4–5: 6-monthly • Years 6–10: annually
Imaging surveillance	CT scan of the chest, abdomen and pelvis *or* PET-CT total body scan, and MRI head scan: • Baseline • Through Year 3 (after staging): 6-monthly • Years 4–5: annually

Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging.
Source: Consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians.[56]

Table 35: One-month resource use in the adjuvant setting based on the consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians and clinical expert opinion, by treatment and time

Resource	Dabrafenib plus trametinib				Placebo			
	Months 1–12	Months 13–36	Months 37–60	Months 61–120	Months 1–12	Months 13–36	Months 37–60	Months 61–120
Outpatient visit to medical oncologist	1.000	0.333	0.167	0.083	0.333	0.333	0.167	0.083
CT scan of chest abdomen and pelvis	0.083	0.083	0.042	N/A	0.083	0.083	0.042	N/A
PET-CT scan	0.083	0.083	0.042	N/A	0.083	0.083	0.042	N/A
MRI of brain	0.167	0.167	0.083	N/A	0.167	0.167	0.083	N/A
ECHO	0.167	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MUGA	0.167	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: CT: computerised tomography; NHS: National Health Service; MRI: magnetic resonance imaging; PET: positron emission tomography; MUGA: Multiple-gated acquisition scan; ECHO: echocardiogram
Source: Consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians[56] and clinical expert opinion.[57]

Table 36: Unit costs for follow-up and monitoring in the adjuvant setting

Treatment type	Unit cost (£)	Cost source
Outpatient visits		
Medical oncologist	161.13	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. Total Outpatient Attendances HRG 370 Medical Oncology
Radiological exams		
CT scan of chest, abdomen and pelvis	120.67	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. Weighted average (based on frequency) of ”Total HRGs”: • HRG RD25Z Computerised Tomography Scan of Three Areas, without Contrast (£102.86, Frequency: 33,575) • HRG RD26Z Computerised Tomography Scan of Three Areas, with Contrast (£122.33, Frequency: 360,551)
MRI of brain	142.32	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. Weighted average (based on frequency) of ”Total HRGs”: • HRG RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over (£138.24, Frequency: 1,572,349) • HRG RD02A Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over (£162.23, Frequency: 230,031) • HRG RD03Z Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast (Frequency: £180.48, 48,022)

PET-CT scan	594.82	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. HRG RN01A Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over
ECHO	70.36	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. HRG RD51A Simple Echocardiogram, 19 years and over
MUGA	294.34	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. HRG RN22Z Multi Gated Acquisition (MUGA) Scan

Abbreviations: CT: computerised tomography; NHS: National Health Service; MRI: magnetic resonance imaging; PET: positron emission tomography; MUGA: Multiple-gated acquisition scan; ECHO: echocardiogram
Source: 2016/2017 NHS Reference Costs.[117]

B.3.5.2 Subsequent therapy costs and resource use

Costs associated with the management of LR

Patients with a loco-regional recurrence were assumed to receive a CT scan and a follow-up appointment with a medical oncologist, based on expert clinical feedback.[57] It was further assumed that 90% of patients would be surgically resected, while those who were unresectable (10%) would-be treated with immunotherapy (70%) or targeted therapy (30%). The costs of monitoring were based on the 2016/2017 NHS reference costs where possible, [117] and the costs of immunotherapy or targeted therapy were based on the costs of medication (including PAS), administration, and adverse events for a course of pembrolizumab reported in TA366[6] or a course of dabrafenib and trametinib reported in TA396.[20]

TA366 was used since the cost reported included the PAS, and therefore more likely reflects the true cost to the NHS (Table 37). UK expert clinical opinion suggested that whilst it was reasonable to assume the cost of pembrolizumab as monotherapy immunotherapy, the combination ipilimumab/nivolumab would be likely to be used first-line in patients with a LR that are fit enough. Although the cost (including PAS) associated with a course of combination immunotherapy is not publicly available, it is likely that the cost associated with immunotherapy may be higher than the cost estimated, and therefore the costs of immunotherapy in the analysis may be underestimated.

Table 37: Resource utilisation and costs for treatment of LR

Treatment type	LR		Unit cost (£)	Cost source
	Patients (%)	Units		
Outpatient visit to medical oncologist	100%	1	161.13	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. " Total Outpatient Attendances HRG 370 Medical Oncology [117]
Surgical resection	90%	1	1,816.32	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. Elective Inpatient HRG JC42A Intermediate Skin Procedures, 13 years and over[117]

Treatment type	LR		Unit cost (£)	Cost source
	Patients (%)	Units		
CT scan of chest, abdomen, and pelvis	100%	1	120.67	NHS Ref Costs 2016-17 NHS Trusts and Foundation Trusts. Weighted average (based on frequency) of "Total HRGs": • HRG RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over (£138.24, Frequency: 1,572,349) • HRG RD02A Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over (£162.23, Frequency: 230,031) • HRG RD03Z Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast (Frequency: £180.48, 48,022)[117]
Immunotherapy	10%	1	68,887.00	Costs of medication (including PAS), administration, and adverse events for a course of pembrolizumab (70% of patients with unresectable LR) reported in TA366[6] or a course of dabrafenib and trametinib (30% of patients with unresectable LR) reported in TA396.[20]

Abbreviations: CT: computed tomography; LR: loco-regional recurrence.

Costs and QALYs associated with the management of DR

Upon DR, patients were assumed to have one outpatient visit to a medical oncologist, and one CT scan or PET-CT scan, based on expert clinical feedback.[57] Further to these costs, and as highlighted in Section B.3.2.2, the additional costs and QALYs associated with the management of DR and terminal care were incorporated into the model as one-off costs and QALYs at the point of recurrence, using estimates reported in previous NICE appraisals. Whilst the limitations of this approach are acknowledged, it was considered a pragmatic and has been previously reviewed and considered reasonable by the Appraisal Committees of prior technology appraisals.

Specifically, costs reported for pembrolizumab in TA366 (£83,282)[118] and dabrafenib and trametinib in TA396 ([redacted])[20] were weighted according to relative receipt of the pooled proportions of immunotherapies (44%) and targeted therapies (56%) received as first-line post-DR systemic anti-cancer therapies in COMBI-AD.[34] Advice from clinical experts indicated there is limited evidence of the impact of prior adjuvant therapy on distant metastasis,[57] in addition, there were no statistically significant differences (p=0.27) observed in the post-DR OS of patients receiving adjuvant dabrafenib plus trametinib or placebo in COMBI-AD (Figure 26).

In addition, UK clinical experts further noted that the recording of post-recurrence therapies may not have been fully complete and the trial data may need to be interpreted with caution[57] (information was not recorded for 59 patients).[34] In addition, 14 patients received a mix of immunotherapy and targeted therapy and 10 patients received chemotherapy.[34, 55]

Consequently, the pooled distribution of therapies from the COMBI-AD trial was used, and applied to both treatment arms in the model to reduce biasing the results toward one treatment or another

if it were assumed that outcomes were associated with the initial treatment arm (i.e. different costs and QALYs following a DR according to the initial arm).

The weighted costs and QALYs for DR were calculated to be £142,699 (0.439 x £83,282+0.561 x [redacted]) and 3.23 (0.439 x 2.960 + 0.561 x 3.443) respectively (Table 38), and whilst there are uncertainties associated with these estimates, a number of scenario analysis were conducted, with only a modest impact on the cost-effectiveness results (Section B.3.8.3).

Table 38: Estimate of total costs and QALYs

	Immunotherapy	Targeted therapy	Source	Combined
Proportion of patients starting first-line treatment in metastatic disease	43.9%	56.1%	COMBI-AD CSR[34]	-
Total discounted costs (including PAS)	£83,282	[redacted]	TA366 ERG report[118] TA396[20]	**£142,699**
Total discounted QALYs	2.960	3.443	TA366[90] TA396[20]	**3.23**

Abbreviations: CSR: Clinical Study Report; ERG: Evidence Review Group; QALY: quality-adjusted life year.

In this approach, TA396 for dabrafenib plus trametinib[20] was used to represent targeted therapies since clinical advice indicated that combination targeted therapies have largely replaced targeted monotherapies in the UK.[57] TA366 for pembrolizumab was used to represent immunotherapies.[90] In recent years, a number of immunotherapies have become available, with a number of NICE appraisals assessing the cost-effectiveness of these treatment strategies including ipilimumab monotherapy (TA319),[98] pembrolizumab monotherapy (TA366),[90] nivolumab monotherapy (TA384)[75] and ipilimumab in combination with nivolumab (T400).[76] The total costs and QALYs from TA366 in people receiving pembrolizumab were used for the following reasons:

- There has been no NICE assessment of all of immunotherapies relative to one another and since none of these therapies have been assessed within the same framework, it is unclear how similar or different the outcomes between the different regimens may be given the large differences in assumptions and outcomes (costs, QALYs, LYG) between the different appraisals.
- An ERG base case was defined in TA366 and the total costs included the PAS for pembrolizumab, reflecting the true cost to the NHS.
- It was unclear what the ERG preferred base case was in TA400 (nivolumab monotherapy)[76] and TA384 (nivolumab plus ipilimumab).[75] Furthermore, the majority of information in TA400 (nivolumab monotherapy)[76] and TA384 (nivolumab plus ipilimumab)[75] was marked as confidential, including costs. The ERGs also expressed a number of concerns with some of the company assumptions, reducing the number of QALYs significantly when conducting scenarios that were deemed plausible by the ERG.[119, 120] For instance, in TA400, in a scenario analysis conducted by the ERG removing nested long-term post-progression survival mortality, the total QALYs reduced from 4.85 to 2.53 (p. 239, ERG report, Table 115, TA400).[119] Similarly in TA384, using a different assumption for extrapolation of OS (using data from nivolumab instead of ipilimumab), the ERG estimated the total QALYs to be reduced from 4.27 to 2.85 (p. 105, ERG report, Table 31, TA384).[120]

- Clinical opinion further expected the outcomes for pembrolizumab and nivolumab monotherapy to be the same.[57] Although clinical opinion indicated combination nivolumab plus ipilimumab may be more effective than pembrolizumab or nivolumab monotherapy in patients with low PDL-1 expression,[57] data from a recent multiple treatment comparison of seven drugs for the treatment of metastatic melanoma indicated similar efficacy for PFS and OS for pembrolizumab monotherapy, nivolumab monotherapy and nivolumab plus ipilimumab.[121]

A number of limitations exist with the simplified approach, namely that the treatment pathway in melanoma is constantly evolving, with more effective and potentially costly treatment used after disease progression. Notably, since TA366, dabrafenib plus trametinib[20] has been recommended by NICE and is used in the metastatic setting as a first-line treatment option or second-line option following immunotherapy in BRAF positive patients. In addition, whilst the decision to use pembrolizumab to represent the class of immunotherapies, was a pragmatic decision based on discussion with clinical experts and the available evidence,[57] it remains unclear whether the costs associated with other immunotherapies are similar to that of pembrolizumab when their confidential PAS are incorporated. Finally, given the different assumptions used in TA366 and TA396,[20, 90] any direct comparisons are difficult.

B.3.5.3 Health-state unit costs and resource use

Resource use and associated costs for each health state in the model are summarised in Table 39.

Table 39: List of health states and associated costs in the economic model

Health states	Items	Dabrafenib plus trametinib	Routine surveillance (placebo)
RFS	*One-off costs at state entry*		
	Technology (medication and dispensing)	[redacted]	£0.00
	AEs	£692.26	£198.12
	Total one-off costs	[redacted]	**£198.12**
	Monthly costs of follow-up and monitoring		
	Months 1–12, on treatment	£297.76	N/A
	Months 1–12, off treatment	£137.06	£137.06
	Months 13–36	£137.06	£137.06
	Months 37–60	£68.53	£68.53
	Months 61–120	£13.43	£13.43
LR	*One-off costs at state entry*		
	AEs	£198.12	£198.12
	Recurrence	£8,805.19	£8,805.19
	Total one-off costs	**£9,003.31**	**£9,003.31**
	Monthly costs of follow-up and monitoring		
	Months 1–12	£137.06	£137.06
	Months 13–36	£137.06	£137.06
	Months 37–60	£68.53	£68.53
	Months 61–120	£13.43	£13.43

DR	*One-off costs at state entry*		
	Recurrence	£518.88	£518.88
	All other healthcare	£142,699.24	£142,699.24
	Total one-off costs	**£143,218.12**	**£143,218.12**
Death	**Total costs**	**£0.00**	**£0.00**

Abbreviations: AE: adverse event; DR: distant recurrence; LR: loco-regional recurrence; N/A: not applicable; RFS: relapse-free survival.

B.3.5.4 Adverse reaction unit costs and resource use

The model includes costs of serious adverse events (SAE) leading to hospitalisation. It was assumed that other events would be self-limiting, and would not be associated with any meaningful management costs or impact on HRQoL.

Pyrexia is a known AE associated with the use of dabrafenib plus trametinib, and in most cases can be simply managed with anti-pyretic medication and/or treatment interruption without hospital admission since it is unrelated to neutropenic sepsis.[20] In COMBI-AD, SAEs leading to hospitalization (Table 40) occurred in [redacted] of patients in the dabrafenib plus trametinib arm and [redacted] of patients in the placebo arm. Among these, [redacted] of patients in the dabrafenib plus trametinib arm and [redacted] in the placebo arm experienced hospitalisations due to pyrexia, while [redacted] of patients in the dabrafenib plus trametinib arm and [redacted] in the placebo arm experienced hospitalisation due to SAEs other than pyrexia.

Table 40: SAEs leading to hospitalisations

SAEs leading to hospitalisation	Dabrafenib plus trametinib N=435	Placebo N=432
Pyrexia N (%)	[redacted]	[redacted]
All other SAEs N (%)	[redacted]	[redacted]

Abbreviations: SAE: serious adverse event.
Source: COMBI-AD CSR.[34]

As such, the cost of AEs in the model was calculated by assigning the cost of a hospitalisation for pyrexia to the 11% of patients in the dabrafenib and trametinib arm using the weighted by frequency NHS reference costs for elective inpatient stays and excess bed days for WJ07A (Fever of Unknown Orgin with Interventions, with CC Score 4+ [£3,493.43, Frequency: 13, total costs of excess bed days: £0]), WJ07B (Fever of Unknown Origin with Interventions, with CC Score 0-3 [£4,858.11, Frequency: 11, total costs of excess bed days: £221]), WJ07C (Fever of Unknown Origin without Interventions, with CC Score 4+ [£1,652.21, Frequency: 129, total costs of excess bed days: £13,303]), and WJ07D (Fever of Unknown Orgin without Interventions, CC Score 0-3 [£1,254.89, Frequency: 388, total costs of excess bed days: £486,896]) (£1,547.64) and a cost of hospitalisation to the 14% and 6% of patients with SAEs other than pyrexia in each arm using the average NHS reference costs for an elective inpatient stay and excess bed days (£3,780.75). Consequenly the cost of hospitalisations for SAEs is reported in Table 41.

Table 41: Adverse reaction unit costs and resource use

SAEs leading to hospitalisations	Pyrexia	All other SAEs	Reference in submission
	£1,547.64	£3,788.75	NHS reference costs for elective inpatient stay and excess bed days for fever of unknown origin for pyrexia (HRGs WJ07A, WJ07B, WH07C, WJ07D) and total elective inpatient stay for all other SAEs

Abbreviations: SAE: serious adverse event.
Source: 2016/2017 NHS reference costs[117]

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the base case model inputs is provided in Table 42.

Table 42: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Time horizon	50 years	N/A	Section B.3.2.2
Discount rate (benefits)	3.5%	N/A	
Discount rate (costs)	3.5%	N/A	
Patient characteristics			
Mean age	50.4	49.5–51.3	Section B.2.3.3
% female	45.0%	41.7%–48.3%	
RFS			
Kaplan-Meier curve RFS COMBI-AD	Log-logistic unrestricted mixture model	N/A (Bootstrap sample)	Section B.3.3.1
Hazard of recurrence estimated from EORTC 18071	Generalised-F	N/A (Bootstrap sample)	
Distribution of RFS events – dabrafenib plus trametinib (COMBI-AD)			
% events that are death	1.9%	0%–4.02% (Bootstrap sample)	Section B.3.3.1
% events that are LR	33.8%	26.42%–41.08% (Bootstrap sample)	
% events that are DR	64.4%	56.95%–71.80% (Bootstrap sample)	
Distribution of RFS events – placebo (routine surveillance) (COMBI-AD)			
% events that are death	0.4%	0.00%–1.23% (Bootstrap sample)	Section B.3.3.1
% events that are LR	44.4%	38.11%–50.68% (Bootstrap sample)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
% events that are DR	55.2%	48.90%–61.48% (Bootstrap sample)	
Distribution of RFS events (EORTC 18071)			
% events that are death	3.1%	1.24%–4.96% (Beta[a])	Section B.3.3.1
% events that are LR	35.3%	30.08%–40.51% (Beta[a])	
% events that are DR	61.7%	56.31%–66.91% (Beta[a])	
Transition from LR			
HR for RFS in people with LR	2.53	N/A	Section B.3.3.2
Distribution of LR events – White *et al* (2002)[100]			
% events that are death	4.9%	3.88%–5.94% (Beta[a])	Section B.3.3.2
% events that are LR	32.0%	29.77%–34.22% (Beta[a])	
% events that are DR	63.1%	60.80%–65.40% (Beta[a])	
Utility values			
RFS On-treatment	0.85	0.8426–0.8653	Section B.3.4.5
RFS off treatment	0.87	0.8601–0.8786	
After LR	0.84	0.81–0.8616	
One-off QALYs			
QALYs in DR	3.23	N/A	Section B.3.5.2
Costs			
Pack of dabrafenib	[redacted]	N/A	Section B.3.5.1
Pack of trametinib	[redacted]	N/A	
Dispensing	£13.90	N/A	
Treating SAEs other than pyrexia	£3,780.75	N/A	Section B.3.5.4
Treating pyrexia	£1,547.64	N/A	
Outpatient visit to medical oncologist	£161.13	N/A	Section B.3.5.1
CT scan of chest, abdomen, and pelvis	£120.67	N/A	
PET/CT scan	£594.82	N/A	
MRI of brain	£142.32	N/A	
Echography	£70.36	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
MUGA	£249.34	N/A	
Surgical resection	£1,816.32	N/A	Section B.3.5.2
Immunotherapy	£ 68,887.00	N/A	
Healthcare costs following DR	£142,699	N/A	
Healthcare resource utilisation			
Packs of dabrafenib	[redacted]	30.6–33.8	Section B.3.5.1
Packs of trametinib	[redacted]	8.13–8.87	
Prescriptions of dabrafenib	[redacted]	8.03–8.81	
Prescriptions of trametinib	[redacted]	8.13–8.87	
Dabrafenib plus trametinib incidence of SAE other than pyrexia requiring hospitalisation	13.8%	N/A	Section B.3.5.4
Dabrafenib plus trametinib incidence of pyrexia requiring hospitalisation	11.0%	N/A	
Placebo incidence of SAE other than pyrexia requiring hospitalisation	4.9%	N/A	
Placebo incidence of pyrexia requiring hospitalisation	0.9%	N/A	
Dabrafenib plus trametinib Months 1–12			
Outpatient visit to medical oncologist	1.00	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.083	N/A	
PET/CT scan	0.083	N/A	
MRI of brain	0.167	N/A	
Echography	0.167	N/A	
MUGA	0.167	N/A	
Dabrafenib plus trametinib Months 13–36			
Outpatient visit to medical oncologist	0.333	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.083	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
PET/CT scan	0.083	N/A	
MRI of brain	0.167	N/A	
Dabrafenib plus trametinib Months 37–60			
Outpatient visit to medical oncologist	0.167	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.042	N/A	
PET/CT scan	0.042	N/A	
MRI of brain	0.083	N/A	
Dabrafenib plus trametinib Months 61–120			
Outpatient visit to medical oncologist	0.083	N/A	Section B.3.5.1
Routine surveillance (placebo) Months 1–12			
Outpatient visit to medical oncologist	0.333	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.083	N/A	
PET/CT scan	0.083	N/A	
MRI of brain	0.167	N/A	
Routine surveillance (placebo) Months 13–36			
Outpatient visit to medical oncologist	0.333	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.083	N/A	
PET/CT scan	0.083	N/A	
MRI of brain	0.167	N/A	
Routine surveillance (placebo) Months 37–60			
Outpatient visit to medical oncologist	0.333	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.042	N/A	
PET/CT scan	0.042	N/A	
MRI of brain	0.083	N/A	
Routine surveillance (placebo) Months 61–120			
Outpatient visit to medical oncologist	0.083	N/A	Section B.3.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Loco-regional recurrence			
Outpatient visit to medical oncologist	1.00	N/A	Section B.3.5.1
Surgical resection	0.90	N/A	
CT scan	1.00	N/A	
Immunotherapy	0.10	N/A	
Distant recurrence			
Outpatient visit to medical oncologist	1.00	N/A	Section B.3.5.1
CT scan of chest abdomen and pelvis	0.50	N/A	
PET/CT scan	0.50	N/A	

[a]Beta distributions were normalised to ensure sum of probabilities do not exceed one.
Abbreviations: CI: confidence interval; CT: computed tomography; DR: distant recurrence; ECHO: echocardiogram; HR: hazard ratio; LR: loco-regional recurrence; MUGA: multiple-gated acquisition scan; QALY: quality-adjusted life year; PET: positron emission tomography; RFS: relapse-free survival; SAE: serious adverse event.

B.3.6.2 Assumptions

The assumptions used in the base case analysis are described in Table 43, with a description of the scenarios conducted to explore the potential impact of these assumptions, where appropriate.

Table 43: List of assumptions for the base case analysis

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
Model structure			
Patients with LR may experience further LR events.	Patients who experienced an initial LR were assumed to be at greater risk of subsequent LR and DR events, with a small decrement in QoL.	This assumption reflects the natural disease history of melanoma as confirmed by clinical experts.[57]	In a scenario analysis, it was assumed that patients with LR could only experience a DR or death.
Patients with DR cannot return to RFS.	Patients with a DR were assumed to remain in this health state until death.	Although clinical experts indicated that patients with distant solitary metastasis might be able to return to RFS, it is an extremely rare event.[57] Consequently, the simplifying assumption that patients remaining in DR could only transition to death was considered reasonable by clinical experts.	In the absence of any empirical evidence to model this rare transition, no scenario analysis was conducted.
DR is *approximated* to be associated with costs and QALYs of £142,699, and 3.23, respectively. These costs and QALYs were applied as a one-off outcome at the point of DR.	The costs and benefits associated with metastatic disease (DR) were assumed to be independent of receipt of dabrafenib plus trametinib or placebo.	Modelling the treatment pathway in melanoma is challenging given the large number of treatment options available and little data on the optimal treatment sequence. In the absence of evidence pertaining to outcomes of prior adjuvant therapy on metastatic disease and to avoid making arbitrary assumptions on the treatment pathway, adding un-necessary complexity to the model and increasing uncertainty in the model, data on the outcomes of metastatic disease was taken from previous NICE appraisals of first line treatments in metastatic therapies.[20, 90]	A range of scenario analyses varying the estimate for total costs and QALYs was conducted to reflect the uncertainty in these parameters.

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
		These appraisals demonstrate difficulty in attempting to model the pathway in melanoma given the large variation between appraisals; moreover clinical experts also indicated that there are no approved sequencing guidelines with treatment option dependent on physician (and patient choice).[57] This approach is similar to the model developed for the NICE clinical guideline in melanoma, where a one-off cost was applied at the point of DR.[97] The approach in the NICE clinical guideline is extended in this current model to include QALYs, which include an underlying survival function.	
Modelling of RFS during the observed period			
The best use of all available trial data was made by fitting a parametric survival function to the COMBI-AD Kaplan-Meier curve for RFS during the observed period of the trial (up to month 50)	The log-logistic parametric unrestricted mixture-cure distribution was applied up until month 50.	The log-logistic parametric function provided the best visual fit to the observed data.	A range of scenario analyses was performed using: a) alternate cut-offs for both treatments b) the last censor in each arm as the cut-off c) the Kaplan-Meier curve directly (non-parametric)
Modelling of RFS in the long-term			
The hazard (time varying) of recurrence was	The hazard (time varying) for recurrence was estimated from the extrapolation of the	The extrapolation of clinical trial data beyond the observed period is often challenging and is highly uncertain and in the absence of	A number of scenario analyses were conducted assuming a range of non-mixture and mixture models

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
assumed the same in both treatment arms following the observed period of the COMBI-AD trial and assumed to be the same as long term data from the EORTC 18071 trial	RFS curve for placebo from this trial using the generalised-F parametric function. Validation from clinical experts suggests the generalised-F provides a conservative estimate.[57] The same hazard was used for both the dabrafenib plus trametinib and placebo arms after the observed period.	direct data, Clinical experts considered that data from the placebo arm of the EORTC 18071 should be used as this provided a longer follow-up.[57] Clinical experts also indicated that after the observed period, there is no evidence to suggest that the hazard of recurrence, would be higher in the adjuvant dabrafenib plus trametinib arm, and there is no reason to believe the hazard of recurrence would be different between treatment arms. Consequently, clinical opinion considered it reasonable to assume the same hazard for recurrence in both treatment arms after the observed period.	that were deemed clinically plausible by clinical experts. [57]
Beyond the observed period of the COMBI-AD trial, the distribution of events in RFS was assumed to be the same in both treatment arms	The distribution of RFS events was derived from the EORTC 18071 and assumed to be constant.[81]	In the absence of direct data, external data from the EORTC 18071 was used to help inform the distribution of events after the COMBI-AD trial.[81]	In the absence of direct evidence, different (arbitrary) distributions of RFS events were explored. No scenario analysis was conducted regarding the assumption that the distribution of event is constant in the absence of any data or indication.
Transition from LR			
Transition from the LR health state was based on RFS adjusted by a HR calibrated to the COMBI-AD data	The transition from the LR health state was calibrated to the COMBI-AD trial, so that the post-OS LR observed in the trial was similar to the post-OS LR that would be predicted in the model (if everyone started in that health state).	The transition from the LR health state was not directly observed in the COMBI-AD trial. Clinical experts considered that patients with a history of LR were at higher risk of recurrence.[57]	This parameter is highly uncertain. A range of scenario analysis was conducted varying the HR for the risk of recurrence in LR compared with RFS.

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
	The RFS curve from placebo was used as baseline, and adjusted by a HR (which was estimated through calibration). The HR was found to be 2.53	Calibrating this transition provided a means to estimate this transition to reflect data observed in the trial.	
Outcomes following a LR			
The distribution of events in LR was taken from White *et al.* (2002).[100]	The distribution of events in LR was taken from White *et al.* (2002).[100]	There is limited evidence available. Clinical experts indicated that they expect the distribution to be different to RFS; in particular, clinical experts expected more death and more DR, compared with what was observed in RFS.[57] Therefore, evidence from the White *et al.* (2002)[100] was used in the absence of alternative evidence, despite population not being exactly the same as that of COMBI-AD.	This parameter is highly uncertain. Consequently, a range of scenario analyses were conducted, varying the % of DR events to range up to 100%.
Outcomes following a DR			
Costs and QALYs associated with a DR were taken from two previous NICE appraisals.[20, 90]	At the point of DR, patients were assumed to receive either (a) immunotherapy or (b) targeted therapy. The proportion of each treatment was taken from the COMBI-AD trial and assumed to be the same between arms.[34] Estimates from TA366 for pembrolizumab were used to reflect the total costs and outcomes in people receiving first-line immunotherapy.[90]	Clinical experts indicated that after a DR, patients typically receive an immunotherapy or a targeted therapy.[57] Clinical experts further indicated that assuming the same proportion of treatment between arms would avoid biasing results toward one arm.[57] Evidence from a meta-analysis suggested that immunotherapies currently used in the UK are relatively similar.[122] Furthermore,	The use of estimates from previous NICE appraisals may be conservative given the availability of further therapies that may be considered more effective and/or more costly since TA366. As such, a scenario analyses were conducted varying the total costs and total QALYs by ±25% to assess the uncertainty in the estimates

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
	Estimates from TA396 were used to reflect the total costs and outcomes in people receiving targeted therapy.[20]	estimates on total costs including the PAS were available for pembrolizumab.[90] Clinical experts indicated that targeted monotherapy is no longer used in the UK and has been replaced by combination therapy.[57]	
Post-DR OS from the COMBI-AD trial was used followed by extrapolation from previous NICE appraisals	Post-DR OS from the COMBI-AD was used directly up to the last event, followed by extrapolation from previous NICE appraisals.	Data from the COMBI-AD trial were used to reflect outcomes from the trial.	Scenario analyses were not conducted as this does not impact results. Post-DR OS was included in the model for validation only
Routine surveillance			
Routine surveillance corresponds to the consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians[56]	Clinical review (treated in the model as an outpatient visit to a medical oncologist) is performed every 3 months for 3 years, then every 6 months up to 5 years, and then annually up to 10 years, together with imaging (CT chest, abdomen and pelvis *or* PET-CT total body scan, plus MRI head scan) at baseline and then every 6-months through year 3, and annually up to year 5.[56]	This source was recommended by clinical expert advice and provides a more comprehensive description of surveillance in UK.[57]	Scenario analysis was conducted varying the costs by ± 25% to assess the uncertainty in the estimates

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CT: computed tomography; DR: distant recurrence; HR: hazard ratio; LR: loco-regional recurrence; MRI: magnetic resonance imaging; OS: overall survival; PAS: patient access scheme; QALY: quality-adjusted life year; PET: positron emission tomography; RFS: relapse-free survival.

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

Table 44 presents the base case results of the economic evaluation. A confidential net PAS already exists for dabrafenib plus trametinib in unresectable or metastatic melanoma and the same PAS is available for this proposed indication. Consequently, all the cost-effectiveness analyses presented in this submission incorporate the PAS, representing the true drug acquisition costs to the NHS.

The base case results show that over a lifetime horizon, the total costs associated with adjuvant dabrafenib plus trametinib are estimated to be [redacted] compared to £104,755 for patients receiving routine surveillance (placebo) (an incremental cost of [redacted]).

The total QALYs for patients receiving adjuvant dabrafenib plus trametinib are estimated to be [redacted] compared to 7.67 for patients receiving routine surveillance (placebo) (an incremental QALY gain of [redacted]). As such, dabrafenib plus trametinib represents a cost-effective treatment option for patients with completely resected stage III BRAF V600 positive melanoma compared with routine surveillance (placebo) with an ICER of £20,039/QALY gained.

Table 44: Base case results (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Dabrafenib plus trametinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance (Placebo)	104,755	9.99	7.66	[redacted]	[redacted]	[redacted]	20,039

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

The proportion of the cohort in each health state over time (Markov trace), and the disaggregated results of the base-case incremental cost-effectiveness analysis are reported in Appendix J.

B.3.7.2 Clinical outcomes from the model

The predicted RFS and OS from the economic model for all patients receiving routine surveillance (placebo) and all patients receiving adjuvant treatment with dabrafenib plus trametinib are provided in Table 45. As expected, patients initiating adjuvant treatment with dabrafenib plus trametinib have a predicted survival advantage compared with patients receiving routine surveillance (placebo), in line with the survival gain observed in the COMBI-AD trial.

Table 45: Summary of model outcomes versus COMBI-AD trial results

Outcome	Model results		COMBI-AD clinical trial results	
	Dabrafenib plus trametinib	Placebo	Dabrafenib plus trametinib	Placebo
1 Year RFS (%)	87	55	88	56
2 Year RFS (%)	69	44	68	45
3 Year RFS (%)	59	40	60	40
Median RFS (months)	61	15	NR	16.6
1 Year OS (%)	98	95	97	94
2 Year OS (%)	91	84	91	83
3 Year OS (%)	84	74	86	77
Median OS (months)	155	106	NR	NR

Abbreviations: NR: not reported; OS: overall survival; RFS: relapse-free survival.
Source: Long *et al.* (2017).[55]

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters. A Monte-Carlo simulation with 1,000 iterations was performed and in each iteration, model inputs were randomly sampled from the specified probability distributions in Table 46.

Table 46: Probabilistic sensitivity analysis parameters and distributions

Parameter	Distribution	Mean	Alpha	Beta	SE
Patient characteristics					
% female	Normal	0.45	-	-	0.016866617
Cost and resource use					
Number of packs of drugs for adjuvant treatment regimens, dabrafenib	Normal	[redacted]	-	-	0.804711
Number of packs of drugs for adjuvant treatment regimens, trametinib	Normal	[redacted]	-	-	0.188908
Utility					
HSU in RFS, base value (no AEs)	Multivariate normal	0.8694	-	-	0.00472
HSU in LR, base (no AEs)	Multivariate normal	0.8358	-	-	0.01318
HSU in post-DR, base value (no AEs)	Multivariate normal	0.7921	-	-	0.01652
HSU in RFS, Dabrafenib plus trametinib	Multivariate normal	0.854	-	-	0.005787
Survival distributions					

COMBI-AD observed period: Proportion of RFS events that are deaths: Dabrafenib plus trametinib	Bootstrap	0.019	-	-	0.0108
COMBI-AD observed period: Proportion of RFS events that are deaths: Placebo	Bootstrap	0.004	-	-	0.0041
COMBI-AD observed period: Proportion of RFS events that are LR: Dabrafenib plus trametinib	Bootstrap	0.338	-	-	0.0375
COMBI-AD observed period: Proportion of RFS events that are LR: Placebo	Bootstrap	0.444	-	-	0.0321
COMBI-AD observed period: Proportion of RFS events that are DR: Dabrafenib plus trametinib	Bootstrap	0.644	-	-	0.0380
COMBI-AD observed period: Proportion of RFS events that are DR: Placebo	Bootstrap	0.552	-	-	0.0321
Post observed period in COMBI-AD: Proportion of RFS events that are deaths: Dabrafenib plus trametinib	Dirichlet	0.031	-	0.027699	0.009492
Post observed period in COMBI-AD: Proportion of RFS events that are deaths: Placebo	Dirichlet	0.031	-	0.031993	0.009492
Post observed period in COMBI-AD: Proportion of RFS events that are LR: Dabrafenib plus trametinib	Dirichlet	0.352941176	-	0.35097	0.02659
Post observed period in COMBI-AD: Proportion of RFS events that are LR: Placebo	Dirichlet	0.352941176	-	0.366324	0.02659
Post observed period in COMBI-AD: Proportion of RFS events that are DR: Dabrafenib plus trametinib	Dirichlet	0.616	-	0.570314	0.027048
Post observed period in COMBI-AD: Proportion of RFS events that are DR: Placebo	Dirichlet	0.616	-	0.613502	0.027048
COMBI-AD observed period: Proportion of events after LR that are deaths: Dabrafenib plus trametinib	Dirichlet	0.0491	-	0.045491	0.005255
COMBI-AD observed period: Proportion of events after LR that are deaths: Placebo	Dirichlet	0.0491	-	0.050331	0.005255

Proportion of post-LR events that are subsequent LR: Dabrafenib plus trametinib	Dirichlet	0.32	-	0.303019	0.011344
COMBI-AD observed period: Proportion of post-LR events that are subsequent LR: Placebo	Dirichlet	0.32	-	0.319042	0.011344
COMBI-AD observed period: Proportion of post-LR events that are DR: Dabrafenib plus trametinib	Dirichlet	0.6309	-	0.614182	0.011738
COMBI-AD observed period: Proportion of post-LR events that are DR: Placebo	Dirichlet	0.6309	-	0.637371	0.011738
Post observed period in COMBI-AD: Proportion of events after LR that are deaths: Dabrafenib plus trametinib	Dirichlet	0.0491	-	0.048812	0.005255
Post observed period in COMBI-AD: Proportion of events after LR that are deaths: Placebo	Dirichlet	0.0491	-	0.04163	0.005255
Post observed period in COMBI-AD: Proportion of events after LR that are subsequent LR: Dabrafenib plus trametinib	Dirichlet	0.32	-	0.327682	0.011344
Post observed period in COMBI-AD: Proportion of events after LR that are subsequent LR: Placebo	Dirichlet	0.32	-	0.328943	0.011344
Post observed period in COMBI-AD: Proportion of post-LR events that are DR: Dabrafenib plus trametinib	Dirichlet	0.6309	-	0.642193	0.011738
Post observed period in COMBI-AD: Proportion of post-LR events that are DR: Placebo	Dirichlet	0.6309	-	0.62076	0.011738
COMBI-AD observed period: RFS distribution (months 0–50): Placebo	Bootstrap	Log-logistic unrestricted mixture-cure-Placebo RFS (COMBI-AD)	-	-	-
COMBI-AD observed period: RFS distribution (months 0–50): Dabrafenib plus trametinib	Bootstrap	Log-logistic unrestricted mixture-cure-dabrafenib plus trametinib	-	-	-

		RFS (COMBI-AD)			
Post observed period in COMBI-AD RFS distribution (months 51 and subsequent): Placebo	Bootstrap	Gen. F-Placebo RFS (EORTC 18071)	-	-	-
Post observed period in COMBI-AD RFS distribution (months 51 and subsequent): Dabrafenib plus trametinib	Bootstrap	Gen. F-Placebo RFS (EORTC 18071)	-	-	-

Abbreviations: Gen.: generalised; DR: distant recurrence; LR: loco-regional recurrence; RFS: relapse-free survival.

The results of the PSA are presented in Table 47 and show that over a lifetime, adjuvant treatment with dabrafenib plus trametinib is associated with greater QALYs ([redacted]), at a greater cost ([redacted]) compared to routine surveillance (placebo) (7.69 and £107,895 respectively). As such, the PSA ICER was estimated to be £20,037 per QALY gained, with an [redacted] probability of dabrafenib plus trametinib being a cost-effective treatment option at £30,000/QALY threshold.

The cost-effectiveness planes and cost-effectiveness acceptability curves are presented in xxxxxxx28 and xxxxxxx29.

Table 47: Probabilistic sensitivity analysis results

Technologies	Costs (£)	QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Probability of cost-effectiveness[a]
Routine surveillance (placebo)	107,895	7.69	-	-	-	-
Dabrafenib plus trametinib	[redacted]	[redacted]	[redacted]	[redacted]	20,037	[redacted]

[a]The probability of dabrafenib plus trametinib being cost-effective versus routine surveillance at a cost-effectiveness threshold of £30,000/QALY.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

[redacted]

[redacted]

[redacted]

[redacted]

B.3.8.2 Deterministic sensitivity analysis

In order to assess the robustness of the model results, deterministic sensitivity analyses (DSA) were conducted by varying one model input at a time to assess which parameters had the most impact on the ICER. Parameters were varied within their 95% CI where available or by ±25%.

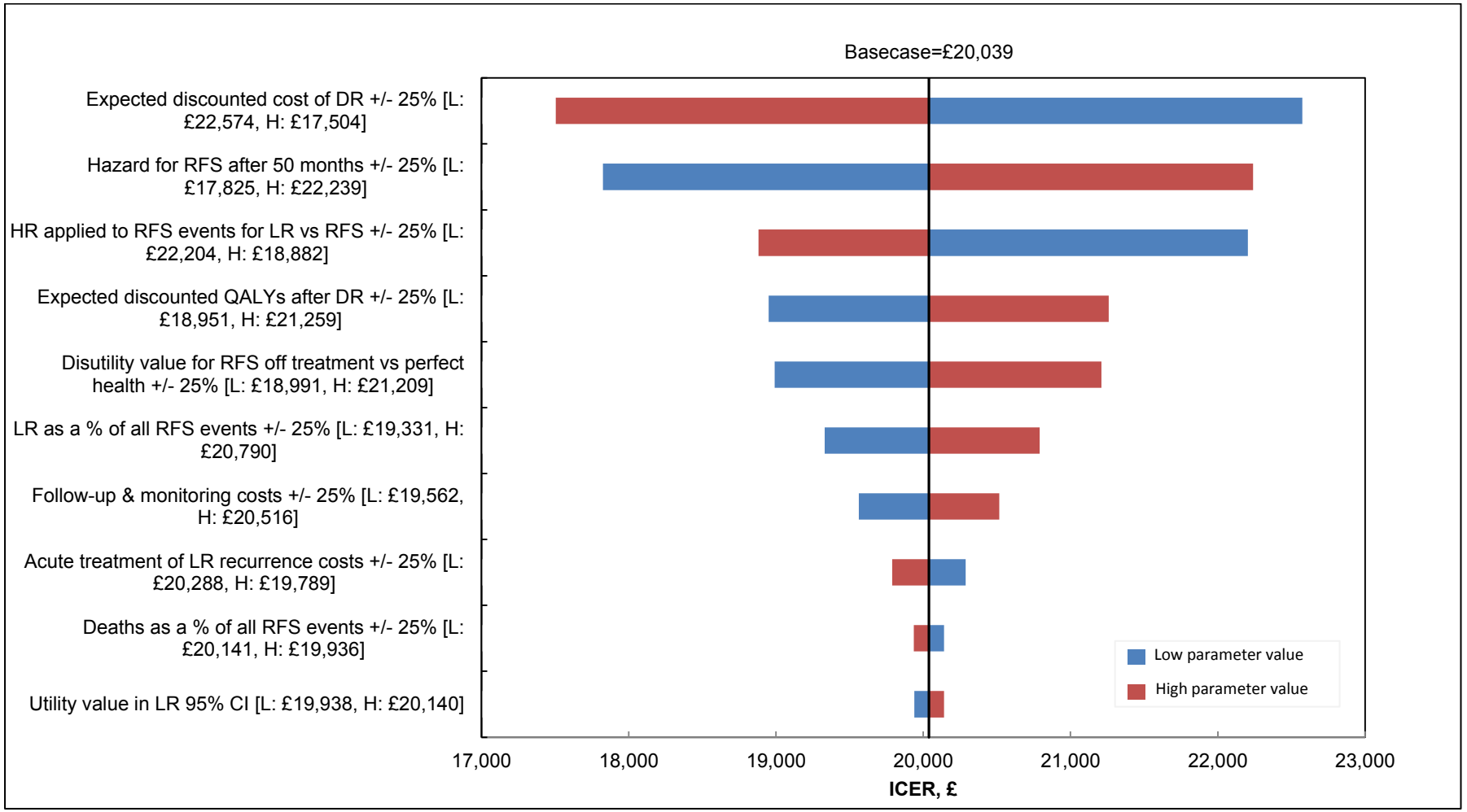
Table 48 summarises the 10 most influential parameters assessed in the DSA and the ICERs calculated at the upper and lower bounds, sorted from the widest to narrowest range of ICER values to highlight the parameters with the strongest influence on the cost-effectiveness results. The results for the 10 most influential parameters are also shown graphically in the tornado diagram in Figure 30. In conclusion, the results of the DSA show that the parameters varied in the DSA have a limited impact on the base case results.

Table 48: Variables assessed in DSA and resulting ICERs

Variable	ICER (lower bound)	ICER (Upper bound)
Expected discounted cost of DR ±25%	£22,574	£17,504
Hazard for RFS after 50 months ±25%	£17,825	£22,239
HR applied to RFS events for LR vs RFS ±25%	£22,204	£18,882
Expected discounted QALYs after DR ±25%	£18,951	£21,259
Disutility for RFS on treatment vs off treatment ±25%	£18,991	£21,209
LR as a % of all RFS events ±25%	£19,331	£20,790
Follow-up and monitoring costs ±25%	£19,562	£20,516
Acute treatment of LR recurrence costs ±25%	£20,288	£19,789
Deaths as a % of all RFS events ±25%	£20,141	£19,936
Utility value in LR 95% CI	£19,938	£20,140

Abbreviations: CI: confidence interval; DR: distant recurrence; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LR: loco-regional recurrence; QALY: quality-adjusted life year; RFS: relapse-free survival.

Figure 30: Tornado diagram based on DSA results for dabrafenib plus trametinib vs. routine surveillance (placebo)



Abbreviations: CI: confidence interval; DR: distant recurrence; DSA: deterministic sensitivity analysis; H: high; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; L: low; LR: loco-regional recurrence; RFS: relapse-free survival.

B.3.8.3 Scenario analysis

Extensive scenario analyses were conducted altering important variables in the model. Results of the scenario analyses are reported below.

1. Alternative time horizons

In the base case analysis, the costs and benefits of treatment were assessed over a lifetime horizon (50 years) as per the NICE reference case to reflect the chronic nature of the disease and to fully capture the costs and benefits of adjuvant treatment with dabrafenib plus trametinib. In the first set of scenario analyses, the time horizon was varied to assess the impact on costs and benefits over a shorter time horizon. Although the ICER increases with a decrease in the horizon, overall a reduction in the time horizon has a limited impact on the ICER (Table 49).

Table 49: Alternative time horizons

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case (50 Years)	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
Time horizon = 20 years	[redacted]	[redacted]	[redacted]	8.32	6.78	102,368	24,684
Time horizon = 30 years	[redacted]	[redacted]	[redacted]	9.49	7.41	104,173	21,213
Time horizon = 40 years	[redacted]	[redacted]	[redacted]	9.93	7.62	104,690	20,182

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

2. Alternative estimation for RFS during the observed period of COMBI-AD

The base case analysis for RFS used the unrestricted log-logistic mixture model fit to individual patient-level data up to month 50 for both treatment arms of the COMBI-AD trial (Section B.3.3.1). The survival distributions for the different parametric distributions explored during the observed period of the COMBI-AD trial is provided in Appendix N (Figure N.2.9). Since the unrestricted log-logistic mixture distribution provided the best visual fit to the observed data (base case assumption), other distributions are likely to introduce biases and as such, were not explored in the scenario analysis.

However, a scenario analysis was conducted using the Kaplan-Meier IPD curve directly (i.e. non-parametric analysis). The results of this analysis are reported in Table 50 and show that the direct use of the Kaplan-Meier curve results in a minimal increase in the ICER. Despite the minimal impact, as previously highlighted, the use of parametric functions is less influenced by events at the tail of the distribution and therefore should be considered more appropriate compared with the use of the Kaplan-Meier curve.

Table 50: Alternative estimation of RFS during the COMBI-AD trial observed period

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
RFS – KM curve based on COMBI-AD IPD	[redacted]	[redacted]	[redacted]	9.99	7.66	104,751	22,651

Abbreviations: ICER, incremental cost-effectiveness ratio; IPD: individual patient-level data; KM: Kaplan-Meier; RFS: relapse-free survival; QALY, quality-adjusted life year.

3. Alternative cut-off points for COMBI-AD RFS

The base case analysis used RFS data from the COMBI-AD trial up to 50 months in both treatment arms (Section B.3.3.1). The scenario analyses assumed alternative cut-off points and show that, as expected, the impact of this cut-off point on the ICER is limited (Table 51).

Table 51: Alternative cut-points on COMBI-AD RFS Kaplan-Meier curves

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
Cut-off in RFS at last censor	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	19,558
Cut-off in RFS at 41 months	[redacted]	[redacted]	[redacted]	9.86	7.54	105,975	19,629
Cut-off in RFS at 46 months	[redacted]	[redacted]	[redacted]	9.93	7.61	105,283	19,941
Cut-off in RFS at 52 months	[redacted]	[redacted]	[redacted]	10.02	7.68	104,494	20,049

Abbreviations: ICER, incremental cost-effectiveness ratio; RFS: relapse-free survival; QALY, quality-adjusted life year.

4. Alternative hazard for RFS after COMBI-AD observed period

In the base case, the hazard of disease recurrence beyond the observed period of the COMBI-AD trial was derived from the hazard of the placebo arm from the EORTC 18071 trial using the generalised-F model and was assumed the same for both treatment arms (Section B.3.3.1).[81] Clinical experts considered the generalised-F model (Figure 20) to be possibly a conservative extrapolation (e.g. the risk of recurrence predicted by the generalised-F model was greater than what would be observed in clinical practice),[57] so scenario analyses were conducted for the range of mixture and non-mixture models that were considered plausible (Section B.3.3.1). Whilst a number of parametric functions were considered, only a limited number of parametric functions were deemed clinically plausible when looking at the long-term extrapolations. Results are only presented for those distributions that were considered clinically plausible by clinical experts (i.e.

the ones in between the generalised-F and Gompertz (see Appendix N, figure N.4.4 for the figures presenting the Kaplan-Meier curves with each parametric function).

As expected, the ICER improved using alternative distributions that were considered clinically plausible by clinical experts (see Appendix N for further details). This is because the generalised-F (used in the base case) was deemed to provide the most conservative extrapolation amongst the plausible distributions.

Table 52: Assuming different extrapolation for the estimation of the hazard of recurrence after the observed period

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
EORTC – Gompertz	[redacted]	[redacted]	[redacted]	10.83	8.31	93,066	13,927
EORTC – Exponential Mixture	[redacted]	[redacted]	[redacted]	11.04	8.49	90,541	12,748
EORTC – Weibull Mixture	[redacted]	[redacted]	[redacted]	10.94	8.40	91,699	13,280
EORTC – Log-Logistic Mixture	[redacted]	[redacted]	[redacted]	10.47	8.02	97,888	16,254
EORTC – Lognormal Mixture	[redacted]	[redacted]	[redacted]	10.07	7.71	102,892	19,203
EORTC – Gompertz Mixture	[redacted]	[redacted]	[redacted]	10.73	8.23	94,225	14,477
EORTC – Gen. Gamma Mixture	[redacted]	[redacted]	[redacted]	10.74	8.24	94,160	14,447

Abbreviations: EORTC: European Organisation for Research and Treatment of Cancer 18071 trial; Gen: generalised; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

5. Alternative parametric functions for RFS during the observed period in COMBI-AD and beyond (up to 50 years)

Because of the difficulty of extrapolating RFS over the long-term using the COMBI-AD trial data only, the base case used the hazard of the placebo arm in the EORTC 18071 trial to estimate the hazard of recurrence beyond the observed period of the COMBI-AD trial (Section B.3.3.1).

For transparency and completeness, scenario analyses are presented whereby parametric functions were fitted directly to the COMBI-AD data throughout the lifetime horizon of the model. A total of 39 models were considered (Appendix N, Figure N.3.1, Table N.3.1) and following visual inspection, 2 parametric models were excluded from the analysis because they did not provide good visual fits to the data, and a further 15 parametric models were excluded from the analysis because they did not provide clinically plausible extrapolations. Clinical experts considered these curves implausible and contradictory to the data observed from the COMBI-AD trial, since the RFS curves for the two treatment arms crossed, implying that patients in the adjuvant dabrafenib plus

trametinib treatment arm would be worse off in the long-term than those in the routine surveillance arm.

As such, scenario analyses were conducted for the remaining 17 parametric models (Table 53), and following further visual inspection and clinical expert validation, the majority of parametric models tested in scenario analyses were considered to predict either a too low or too high risk of recurrence following the observed COMBI-AD trial period compared with what clinical experts expected to see in clinical practice. The results show that all of the ICERs of the scenario analyses remained below the £30,000 per QALY gained threshold.

Similarly, clinical experts considered the parametric distributions that resulted in ICER's below £10,000 per QALY gained were too optimistic and, as such, the results from these scenario analyses should be interpreted with considerable caution given the difficulties, challenges and uncertainty around the long-term predictions. These results also indicate that the approach used in the base case is reasonably robust compared with using data directly from the COMBI-AD trial on its own.

Table 53: COMBI-AD for RFS during and post-observed period

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
RFS – Log-logistic (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	8.32	6.22	123,841	12,147
RFS – Lognormal (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	8.33	6.24	124,184	9,953
RFS – Gompertz (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	10.01	7.62	102,942	3,464
RFS – Gen. Gamma (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	9.14	6.92	114,905	10,355
RFS – RCS Log-logistic (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	8.84	6.67	118,157	7,220
RFS – RCS Lognormal (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	8.66	6.52	120,509	6,666
RFS – RCS Weibull (R) (COMBI-AD only)	[redacted]	[redacted]	[redacted]	8.64	6.52	121,765	6,334
RFS – Exponential Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	10.72	8.23	95,073	6,310
RFS – Weibull Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	11.10	8.54	90,747	7,206
RFS – Log-logistic Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	10.29	7.88	100,888	5,224
RFS – Lognormal Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	9.96	7.61	105,068	4,522

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
RFS – Gompertz Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	11.08	8.53	90,858	7,197
RFS – Gen. Gamma Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	9.91	7.57	105,698	4,420
RFS – Weibull (U) Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	11.41	8.80	86,436	10,450
RFS – Log-logistic (U) Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	11.12	8.56	89,878	13,860
RFS – Gompertz (U) Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	11.15	8.58	89,539	7,583
RFS – Gen. Gamma (U) Mixture (COMBI-AD only)	[redacted]	[redacted]	[redacted]	10.84	8.33	93,488	5,997

Note: Results for Gen. F (R) Mixture, Lognormal (R) Mixture, RCS Log-Logistic (U), RCS Lognormal (U), Lognormal (U) Mixture, Gen. Gamma (R) Mixture, RCS Weibull (U), Gen. Gamma (U), Lognormal (U), Weibull (R) Mixture, Gompertz (U), Exponential (R) Mixture, Gompertz (R) Mixture, Log-Logistic (U), Weibull (U) distributions are not reported because they were considered to be implausible; see Appendix N for more details.
Abbreviations: Gen: generalised; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; R: restricted; RCS: restricted cubic splines; RFS: relapse-free survival; U: unrestricted.

6. Distribution of RFS events after the COMBI-AD observed period

In the base case analysis, the distribution of events after the COMBI-AD trial observed period was derived from the EORTC 18071 trial and assumed to be the same in both treatment arms (Section B.3.3.1). Scenario analyses assumed alternative distributions of events from the COMBI-AD trial, including the proportions derived from the pooled estimates of the two treatment arms, estimates from the placebo arm and estimates from the COMBI-AD dabrafenib plus trametinib arm. The impact of these alternative proportions on the ICER was limited (Table 54).

Table 54: Proportion of events in RFS beyond the duration of the COMBI-AD trial

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
% of RFS events after observed period – pooled COMBI-AD	[redacted]	[redacted]	[redacted]	10.00	7.67	105,135	20,097
% of RFS events after observed period – placebo arm COMBI-AD	[redacted]	[redacted]	[redacted]	10.01	7.67	105,244	20,147
% of RFS events after observed period – dabrafenib plus trametinib arm COMBI-AD	[redacted]	[redacted]	[redacted]	10.00	7.66	104,972	20,072

Abbreviations: ICER, incremental cost-effectiveness ratio; RFS: relapse-free survival; QALY, quality-adjusted life year.

7. Transition from the LR health state

In the base case analysis, the transition from the LR health state was estimated by calibrating a HR to RFS, so that the post-LR OS predicted by the model matched the post-LR OS observed in the COMBI-AD trial. A HR of 2.53 was estimated via this process and applied to the RFS curve for placebo, representing the transition from the LR health state and indicating a 2.5 times higher risk of experiencing a recurrence event after an initial event (Section B.3.3.2).

Clinical experts indicated that the risk of a further LR recurrence or DR in LR health state would be greater compared with RFS,[57] and given the uncertainty in this parameter, a range of scenario analyses were conducted where the HR was varied between 1.5 and 5 for transparency.

Assuming alternative HRs had a moderate impact on the ICER, with the ICER slightly decreasing as the risk of recurrence increases (Table 55). Whilst there are uncertainties around the risk of recurrence in LR, the base case assumption is likely to be more appropriate because of the internal consistency of the model predictions for post-LR OS with the observed post-LR OS in the COMBI-AD trial. In these scenario analyses, the ICERs consistently remained below the usually accepted cost-effectiveness thresholds.

Table 55: HR for transition from LR

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	Life years	QALYs	Costs (£)	Life years	QALYs	Costs (£)	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
HR = 1.5	[redacted]	[redacted]	[redacted]	10.60	8.17	99,769	24,548
HR = 3.5	[redacted]	[redacted]	[redacted]	9.73	7.44	106,780	18,489
HR = 4.5	[redacted]	[redacted]	[redacted]	9.61	7.33	107,691	17,822

Abbreviations: HR: hazard ratio; ICER, incremental cost-effectiveness ratio; LR: loco-regional recurrence; QALY, quality-adjusted life year.

8. Distribution of events following a LR

In the absence of direct evidence from the COMBI-AD trial, the distribution of recurrence/death events following an LR was taken from the literature (Section B.3.3.2).[100] However, given the uncertainties in the relevance of the patient population to the current decision problem, a range of scenario analyses were conducted, assuming the proportion of non-fatal events to be distant recurrences (ranging between 60%–100%) and the distribution of deaths remaining the same (around 4.6%). For internal consistency, it should be noted that the HR was recalibrated for each scenario to ensure that the post-LR OS predicted by the model matched the post-LR OS observed in the COMBI-AD trial.

Table 56 shows that varying the proportions of DR after a LR had a minimal impact on the ICER.

Table 56: Distribution of events after a LR

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	Life years	QALYs	Costs (£)	Life years	QALYs	Costs (£)	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
DR as % of events post-LR 60%	[redacted]	[redacted]	[redacted]	9.96	7.63	104,980	19,877
DR as % of events post-LR 80%	[redacted]	[redacted]	[redacted]	10.02	7.68	104,418	20,235
DR as % of events post-LR 100%	[redacted]	[redacted]	[redacted]	10.05	7.70	104,111	20,438

Abbreviations: HR: hazard ratio; ICER, incremental cost-effectiveness ratio; LR: loco-regional recurrence; QALY, quality-adjusted life year.

9. LR events in the LR health state

The base case analysis assumed that patients may experience subsequent LR events in the LR health state. In the absence of direct evidence from the COMBI-AD trial on the probability of experiencing a subsequent LR following an initial LR, a scenario analysis was conducted with the

assumption that patients experience only one LR event. The results of this analysis show that this simplifying assumption has a limited impact on the ICER (Table 57).

Table 57: LR events scenario results

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
Maximum of one LR event per patient	[redacted]	[redacted]	[redacted]	9.85	7.53	105,715	19,180

Abbreviations: ICER: incremental cost-effectiveness ratio; LR: loco-regional recurrence; QALY: quality-adjusted life year.

10. Costs and outcomes associated with DR

In the base case analysis, one-off costs and QALYs associated with a DR were applied at the point of DR, with costs and QALYs taken from previous NICE appraisals and weighted according to the proportion of treatment (immunotherapy vs targeted therapy) received post-recurrence in the COMBI-AD trial (Section B.3.5.2).[20, 34, 90]

Clinical experts considered that the base case estimate is likely to be an underestimate given that new, more effective and potentially costly treatments have now become available since TA366 (namely combination immunotherapies).[20, 57]

Given the considerable uncertainty associated with these parameters, a range of scenario analyses were conducted (a) assuming the estimate for each specific appraisal, (b) varying the total costs and QALYs by ±25%, (c) varying costs by ±25% with QALYs unchanged and (d) varying QALYs by ±25% with total costs unchanged.

Table 58 shows that overall these parameters have a moderate effect on the ICER, indicating that despite the simplifying assumptions informing this health state, the ICER remained within the usually accepted decision-making thresholds under these extreme scenarios.

Table 58: Estimate for the total costs and QALYs applied at the point of DR

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
Cost and QALY post-DR: NICE TA366 only	[redacted]	[redacted]	[redacted]	9.99	7.47	64,828	23,803
Cost and QALYs post-DR: NICE TA396 only	[redacted]	[redacted]	[redacted]	9.99	7.80	136,038	16,987

Description	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
	Life years	QALYs	Costs (£)	Life years	QALYs	Costs (£)	
Cost and QALYs post-DR: Base case +25%	[redacted]	[redacted]	[redacted]	9.99	8.20	128,727	18,570
Cost and QALYs post-DR: Base case -25%	[redacted]	[redacted]	[redacted]	9.99	7.11	80,782	21,349

Abbreviations: DR: distant recurrence; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TA: technology appraisal.

11. Drug costs scenario

In the base case analysis, drug costs for dabrafenib and trametinib were calculated based on the mean of the number of packs needed to achieve each patients' cumulative dose, as recorded in the COMBI-AD trial. Scenario analyses were conducted using drug costs based on the mean cumulative dose (i.e. assuming no package wastage).

Table 59: Package wastage scenario results

Description	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
	Life years	QALYs	Costs (£)	Life years	QALYs	Costs (£)	
Base case (Assumes wastage)	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
Drug costs (Assuming no wastage)	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	19,253

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

12. Discount rate

Consistent with the NICE reference case, the base case analysis discounts both costs and benefits at 3.5%. As expected, the scenario analyses show that the ICER decreases with a reduction in the discount rate (Table 60).

Table 60: Discount rate scenario results

Description	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
	Life years	QALYs	Costs (£)	Life years	QALYs	Costs (£)	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	20,039
Discount rate = 0.0%	[redacted]	[redacted]	[redacted]	15.00	10.45	117,130	13,743
Discount rate = 1.5%	[redacted]	[redacted]	[redacted]	12.39	9.00	111,025	16,275

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Discount rate = 2.5%	[redacted]	[redacted]	[redacted]	11.07	8.26	107,671	18,100

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

13. Utility values

The base case analysis assumed that patients in the LR state have a lower utility value than those off treatment in the RFS state. Scenario analysis were conducted to assume that the utility value for patients in the LR health state is the same as for patients who are off treatment in the RFS health state, as well as scenarios that assumed no decrements on treatment and no decrements with age. The results show that these scenarios have a limited impact on the ICER (Table 61).

Table 61: Utility values scenario results

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.666	104,755	20,039
Utility in LR same as RFS	[redacted]	[redacted]	[redacted]	9.99	7.68	104,755	20,171
No utility decrement on treatment	[redacted]	[redacted]	[redacted]	9.99	7.66	104,755	19,868
No utility decrement with age	[redacted]	[redacted]	[redacted]	9.99	7.94	104,755	18,767

Abbreviations: ICER, incremental cost-effectiveness ratio; LR: loco-regional recurrence; QALY, quality-adjusted life year; RFS: relapse-free survival.

14. Routine surveillance (placebo) resource use and monitoring costs

The base case analysis assumed that routine surveillance (placebo) comprised the follow-up and monitoring schedule of the consensus guidelines for the follow-up of high-risk cutaneous melanoma in the UK developed by UK melanoma clinicians.[56] Scenario-analyses were conducted to vary the costs associated with this schedule by ±25% (Table 62). The results show that these changes have a very limited impact on the ICER.

Table 62: Routine surveillance (placebo) resource use and monitoring costs scenario results

	Adjuvant treatment with dabrafenib plus trametinib			Routine surveillance (placebo)			ICER (£/QALY)
Description	**Life years**	**QALYs**	**Costs (£)**	**Life years**	**QALYs**	**Costs (£)**	
Base case	[redacted]	[redacted]	[redacted]	9.99	7.666	104,755	20,039
Health resource associated with follow-up and monitoring +25%	[redacted]	[redacted]	[redacted]	9.99	7.66	105,797	20,516
Health resource associated with follow-up and monitoring -25%	[redacted]	[redacted]	[redacted]	9.99	7.66	103,712	19,562

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.4 Summary of sensitivity analyses results

An extensive range of sensitivity and scenario analyses were conducted to test the robustness of the model inputs and structural assumptions of the economic analysis. Overall, the base case results were robust to most parameters and structural assumptions, with the ICERs across the majority of the analyses performed remaining below the usual cost-effectiveness threshold of £30,000 per QALY gained.

In conclusion, the probability of dabrafenib plus trametinib being a cost-effective option compared to routine surveillance (placebo) is [redacted] at the £30,000 per QALY gained threshold.

B.3.9 Subgroup analysis

The clinical data from the COMBI-AD trial indicated that the benefit of dabrafenib plus trametinib compared to routine surveillance (placebo) was consistent across all pre-specified patient subgroups (Section B.2.7). Consequently, subgroup analyses were not explored in the economic analysis.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

During the model development, five clinical experts and four health economists were consulted to develop and evaluate the model structure, key assumptions, parameters and efficacy estimates.[57]

The clinical experts were consultant oncologists specialising in the treatment of malignant melanoma and the health economic experts were leading experts in health economics practice and methodology or with prior experience in the capacity of former NICE ERG's. The experts were in general agreement with the modelling methods, particularly the simplified approach and key feedback was incorporated into the analysis (Section B.3.6.2).

Quality-control (QC) procedures for verification of input data and coding were performed and a checklist was used to ensure that the model generated accurate results and were consistent with input data and robust to extreme values. The checks are documented in Appendix P.

To ensure external validity, model predictions were compared to observed data where possible and as described in Section B.3.3.3 the short-term outcomes predicted by the model are in-line with those observed in the COMBI-AD trial. In the absence of long-term data, the long-term predictions were considered clinically plausible by clinical experts.[57] Finally, the use of data in the DR health state from previous NICE appraisals in metastatic disease, is consistent with previous decisions by NICE.

B.3.11 Interpretation and conclusions of economic evidence

No studies assessing the cost-effectiveness of adjuvant dabrafenib plus trametinib in resected stage III BRAF V600 positive melanoma patients were identified from the economic SLR described in Appendix G. Consequently, it was not possible to compare the results of the economic model developed in this submission with any other studies.

The deterministic results of base case economic analysis of the *de novo* cost-utility model developed for the economic evaluation show that dabrafenib plus trametinib is associated with higher costs but also higher QALYs than routine surveillance (placebo), with an incremental cost per QALY gained of £20,039 with the existing confidential PAS. This ICER is well below the cost-£30,000 per QALY threshold accepted by NICE.

Strengths of the economic analysis include:

- The economic analysis is underpinned by a large, well designed RCT that is broadly representative of the population expected to be treated in England and Wales.
- The model structure and assumptions were developed with input from multiple clinical and health economic experts and as described in Section B.3.3.3, the short-term outcomes predicted by the model are in-line with those observed in the COMBI-AD trial, and the long-term predictions were considered clinically plausible by clinical experts.[57]
- Uncertainty in the model inputs and assumptions has been explored in a large number of sensitivity analyses that show the robustness of the model results.

Limitations of the analysis include:

- Limited long-term clinical data are available for dabrafenib plus trametinib in the adjuvant setting, thus the model relies on the extrapolation of clinical outcomes using data from other studies in patients with resected stage III disease to predict long-term outcomes with dabrafenib plus trametinib.
- It is uncertain how generalisable the patient population and outcomes observed in these studies are to the COMBI-AD trial, however in the absence of long-term data, the approach taken is considered reasonable.
- There are limited data available on the impact of adjuvant therapies on outcomes in metastatic disease. OS data from the COMBI-AD trial are still relatively immature and as such, assumptions on OS (based on the QALYs from previously accepted decisions by NICE) were explored in the sensitivity analyses.

Concluding remarks

Dabrafenib plus trametinib is the first combination targeted therapy to show a clinically and statistically significant reduction in the risk of disease recurrence in resected BRAF V600 positive stage III melanoma patients, with a favourable trend towards an overall survival benefit.

The cost-effectiveness analysis shows that adjuvant treatment with dabrafenib plus trametinib represents a cost-effective option compared to routine surveillance for patients with resected BRAF V600 positive stage III melanoma.

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Appendices

The following sections are included in the 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 analysis
- 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: Full eligibility criteria for COMBI-AD
- Appendix M: Post-treatment anti-cancer therapy in COMBI-AD
- Appendix N: Additional information for models for extrapolation of clinical trial data
- Appendix O: Comparison of COMBI-AD and clinical efficacy data sources
- Appendix P: Model validation checks

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Single technology appraisal

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

Dear Lesley,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 17 April 2018 from Novartis. 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 Thursday 24 May 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
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Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority question**: The clinical expert (see company submission (CS) Document B, Reference 57) expressed the expectation that competing risk analysis would have been undertaken for relapse free survival (RFS). For the RFS data depicted in Figure 6 of the CS Document B (page 37), please conduct a competing risk analysis, separately by arm, employing the following as competing risks for recurrence (both collectively and individually):

i] events due to death;
ii] censorings due to new primary; and
iii] censoring due to premature withdrawal from study without having experienced a recurrence.

A2. **Priority question**: Please split Table 16 of the CS Document B (page 43) into six tables:

1. Prior to any recurrence and remaining on treatment (taking placebo tablets being treated as remaining on treatment in the placebo arm)
2. Prior to any recurrence and ceased treatment (formally having ceased taking placebo tablets being treated as ceased treatment in the placebo arm)
3. At/post a 1st recurrence of loco-regional recurrence (LR)
4. At/post a 1st recurrence of distant recurrence (DR)
5. At/post a 1st secondary primary melanoma (SPM)
6. Recurrence status unknown (if required)

Please augment each of these tables with the number of patients eligible to report EQ-5D-3L by arm so that reporting rates can be calculated.

A3. **Priority question**: Please tabulate the data of Figure 27 of the CS Document B (page 95). Please tabulate the number of packs of dabrafenib and the number of packs of trametinib that were dispensed in the dabrafenib arm of COMBI-AD by week (1 table), together with the total number of packs dispensed during the trial. If weekly data is not available, please provide this for the shortest time period for which it is available. Please see example table below:

	Dabrafenib packs		Trametinib packs	
	50mg	75mg	0.5mg	2mg
Week 0	N=???	N=???	N=???	N=???
Week 1	N=???	N=???	N=???	N=???

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Week 2	N=???	N=???	N=???	N=???
Etc…	N=???	N=???	N=???	N=???
Totals	N=???	N=???	N=???	N=???

A4. **Priority question**: In this and the following question, all Kaplan Meier data can be supplied within an Excel workbook if this is simpler, with separate worksheets for type of Kaplan Meier data, arm and where applicable trial. Please provide the RFS Kaplan Meier data that underlies Figure 6 of the CS Document B (page 37) in the following disaggregate form for each arm (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes, DR, LR, SPM
- Censoring: C_{EoT}, End of trial, C_O, Other

For a patient with more than one event recorded at a given time point please ascribe this hierarchically to D_M then D_O then DR then LR then SPM; i.e., a patient with a DR and an LR at the same time point should be classed as a DR event. Please clarify if 1-month is 4 weeks or is some other duration.

		Events					Censoring		
t	N at risk	D_M	D_O	DR	LR	SPM	C_{EoT}	C_O	S(t)
T=0	N=???	N=0	N=0	N=0	N=0	N=0	N=0	N=0	100%
T=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???	???%
Etc…									

A5. **Priority question**: Please provide the OS Kaplan Meier data that underlies Figure 7 of CS Document B (page 39) in the following disaggregate form for each arm (2 tables): Please clarify if 1-month is 4 weeks or is some other duration.

- Events: D_M, death from melanoma, D_O, death from other causes
- Censoring: C_{EoT}, End of trial, C_O, Other

For a patient with more than one event recorded at a given time point, please ascribe this hierarchically to D_M then D_O then DR then LR.

		Events		Censoring		
T	N at risk	D_M	D_O	C_{EoT}	C_O	S(t)

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T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

A6. **Priority question**: Please explain why the clinical experts advised that SPM should not be considered an RFS event given the trial protocol and Figure 6 of the CS Document B (page 37). Please provide the RFS Kaplan Meier data that underlies Figure 13 of the CS Document B (page 71) in the following disaggregate form for each arm (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes, DR, LR.
- Censoring: C_{SPM}, SPM event, C_{EoT}, End of trial, C_O, Other

Please clarify if 1-month is 4 weeks or is some other duration.

		Events				Censoring			
t	N at risk	D_M	D_O	DR	LR	C_{SPM}	C_{EoT}	C_O	S(t)
T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

A7. **Priority question**: Please provide details regarding:

- The number of patients in the active treatment arm of COMBI-AD that completed 12 months of treatment (n=???), completed more than 12 months of treatment (n=???), continued treatment after LR (n=???), continued treatment after DR (n=???), continued treatment after SPM (n=???).
- The data definition for the Average Mean Daily dose and the Cumulative dose in Table 19 of CS Document B (page 79), outlining how dose interruptions, reductions and escalations are handled and how treatment discontinuations are handled.
- The disaggregate time to treatment discontinuation Kaplan Meier data of COMBI-AD (2 tables):
    - Events: D, death, Recurrence, R, Adverse events, AE, Lost to follow up, End of 12-month course, EoC, (and a separate Other catchall if required)
    - Censoring: CEoT, End of trial, C_O, Other

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Please clarify if 1-month is 4 weeks or is some other duration.

		Events					Censoring		
t	N at risk	D	R	AE	LTFU	EoC	C_{EoT}	C_O	S(t)
T=0	N=???	N=0	N=0	N=0	N=0	N=0	N=0	N=0	100%
T=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???	???%
Etc…									

A8. Please provide the OS Kaplan Meier data for COMBI-AD LR patients treating the point of LR as the baseline t=0 (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes.
- Censoring: C_{EoT}, End of trial, C_O, Other

		Events		Censoring		
t	N at risk	D_M	D_O	C_{EoT}	C_O	S(t)
T=0	N=???	N=0	N=0	N=0	N=0	100%
T=???	N=???	N=???	N=???	N=???	N=???	???%
Etc…						

A9. Please provide the OS Kaplan Meier data for COMBI-AD DR patients treating the point of DR as the baseline t=0 (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes.
- Censoring: C_{EoT}, End of trial, C_O, Other

		Events		Censoring		
t	N at risk	D_M	D_O	C_{EoT}	C_O	S(t)
T=0	N=???	N=0	N=0	N=0	N=0	100%
T=???	N=???	N=???	N=???	N=???	N=???	???%
Etc…						

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A10. Please provide the Kaplan Meier data (timepoint, N at risk, N events, N censoring events, S(t)) that underlies the curves of the *Survival_Distributions_Enter_KM* worksheet columns C:D, R:S, U:V, X:Y. For columns R:S if it is possible, it would be appreciated if this could be split into the two trials and then the method for combining this data to arrive at the values in columns R:S presented.

A11. Please provide separate Kaplan Meier plots by arm comparing the RFS analyses done by method in Figure 6 (page 37) and Figure 13 (page 71) of the CS Document B.

A12. For Figure 13 (page 71) of the CS Document B, please report outcome details pertaining to the analysis (log-rank test, HR, medians, etc.).

A13. In the placebo arm, what was the compliance of taking 2 tablets / day for 12 months?

A14. The CS Document B notes that "region" is a pre-specified subgroup, but does not provide any subgroup analyses for this subgroup. Please summarise all the subgroup analyses that have been conducted based upon "region", together with any forest plots.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide details of other quality of life modelling using the COMBI-AD that was explored in addition to that reported in Table 31 of CS Document B (page 91). Please also provide the results. Please provide additional analyses (8 tables) paralleling the GEE analysis of Table 31 of the CS Document B that:

1. Splits the RFS On Treatment variable by arm with those remaining on placebo treated as being *RFS On Treatment in the placebo arm*; i.e., splitting the 2,140 EQ-5D RFS Off treatment observations in the placebo arm into (A) those where placebo tablets were still being received and (B) those where the patient formally had discontinued from receiving placebo tablets for whatever reason
2. Splits the RFS Off treatment variable by arm
3. Splits both the RFS On Treatment variable by arm and the RFS Off treatment variable by arm
4. Includes an SAE variable, defined as a patient having experienced any SAE
5. Includes an SAE variable split by arm
6. Splits both the RFS On Treatment variable by arm and the RFS Off treatment variable by arm and includes an SAE variable split by arm
7. Includes a time (months) variable
8. Splits both the RFS On Treatment variable by arm and the RFS Off treatment variable by arm, includes an SAE variable split by arm and includes a time (months) variable

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Please also outline how many assessments there are for RFS on treatment in the placebo arm, and provide a narrative assessment of the above analyses and which has the best statistical performance.

B2. **Priority question**: The submission makes repeated reference to the AJCC registry data. To what extent does this data support the base case model estimates of:
- RFS in the placebo arm at 5 yearly intervals
- LR survival in the placebo arm without death or recurrence at 5 yearly intervals

B3. Given the interaction between the RFS and the OS data, with the RFS data being relatively simply adjusted for fixed proportions of deaths, LR and DR within the model, please explain why no consideration was given to fitting multi-state models to the COMBI-AD data, or why this approach was considered but rejected.

B4. Please augment the values of CS Appendix N Tables N.2.1 and N.4.1 with the mean days of undiscounted RFS for each arm to: (A) the period of maximum censoring in the placebo arm (50 months); and to (B) extrapolation the end of the model time horizon (2 tables, 4 sets of values for N.2.1 and 2 sets of values for N.4.1).

B5. Does the RFS modelled in Figure 20 (page 80) and in Figure 21 (page 81) of the CS Document B include deaths as an RFS event? If the Kaplan Meier data extracted from the EORTC 18071 that underlies Figure 16 of the CS Document B (page 76) differs from that underlying columns C:D of the *Survival_Distributions_Enter_KM* worksheet, please provide it in a similar format to that requested for the COMBI-AD Kaplan Meier data. There is no requirement to disaggregate events or to disaggregate censoring in this.

B6. Based upon the electronic model, the RFS and LR probabilities are augmented with the general population mortality risk but the DR probabilities are only augmented with the general population mortality risk from year 10. Is this the case, and if so why?

B7. The ERG is grateful for the early company clarification around the LR-OS modelling and the calibration of the hazard ratio (HR) for this. There remains some ambiguity in section 3.2.2 of CS Document B (page 62-68) that the ERG would be grateful for further clarification on:

1. The calibration HR is based upon post LR OS in the model compared with post LR OS in COMBI-AD. The submission suggests that the post DR OS in the model is something of an artefact and does not contribute to the cost effectiveness estimates. How, if at all, does the post DR OS in the model contribute to the post LR OS in the model given the model structure where LR patients can worsen to DR. And in turn, how does the DR OS in the model contribute to the comparison of post LR OS in the model with post LR OS in COMBI-AD when arriving at the calibration HR? Would changing the post DR OS curve/probabilities in the model

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affect the calculation of the LR OS calibration HR, and if so what effect would a worse post DR OS curve/probabilities have upon the computed LR OS calibration HR?

2. Section B.3.2.2 of CS Document B appears to confuse an LR recurrence HR and an LR OS HR. The text states that *"…after which the hazard of recurrence for LR was assumed to be the same as for RFS*". The ERG recognises that constant proportions of events are assumed for LR, DR and death, but should this be the hazard for LR OS rather than the hazard for LR recurrence? Or is the calibration hazard ratio only applied to the risk of LR recurrence?
3. Is the LR OS calibration HR applied only during the 1st 50 months of the model or is it applied throughout the model time horizon? If the LR OS calibration HR is not applied throughout the model time horizon what is the rationale for this in the base case? How reasonable is this if LR OS is extrapolated beyond 50 months using extrapolated COMBI-AD LR OS curve(s).

B8. For the curves of the base case but excluding general mortality, in the dabrafenib+ trametinib arm:

- For a patient experiencing a 1st LR event at cycle 30 who remains in LR to cycle 40, what is that patient's probability of an LR event, a DR event and a death in cycle 40? Please provide the three cell references for these probabilities, an account of the source data and values contributing to each of the three cells, and how it is combined to arrive at the final set of probabilities.
- For a patient experiencing a 2nd LR event at cycle 30 who remains in LR to cycle 40, what is that patient's probability of an LR event, a DR event and a death in cycle 40? Please provide the three cell references for these probabilities, an account of the source data and values contributing to each of the three cells, and how it is combined to arrive at the final set of probabilities.

There is no requirement to provide another copy of the model, though the response on the combination of the data inputs can be within an Excel spreadsheet if this is simpler. Does a 2nd LR event effectively reset the patient back to the baseline of the LR curve and its associated probabilities?

B9. In the model it appears the when Kaplan Meier curves are selected these are extrapolated assuming an exponential based upon the last two values of the Kaplan Meier curve. When these last two values are equal, as is typically the case, this appears to mean that the Kaplan Meier curve is extrapolated to be flat and unchanging from the last two observations. Is this correct, and if it is what does it imply for the reliability of these scenarios?

B10. Within the *SurvCalc* worksheet it appears that in the *Adjusted* columns the model does not permit hazard ratios of less than 1 to be applied. Why is this? What implication does this have for sampling within the PSA?

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B11. Please explain why the break points of the model for Segment 1 to Segment 2 for RFS and LR are 50 months, but for DR are only 30 months.Please outline if Table 35 and Table 36 of the CS Document B (page 97) apply to both RFS and LR. If not, please tabulate the routine follow-up resource use for LR in a format similar to Table 35 of the CS Document B, and any additional unit costs in a format similar to Table 36 of the CS Document B. The submission and model calculate an incident cost of LR of £8805 based upon TA366. This is based upon surgical resection to the skin for 90% of patients. Please provide details on the proportion of patients that would require lymph node dissection and why. Please provide the cost that would have been applied had TA396 been used, with an outline of the source data and the arithmetic required to arrive at the final incident cost estimate.

B12. The resource use of Table 35 of the CS Document B (page 97) does not suggest any ophthalmic monitoring. The links to summary of product characteristics (SmPCs) provided by the company suggest that ophthalmic risks are a concern. Please confirm whether it is anticipated that there will be no ophthalmology monitoring requirement in the adjuvant setting. Furthermore, the FDA (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202806s002lbl.pdf) suggest that Dabrafenib causes a risk of cardiomyopathy by reducing LVEF ≥10%, hence all patients who take the medication are likely to need baseline and possibly subsequent serial echo-cardiography. Please outline what the cost implications of this may be.

B13. Please tabulate the NICE committee preferred undiscounted LY, and discounted cost and discounted QALY estimates of each of the arms of the different models of metastatic disease references on CS Document B Page 65 (References 75, 76, 90 and 98) plus TA396 (Reference 20) of the submission. Please indicate, indicating which include the effects of any relevant patient access schemes and so have relevant total costs and which do not include the effects of any relevant patient access schemes and so do not have relevant total costs.

Section C: Textual clarifications and additional points

C1. Of the curves within the model, please list those that can sensibly be used for:

- Initial RFS to 50 months
- Extrapolation of RFS from 50 months
- Initial LR to 50 months
- Extrapolation of LR from 50 months
- Initial DR to 30 months
- Extrapolation of DR from 30 months

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These lists should not be restricted to the base case and may overlap; e.g., COMBI-AD RFS curves for both RFS to 50 months and extrapolation from 50 months. Please also clearly identify which trial each curve is drawn from as this is not unambiguous within the model.

C2. On page 48 of the CS Document B the following was noted: *"serious adverse events (SAEs) occurred in 155 patients (36%) in the dabrafenib plus trametinib arm and in 44 patients (10%) in the placebo arm. One fatal SAE (pneumonia) was reported in the dabrafenib plus trametinib arm".* Please clarify:

1. Why patients taking the placebo experience adverse events, especially serious adverse events.
2. Whether these adverse events were due to the placebo substance or due to progression of underlying stage III melanoma disease.
3. Whether there are any other possible explanations for adverse events in the placebo arm.

C3. Please provide unredacted copies of the TA396 submission and the accompanying electronic model.

C4. On page 48 of the CS Document B the following was noted: *"As of the primary data cut-off (30th June 2017), a total of 153 deaths had occurred; 60 (14%) in the dabrafenib plus trametinib arm and 93 (22%) in the placebo arm. In both trial arms, the most common cause of death was melanoma (54 patients [12%] in the dabrafenib plus trametinib group and 77 patients [18%] in the placebo group)."*

Of the 12% of patients who took combined therapy with dabrafenib and trametinib and who died due to a fatal recurrence of their melanoma, please confirm whether this is likely to be due to:

1. Underlying disease progression or to 'escape' of the tumour from the suppressive effects of the dabrafenib/trametinib combination
2. Recurrence of melanoma in the same form of the disease that the patients experienced initially? i.e., BRAF V600E mutation

C5. Long et al., (2017) on page 1819 of their publication state that non-cutaneous cancers were reported in 10 and 4 adjuvant and placebo patients, respectively. This does not appear to tally with the data presented in Table 24 of the CS Document B. Similarly, new primary melanoma in Long et al., (2017) was reported for 11 and 10 adjuvant and placebo patients, respectively. By contrast, Table 24 in the CS Document B implies different numbers. In addition, the text on page 71 of the CS Document B states that 7 and 6 adjuvant and placebo patients, respectively, experienced new primary melanoma without concomitant LR or DR. Please clarify these apparent discrepancies and tabulate all malignancies by category that were reported in each group during the study period.

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C6. Table 24 of the CS Document B reports the percentages of patients experiencing diarrhoea by grade and treatment. The ERG would like clarification on whether patients who experienced diarrhoea had their treatment stopped due to malabsorption, as the treatments are given orally. Is the diarrhoea side effect transient? If possible, please provide alternative formulations of the drug combination for patients who cannot take an oral formulation and the costs of doing this

C7. Please clarify why there is a difference in numbers/percentages (as stated in the table below) between the reported outcomes in the CS Document B and Long et al. (2017) paper?

Location	Outcome	Combination-therapy	Placebo
CS Document B (page 35)	RFS events Disease recurrence or death	166/438 (38%)	248/432 (57%)
Long et al., (2017) (Page 1816)	Disease recurrence	163/438 (37%)	247/432 (57%)

C8. The ERG note that there were nine missing references cited in the CS Document B that were not listed in the reference pack. The ERG have identified the majority of these from our own sources. The only reference we haven't been able to identify is reference 64: "Novartis. Data on File. Novartis Internal Estimates." Cited in Table 4 in the CS Document B. In addition, we have not found the draft SmPCs. In Appendix C, the company state that 'The draft SmPCs for this indication can be found in the accompanying reference pack to this submission', but the ERG can only see the current SmPCs downloaded from www.medicines.org.uk in the reference packs. Please provide these references and the draft SmPCs.

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24th May 2018

Dear Zoe,

Re: NICE ERG Clarification Questions; dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group in this current appraisal.

Further to this, please find below our responses, which we hope address the questions adequately.

Please note that given the volume of data and analysis requested, you will find the data and analyses in the enclosed excel workbook titled *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx*

In addition, please note that all information highlighted in [redacted] and [redacted] in this response and the associated documents should be considered as confidential in nature; - you will find further details in the enclosed confidentiality checklist (Appendix D).

Please do not hesitate to contact me should you require any further information.
Yours sincerely

[redacted]
Health Economics Outcomes Research Manager
Email: [redacted]

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Section A: Clarification on effectiveness data

A1. **Priority question**: The clinical expert (see company submission (CS) Document B, Reference 57) expressed the expectation that competing risk analysis would have been undertaken for relapse free survival (RFS). For the RFS data depicted in Figure 6 of the CS Document B (page 37), please conduct a competing risk analysis, separately by arm, employing the following as competing risks for recurrence (both collectively and individually):

i] events due to death;
ii] censorings due to new primary; and
iii] censoring due to premature withdrawal from study without having experienced a recurrence.

Response:

A competing risk analyses was conducted to collectively consider the following competing risks:

a. Death from any cause other than melanoma in a patient who has not experienced an observed relapse

b. Patients with a new primary melanoma

c. Loss to follow up without having an observed relapse

Two different models were used for the analysis; the cause-specific hazard model and subdistribution hazard model and the hazard ratio was adjusted for randomized strata: Disease Stage and BRAF mutation status. New primary melanomas were excluded.

The results of the competing risk analysis show that accounting for competing risk factors has a limited impact on the RFS benefit of dabrafenib+trametinib as compared to placebo. Please refer to Table A1.1 and Figure A1.1 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.*

A2. **Priority question**: Please split Table 16 of the CS Document B (page 43) into six tables:

1. Prior to any recurrence and remaining on treatment (taking placebo tablets being treated as remaining on treatment in the placebo arm)
2. Prior to any recurrence and ceased treatment (formally having ceased taking placebo tablets being treated as ceased treatment in the placebo arm)
3. At/post a 1st recurrence of loco-regional recurrence (LR)
4. At/post a 1st recurrence of distant recurrence (DR)
5. At/post a 1st secondary primary melanoma (SPM)
6. Recurrence status unknown (if required)

Please augment each of these tables with the number of patients eligible to report EQ-5D-3L by arm so that reporting rates can be calculated.

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Response:

Please refer to Table A2.1 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the requested detailed analyses of the COMB-AD EQ-5D-3L data.

A3. **Priority question**: Please tabulate the data of Figure 27 of the CS Document B (page 95). Please tabulate the number of packs of dabrafenib and the number of packs of trametinib that were dispensed in the dabrafenib arm of COMBI-AD by week (1 table), together with the total number of packs dispensed during the trial. If weekly data is not available, please provide this for the shortest time period for which it is available. Please see example table below:

	Dabrafenib packs		Trametinib packs	
	50mg	75mg	0.5mg	2mg
Week 0	N=???	N=???	N=???	N=???
Week 1	N=???	N=???	N=???	N=???
Week 2	N=???	N=???	N=???	N=???
Etc…	N=???	N=???	N=???	N=???
Totals	N=???	N=???	N=???	N=???

Response:

Novartis do not currently hold this information in our database. The IVRS team was contacted with regards to drug accountability data, however at the time of preparing this response document, this information was still unavailable. Novartis appreciate that this is an ERG priority question and will endeavour to provide an update on the requested information as soon as possible

A4. **Priority question**: In this and the following question, all Kaplan-Meier data can be supplied within an Excel workbook if this is simpler, with separate worksheets for type of Kaplan-Meier data, arm and where applicable trial. Please provide the RFS Kaplan-Meier data that underlies Figure 6 of the CS Document B (page 37) in the following disaggregate form for each arm (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes, DR, LR, SPM
- Censoring: C_{EoT}, End of trial, C_O, Other

For a patient with more than one event recorded at a given time point please ascribe this hierarchically to D_M then D_O then DR then LR then SPM; i.e., a patient with a DR and an LR at the same time point should be classed as a DR event. Please clarify if 1-month is 4 weeks or is some other duration.

	Events	Censoring

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t	N at risk	D_M	D_O	DR	LR	SPM	C_{EoT}	C_O	S(t)
T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

Response:
Please refer to Tables A4.1 and A4.2 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the RFS data requested for dabrafenib plus trametinib and placebo, respectively.

One month is defined as 30.4375 (365.25/12) days. Days were calculated as End Date – Start Date + 1.

A5. **Priority question**: Please provide the OS Kaplan-Meier data that underlies Figure 7 of CS Document B (page 39) in the following disaggregate form for each arm (2 tables): Please clarify if 1-month is 4 weeks or is some other duration.

- Events: D_M, death from melanoma, D_O, death from other causes
- Censoring: C_{EoT}, End of trial, C_O, Other

For a patient with more than one event recorded at a given time point, please ascribe this hierarchically to D_M then D_O then DR then LR.

		Events		Censoring		
T	N at risk	D_M	D_O	C_{EoT}	C_O	S(t)
T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

Response:
Please refer to Tables A5.1 and A5.2 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the OS data requested for dabrafenib plus trametinib and placebo, respectively.

One month is defined as 30.4375 (365.25/12) days. Days were calculated as End Date – Start Date + 1.

A6. **Priority question**: Please explain why the clinical experts advised that SPM should not be considered an RFS event given the trial protocol and Figure 6 of the CS Document B (page 37).

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Please provide the RFS Kaplan-Meier data that underlies Figure 13 of the CS Document B (page 71) in the following disaggregate form for each arm (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes, DR, LR.
- Censoring: C_{SPM}, SPM event, C_{EoT}, End of trial, C_O, Other

Please clarify if 1-month is 4 weeks or is some other duration.

		Events				Censoring			
t	N at risk	D_M	D_O	DR	LR	C_{SPM}	C_{EoT}	C_O	S(t)
T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

Response:

Clinical experts advised that an SPM should not be considered as an RFS event since the management of an SPM is similar to any primary cutaneous melanoma in patients with no prior history of melanoma. The experts also stated that since the majority of SPMs are likely to be "thin" melanomas managed by simple surgical excision, the management of an SPM would be different to that of an LR, with the latter associated with poorer outcomes and potential systemic therapy.

As such, for the purposes of the economic analysis, the clinical experts advised that SPMs should be excluded or considered as an unrelated event and not a recurrence event.

Please refer to Tables A6.1 and A6.2 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the RFS data requested for dabrafenib plus trametinib and placebo, respectively.

One month is defined as 30.4375 (365.25/12) days. Days were calculated as End Date – Start Date + 1.

A7. **Priority question**: Please provide details regarding:

- The number of patients in the active treatment arm of COMBI-AD that completed 12 months of treatment (n=???), completed more than 12 months of treatment (n=???), continued treatment after LR (n=???), continued treatment after DR (n=???), continued treatment after SPM (n=???).
- The data definition for the Average Mean Daily dose and the Cumulative dose in Table 19 of CS Document B (page 79), outlining how dose interruptions, reductions and escalations are handled and how treatment discontinuations are handled.
- The disaggregate time to treatment discontinuation Kaplan-Meier data of COMBI-AD (2 tables):

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- Events: D, death, Recurrence, R, Adverse events, AE, Lost to follow up, End of 12-month course, EoC, (and a separate Other catchall if required)
- Censoring: CEoT, End of trial, C_O, Other

Please clarify if 1-month is 4 weeks or is some other duration.

		Events					Censoring		
t	N at risk	D	R	AE	LTFU	EoC	C_{EoT}	C_O	S(t)
T=0	N=???	N=0	N=0	N=0	N=0	N=0	N=0	N=0	100%
T=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???	???%
Etc…									

Response:

Please refer to Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the requested analyses (Tables A7.1, A7.2 and A7.3)

- In the COMBI-AD trial, the number of patients in the dabrafenib plus trametinib arm that completed 12 months of treatment, completed more than 12 months of treatment, and continued treatment after an LR, DR or SPM was [redacted] and [redacted] respectively (Table A7.1). In this analysis, 12 months of treatment is defined as 12*28 days =336 days, and as such, [redacted] patients completed at least 12 months of treatment [redacted]

- In Table 19 (page 50) of the manufacturer submission, the cumulative dose is defined as the sum of all doses administered to an individual patient whilst in the trial and the average mean daily dose is defined as the cumulative dose for each patient divided by the duration of exposure for each patient.

  Dose interruptions, reductions and escalations and treatment discontinuations were managed in the COMBI-AD trial as described in Section 5 of the study protocol[1] and guidance included algorithms to manage AEs.

  The disaggregate time to treatment discontinuation Kaplan-Meier data for dabrafenib plus trametinib and placebo is reported in Tables A7.2 and A7.3 respectively

- One month is defined as 30.4375 (365.25/12) days. Days were calculated as End Date – Start Date + 1.

A8. Please provide the OS Kaplan-Meier data for COMBI-AD LR patients treating the point of LR as the baseline t=0 (2 tables):

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- Events: D_M, death from melanoma, D_O, death from other causes.
- Censoring: C_{EoT}, End of trial, C_O, Other

		Events		Censoring		
t	N at risk	D_M	D_O	C_{EoT}	C_O	S(t)
T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

Response:
Please refer to Tables A8.1 and A8.2 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the post-LR OS data requested for dabrafenib plus trametinib and placebo, respectively.

A9. Please provide the OS Kaplan-Meier data for COMBI-AD DR patients treating the point of DR as the baseline t=0 (2 tables):

- Events: D_M, death from melanoma, D_O, death from other causes.
- Censoring: C_{EoT}, End of trial, C_O, Other

		Events		Censoring		
t	N at risk	D_M	D_O	C_{EoT}	C_O	S(t)
T=0 T=??? Etc…	N=??? N=???	N=0 N=???	N=0 N=???	N=0 N=???	N=0 N=???	100% ???%

Response:
Please refer to Tables A9.1 and A9.2 in Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the post-DR OS data for dabrafenib plus trametinib and placebo respectively.

A10. Please provide the Kaplan-Meier data (timepoint, N at risk, N events, N censoring events, S(t)) that underlies the curves of the *Survival_Distributions_Enter_KM* worksheet columns C:D, R:S, U:V, X:Y. For columns R:S if it is possible, it would be appreciated if this could be split into the two trials and then the method for combining this data to arrive at the values in columns R:S presented.

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Response:
The Kaplan-Meier data underpinning the curves of the *Survival_Distributions_Enter_KM* worksheet columns C:D, R:S, U:V, X:Y in the economic model is provided in Tables A10.1 – A10.4 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx*

Since columns R:S of the *Survival_Distributions_Enter_KM* worksheet in the economic model relate to the weighted Kaplan-Meier data from the KEYNOTE-006 and COMBI-V/COMBI-D trials, the formulae used to combine these data can be found in column Q of Table A10.2.

A11. Please provide separate Kaplan-Meier plots by arm comparing the RFS analyses done by method in Figure 6 (page 37) and Figure 13 (page 71) of the CS Document B.

Response:
Please refer to Figures A11.1 and A11.2 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the comparison of dabrafenib plus trametinib and placebo in Figures 6 and 13 of our submission, respectively.

A12. For Figure 13 (page 71) of the CS Document B, please report outcome details pertaining to the analysis (log-rank test, HR, medians, etc.).

Response:
Please refer to Figure A12.1 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for the information requested. The hazard ratio for relapse is 0.47 (95% CI, 0.38–0.57) P<0.001 is very similar to that in Figure 6 of the submission (HR 0.47 (95% CI, 0.39–0.58) P<0.001)

A13. In the placebo arm, what was the compliance of taking 2 tablets / day for 12 months?

Response:
The mean percentage (± standard deviation [SD]) of overall compliance in the placebo arm was 97.0% ± 7.21 for dabrafenib/placebo and 98.7% ± 4.20 for trametinib/placebo.

A14. The CS Document B notes that “region” is a pre-specified subgroup, but does not provide any subgroup analyses for this subgroup. Please summarise all the subgroup analyses that have been conducted based upon “region”, together with any forest plots.

Response:
Per study protocol, region was a pre-specified subgroup for the analyses of RFS. The analyses conducted for this subgroup were North America (US and Canada), Europe (all countries in Europe plus Israel), Asia/Pac (all Asian countries excluding Australia and New Zealand), South America (All countries in South America) and Australia and New Zealand.

Please see Table A14.1 and Figure A14.1 for the results of the region subgroup analyses.

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Table A14.1. Summary of RFS by region

	North America		Europe and Israel		Asia/Pac (all Asian countries excluding Australia and New Zealand)		South America		Australia and New Zealand	
	Dabrafenib plus trametinib (N=48)	Placebo (N=48)	Dabrafenib plus trametinib (N=330)	Placebo (N=320)	Dabrafenib plus trametinib (N=5)	Placebo (N=4)	Dabrafenib plus trametinib (N=5)	Placebo (N=3)	Dabrafenib plus trametinib (N=50)	Placebo (N=57)
Number of subjects, n (%)										
Relapsed (event)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Died (event)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimates for RFS (months)[a]										
1st quartile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[a]Quartiles estimated using the Brookmeyer-Crowley method. [b]Hazard ratio is estimated using Pike estimator. A hazard ratio <1 indicates a lower risk with dabrafenib plus trametinib compared with placebo.
Abbreviations: CI: confidence interval; NA: not applicable; RFS: relapse-free survival.
Source: COMBI-AD CSR[2]

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Figure A14.1. Hazard ratios and 95% confidence intervals for RFS subgroup analyses (ITT population)

Note: Hazard ratios were estimated using Pike estimator.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide details of other quality of life modelling using the COMBI-AD that was explored in addition to that reported in Table 31 of CS Document B (page 91). Please also provide the results. Please provide additional analyses (8 tables) paralleling the GEE analysis of Table 31 of the CS Document B that:

1. Splits the RFS On Treatment variable by arm with those remaining on placebo treated as being *RFS On Treatment in the placebo arm*; i.e., splitting the 2,140 EQ-5D RFS Off treatment observations in the placebo arm into (A) those where placebo tablets were still being received and (B) those where the patient formally had discontinued from receiving placebo tablets for whatever reason
2. Splits the RFS Off treatment variable by arm
3. Splits both the RFS On Treatment variable by arm and the RFS Off treatment variable by arm
4. Includes an SAE variable, defined as a patient having experienced any SAE
5. Includes an SAE variable split by arm
6. Splits both the RFS On Treatment variable by arm and the RFS Off treatment variable by arm and includes an SAE variable split by arm
7. Includes a time (months) variable
8. Splits both the RFS On Treatment variable by arm and the RFS Off treatment variable by arm, includes an SAE variable split by arm and includes a time (months) variable

Please also outline how many assessments there are for RFS on treatment in the placebo arm, and provide a narrative assessment of the above analyses and which has the best statistical performance.

Response:

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Please refer to Table B1.1 for the quality of life models and Table B1.2, and Figure B1.1 for a comparison of the statistical models in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx*.

The results in Table B1.2 and Figure B1.1 show that the original model used in our submission has the best statistical fit (lowest QIC and QICu). It appears that RFS on treatment with placebo is associated with a significantly worse utility than RFS off treatment and that month of assessment is a positive predictor, though the impact is not clinically meaningful given the very small coefficient. This may reflect informative censoring as healthier patients may be more likely to continue to complete the assessments.

Additionally, there is no difference in RFS off treatment for dabrafenib plus trametinib and RFS off treatment for placebo, and SAEs are not predictive factors.

The number of assessments included for RFS on treatment, RFS off treatment, distant recurrence and loco-regional recurrence are reported below in Table B1.3.

Table B1.3. Numbers of assessments contributing to analyses of EQ-5D-3L assessments in COMBI-AD

	Dabrafenib plus trametinib	Placebo	Total
Number of assessments			
RFS on treatment	941	817	1758
RFS off treatment	2039	1323	3362
On or after loco-regional recurrence	47	67	114
On or after distant recurrence	57	83	140

Abbreviations: EQ-5D-3L: EuroQol Five Dimensions Three-Level; RFS: relapse-free survival.

B2. **Priority question**: The submission makes repeated reference to the AJCC registry data. To what extent does this data support the base case model estimates of:

- RFS in the placebo arm at 5 yearly intervals
- LR survival in the placebo arm without death or recurrence at 5 yearly intervals

Response:

Please note that the AJCC registry data is referenced *once* in our submission (section B.3.3.1, page 82), where we describe how the RFS curves for the majority of the mixture models explored in the placebo arm of the EORTC 18071 trial begin to plateau at approximately 10 years (Figure 21, page 81). We then discuss how UK clinical experts describe this data trend to be similar to the plateau observed in the melanoma-specific survival (OS after 10 years in the AJCC registry data, suggesting a low likelihood of disease recurrence after 10 years).

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To contextualise this further, please note that the AJCC registry[3] represents a large sample of prospective data on 30,946 patients with stage III melanoma and 7,972 patients with stage IV disease. The AJCC registry provides long-term follow-up for survival (~15 years), and although a correlation between RFS and OS has been previously documented in melanoma[4], it is difficult to draw direct comparisons between the OS data provided by the AJCC registry and the predictions for RFS in our submission.

B3. Given the interaction between the RFS and the OS data, with the RFS data being relatively simply adjusted for fixed proportions of deaths, LR and DR within the model, please explain why no consideration was given to fitting multi-state models to the COMBI-AD data, or why this approach was considered but rejected.

Response:
The fitting of a "multistate model" was not considered, as the approach used is the economic analysis was consistent with that the approach used in prior economic assessments of adjuvant therapies. In addition, there was no evidence that the distribution of RFS events by type changes over time, and it is unlikely that the use of a different approach would materially impact the model results.

B4. Please augment the values of CS Appendix N Tables N.2.1 and N.4.1 with the mean days of undiscounted RFS for each arm to: (A) the period of maximum censoring in the placebo arm (50 months); and to (B) extrapolation the end of the model time horizon (2 tables, 4 sets of values for N.2.1 and 2 sets of values for N.4.1).

Response:
Please refer to Tables B4.1 for the parametric distributions fit to RFS for dabrafenib plus trametinib and placebo in the COMB-AD trial and Table B4.2 for the parametric distributions fit to RFS for placebo in the EORTC-18071 trial (Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx)*.

B5. Does the RFS modelled in Figure 20 (page 80) and in Figure 21 (page 81) of the CS Document B include deaths as an RFS event? If the Kaplan-Meier data extracted from the EORTC 18071 that underlies Figure 16 of the CS Document B (page 76) differs from that underlying columns C:D of the *Survival_Distributions_Enter_KM* worksheet, please provide it in a similar format to that requested for the COMBI-AD Kaplan-Meier data. There is no requirement to disaggregate events or to disaggregate censoring in this.

Response:
The Kaplan-Meier data for RFS in the placebo arm of the EORTC 18071 trial (Figure 20 of our submission) is based on pseudo individual patient-level data generated with the Guyot algorithm.

This does not differ from the data in columns C:D of *Survival_Distributions_Enter_KM* worksheet in the economic model and the data provided in response to question A10 (Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx)*.

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B6. Based upon the electronic model, the RFS and LR probabilities are augmented with the general population mortality risk but the DR probabilities are only augmented with the general population mortality risk from year 10. Is this the case, and if so why?

Response:

The DR probabilities are only augmented with the general population mortality risk from year 10 because post-DR OS in the economic analysis used the weighted hazard from NICE TA366[5] (pembrolizumab) and TA396[6] (dabrafenib plus trametinib), which already account for general population mortality. After 10 years, it is assumed that the hazard rate for post-DR OS is constant, and as such, general population mortality is applied to patients with DR only after 10 years.

B7. The ERG is grateful for the early company clarification around the LR-OS modelling and the calibration of the hazard ratio (HR) for this. There remains some ambiguity in section 3.2.2 of CS Document B (page 62-68) that the ERG would be grateful for further clarification on:

1. The calibration HR is based upon post LR OS in the model compared with post LR OS in COMBI-AD. The submission suggests that the post DR OS in the model is something of an artefact and does not contribute to the cost effectiveness estimates. How, if at all, does the post DR OS in the model contribute to the post LR OS in the model given the model structure where LR patients can worsen to DR. And in turn, how does the DR OS in the model contribute to the comparison of post LR OS in the model with post LR OS in COMBI-AD when arriving at the calibration HR? Would changing the post DR OS curve/probabilities in the model affect the calculation of the LR OS calibration HR, and if so what effect would a worse post DR OS curve/probabilities have upon the computed LR OS calibration HR?
2. Section B.3.2.2 of CS Document B appears to confuse an LR recurrence HR and an LR OS HR. The text states that *"…after which the hazard of recurrence for LR was assumed to be the same as for RFS*". The ERG recognises that constant proportions of events are assumed for LR, DR and death, but should this be the hazard for LR OS rather than the hazard for LR recurrence? Or is the calibration hazard ratio only applied to the risk of LR recurrence?
3. Is the LR OS calibration HR applied only during the 1st 50 months of the model or is it applied throughout the model time horizon? If the LR OS calibration HR is not applied throughout the model time horizon what is the rationale for this in the base case? How reasonable is this if LR OS is extrapolated beyond 50 months using extrapolated COMBI-AD LR OS curve(s).

Response:

1. Post-DR OS in the model is defined as OS for patients experiencing a DR, at which point DR is treated as baseline t=0 (e.g., including patients with LR who later experience DR).

   Post-LR OS is defined as OS for patients experiencing an LR, at which point LR is treated as baseline t=0. Since transitions from the LR health state include death, subsequent LR, and DR, post-DR OS contributes to post-LR OS.

   Please note that changing the post-DR OS curve does not affect the calibration HR for LR because the calibration macro overrides the selected post-DR OS curve and utilises the post-

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DR OS Kaplan-Meier curve from COMBI-AD. This is an assumption that cannot be modified by the user.

Parameter inputs that do affect the calibration HR are the proportions of LR events by type; please refer to the worksheet *RFS Select Locoreg!H8:I9* in the economic model.

2. The calibration HR is applied to the probability of any event in the LR health state (i.e., post-LR RFS), defined as recurrence (i.e., LR or DR) or death. Post-LR OS is not explicitly modelled, but is rather a function of post-LR RFS and post-DR OS.

3. The calibration HR is only applied to the first 50 months of the model since this is the maximum follow-up available in the COMBI-AD trial (segment 1 of the post-LR survival distribution). Please refer to worksheet *RFS Select_Locoreg* of the economic model

   After 50 months, data from the placebo arm of the EORTC-18071 trial is used (segment 2, worksheet *RFS Select_Locoreg* of the economic model).

   The rationale for applying the HR only during the first 50 months is based on making best use of all available data, clinical opinion and a previous study by Salama and colleagues (2013) analysing the timing and patterns of recurrence in early stage melanoma.[7] As discussed in Section B.3.3.3 of our submission, clinical opinion suggested that the shape of the survival distribution for LR is likely to follow the same pattern as RFS (e.g., high hazard initially which decreases with time). This is supported by the study conducted by Salama *et al.*, where the hazard of recurrence following a previous LR was initially higher than the hazard of recurrence in patients without a previous LR, and was initially high, then decreased over time, steadily approached one.[7]

B8. For the curves of the base case but excluding general mortality, in the dabrafenib+ trametinib arm:

- For a patient experiencing a 1st LR event at cycle 30 who remains in LR to cycle 40, what is that patient's probability of an LR event, a DR event and a death in cycle 40? Please provide the three cell references for these probabilities, an account of the source data and values contributing to each of the three cells, and how it is combined to arrive at the final set of probabilities.
- For a patient experiencing a 2nd LR event at cycle 30 who remains in LR to cycle 40, what is that patient's probability of an LR event, a DR event and a death in cycle 40? Please provide the three cell references for these probabilities, an account of the source data and values contributing to each of the three cells, and how it is combined to arrive at the final set of probabilities.

There is no requirement to provide another copy of the model, though the response on the combination of the data inputs can be within an Excel spreadsheet if this is simpler. Does a 2nd LR event effectively reset the patient back to the baseline of the LR curve and its associated probabilities?

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Response:

- For a patient experiencing a 1st LR at cycle 30, who remains in LR until cycle 40, 10 cycles will have elapsed since the patient experienced the LR event and the name for this health state in the economic model is **LRR.10** (please refer to worksheet *Transit* in the model)
    - The transition probabilities in cycle 40 from *LRR.10* to *LRR.1* (i.e., probability of an LR event; *Transit!BM96*), from **LRR.10** to **DR.1** (i.e., probability of a DR event; *Transit!BM98*), and from **LRR.10** to **Dead.Mel.1** (i.e., probability of death excluding general mortality; *Transit!BM99*) are 0.031, 0.061, and 0.005, respectively.
    - Column BM on the *Transit* sheet is used to adjust the transition probabilities to account for general mortality as the model population ages (in this example, we are assuming there is no general mortality), and represents the health state transition probabilities for all transitions between health states occurring in cycle 40.
    - The sources of the aforementioned probabilities of LR, DR and death events are *Transit!U96*, *Transit!U98*, and *Transit!U99*, respectively. Column U contains a formula that looks up event probabilities that vary based on the amount of time spent in a given health state (i.e., time elapsed since experiencing the event). The sources of the values in U96 (i.e., LR event), U98 (i.e., DR event), and U99 (i.e., death event excluding general mortality) are *SurvCalc!BA32*, *SurvCalc!BB32*, and *SurvCalc!BC32*, respectively. Columns BA:BC on the *SurvCalc* sheet calculate the probabilities of LR, DR, and death excluding general mortality for patients with LR at a given time.
- For a patient experiencing a 2nd LR at cycle 30, who remains in LR until cycle 40, 10 cycles will have elapsed since that patient experienced the LR event. The name for this health state in the model is **LRR.10**. The model assumes that transition probabilities for patients with LR vary by time since their *most recent* LR event. As such, the probability of LR, DR, and death for a patient with 2nd (or subsequent) LR residing in the **LRR.10** health state in cycle 40 are the same as for a patient with a 1st LR.
- Please note that a 2nd LR event does effectively reset the patient back to the baseline of the LR curve and its associated probabilities

B9. In the model it appears the when Kaplan-Meier curves are selected these are extrapolated assuming an exponential based upon the last two values of the Kaplan-Meier curve. When these last two values are equal, as is typically the case, this appears to mean that the Kaplan-Meier curve is extrapolated to be flat and unchanging from the last two observations. Is this correct, and if it is what does it imply for the reliability of these scenarios?

Response:

This observation is correct, however, there are no implications for the scenarios which utilise the Kaplan-Meier curves because the hazard rate from EORTC 18071 is assumed after month 50.

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B10. Within the *SurvCalc* worksheet it appears that in the *Adjusted* columns the model does not permit hazard ratios of less than 1 to be applied. Why is this? What implication does this have for sampling within the PSA?

Response:

This observation is incorrect, the only constraint on the HR is that it should be greater than or equal to zero. The formula in the adjusted columns only restricts the survival probabilities such that the probability of survival does not increase over time. This constraint has no material impact on the sampling within the PSA.

B11. Please explain why the break points of the model for Segment 1 to Segment 2 for RFS and LR are 50 months, but for DR are only 30 months. Please outline if Table 35 and Table 36 of the CS Document B (page 97) apply to both RFS and LR. If not, please tabulate the routine follow-up resource use for LR in a format similar to Table 35 of the CS Document B, and any additional unit costs in a format similar to Table 36 of the CS Document B. The submission and model calculate an incident cost of LR of £8805 based upon TA366. This is based upon surgical resection to the skin for 90% of patients. Please provide details on the proportion of patients that would require lymph node dissection and why. Please provide the cost that would have been applied had TA396 been used, with an outline of the source data and the arithmetic required to arrive at the final incident cost estimate.

Response:

The break point in the model for segment 1 to segment 2 for RFS (and post-LR OS) corresponds to the maximum censoring time (approximately month 50) for both treatment arms (refer to page 72 of our submission), to make best use of all available data. The model break point for post-DR OS, however, is month 30 since after this point, the tail end of the Kaplan-Meier curve is uncertain given the extremely low number of patients at risk in both treatment arms (n=1 in the dabrafenib and trametinib arm and n=11 in the placebo arm). Please refer to Figure 25, page 88 of our submission.

It is also important to note that although a number of alternative break points, assumptions or extrapolations could be considered for post-DR OS, they would have no impact on the incremental costs, QALYs and resultant ICER given the simplified modelling approach of applying outcomes following a DR as a one-off at the point of recurrence.

The resource use and unit costs reported in Tables 35 and 36 of our submission (page 97) only apply to RFS. The resource use and unit costs associated with the management of LR are reported in Table 37 (page 98) where the treatment of LR is considered as an 'acute event', and where all patients experiencing an LR receive a one-off cost of an outpatient visit to the medical oncologist and a CT scan of the chest, abdomen and pelvis. Additionally, following clinical expert opinion, it was assumed that 90% of patients with an LR would undergo surgical resection, with the remaining 10% receiving systemic therapy (immunotherapy [70%] or targeted therapy [10%]).

Complete lymph node dissection is not recommended as a curative approach for patients experiencing LR, since it provides similar outcomes to routine surveillance.[8-10] This recommendation follows the results of two large trials (MSLTII and DeCOG-SLT) conducted in patients with stage III node-positive

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disease, and as a result of these data, UK clinical practice is changing with rates of lymph node dissections varying across different institutions.[8, 10] Consequently, the proportion of patients that would require complete lymph node dissection is expected to be in the range of 0-30%. The exact proportion is difficult to ascertain at present since this recommendation has only been recently agreed, however a position paper describing this recommendation is expected to be published by Melanoma focus in the near future.

B12. The resource use of Table 35 of the CS Document B (page 97) does not suggest any ophthalmic monitoring. The links to summary of product characteristics (SmPCs) provided by the company suggest that ophthalmic risks are a concern. Please confirm whether it is anticipated that there will be no ophthalmology monitoring requirement in the adjuvant setting. Furthermore, the FDA (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202806s002lbl.pdf) suggest that Dabrafenib causes a risk of cardiomyopathy by reducing LVEF ≥10%, hence all patients who take the medication are likely to need baseline and possibly subsequent serial echo-cardiography. Please outline what the cost implications of this may be.

Response:
Clinical expert opinion confirmed that in the adjuvant setting, patients would only be referred for ophthalmologic assessments if they experience symptoms. This is consistent with medical management with the use of dabrafenib plus trametinib in the metastatic setting where ophthalmologic monitoring is not routinely undertaken.

In addition, given the risk of reduced LVEF, clinical expert opinion indicated that cardiac monitoring would occur every 3 months whilst on treatment. As such, four echocardiogram/echography (ECHO) or multiple-gated acquisition scan (MUGA) assessments at a cost of £70.36 and £294.34, respectively, have been included in the economic analysis during the 12-month treatment period. Please refer to Tables 35 and 36 (pages 97–98) in our submission accordingly.

B13. Please tabulate the NICE committee preferred undiscounted LY, and discounted cost and discounted QALY estimates of each of the arms of the different models of metastatic disease references on CS Document B Page 65 (References 75, 76, 90 and 98) plus TA396 (Reference 20) of the submission. Please indicate, indicating which include the effects of any relevant patient access schemes and so have relevant total costs and which do not include the effects of any relevant patient access schemes and so do not have relevant total costs.

Response:
Please refer to Table B13.1 below for details on the LYG, cost and QALY estimates from the different appraisals in metastatic disease referenced in our submission.

Please note that the final appraisal documentation (FAD) associated with these appraisals do not explicitly comment on the NICE committee's preferred ICER, and consequently, the decision-making ICER (and associated LYs, costs and QALYs), for these appraisals remain unclear. As such, in Table B13.1, we report the manufacturer and the ERG's preferred estimates, using the discounted values since, with the exception of TA366, the undiscounted values were not reported in the majority of the appraisal documents.

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As described in our submission, the outcomes associated with the management of DR and terminal care were incorporated in the model as one-off costs and QALYs at the point of recurrence, using estimates reported for pembrolizumab in TA366[5] and dabrafenib and trametinib in TA396.[6] The rationale for selecting these specific treatments and their associated appraisals was discussed in Section B.3.5.2 (page 99).

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Table B13.1. Assessment of LYG, costs and QALYs of previous NICE assessments in metastatic appraisals

Appraisal	Document B reference and page number	Intervention	Company base case					ERG preferred case						
			Disc total LYG	Costs		Disc total QALYs	Population[d]	Disc total LYG	Costs		Disc total QALYs	Population[d]	Additional information
				Disc total costs (£)	Price[c]				Disc total costs (£)	Price[c]			
Nivolumab for treating advanced (unresectable or metastatic) melanoma TA384[11]	TA384 CS Tables 3 and 4 p.19 (ID1226 Document B Reference 20) and TA384 ERG Report Table 32 p.105[a]	VEM	2.37	RED	NA	1.70	BRAF+	NR	RED	List	1.70	BRAF+	The ERG noted some uncertainties with regard to the modelling assumptions and data in the company base case. The ERG found that incorporating changes to the method used to estimate OS, the maximum treatment duration and TTP have significant impact on the model results. For example, in a scenario analysis performed by the ERG (albeit not the
		DAB	2.37	RED	NA	1.69	BRAF+	NR	RED	List	1.69	BRAF+	
		IPI	3.40	RED	NA	2.44	BRAF+	NR	RED	List	2.44	BRAF+	
		NIVO	5.70	RED	NA	4.27	BRAF+	NR	RED	List	2.27	BRAF+	
		DTIC	NR	NR	NA	NR	BRAF+	NR	RED	List	1.10	BRAF+	

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Appraisal	Document B reference and page number	Intervention	Company base case					ERG preferred case					
			Disc total LYG	Costs		Disc total QALYs	Population[d]	Disc total LYG	Costs		Disc total QALYs	Population[d]	Additional information
				Disc total costs (£)	Price[c]				Disc total costs (£)	Price[c]			
													preferred case reported in this table) nivolumab was no longer cost effective and was dominated by ipilimumab
Nivolumab in combination with ipilimumab for treating advanced melanoma TA400[12]	TA400 CS Tables 77 and 79 p.205–206 (ID1226 Document B Reference 76) and TA400 ERG Report Table 133 p. 252–253	VEM	2.243	RED	NA	1.743	BRAF+	NR	NR	NA	NR	NA	The ERG presents a single preferred base case scenario including both BRAF+ and BRAF- patients considering the same case mix observed in CheckMate 067. According to the company's assumptions and analyses, BRAF status
		DAB	2.243	RED	NA	1.743	BRAF+	NR	NR	NA	NR	NA	
		IPI	3.376	RED	List	2.593	BRAF+	NR	RED	List	1.75	Mixed	
		NIVO + IPI	6.263	RED	List	4.852	BRAF+	NR	RED	List	2.79	Mixed	

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Appraisal	Document B reference and page number	Intervention	Company base case					ERG preferred case					
			Disc total LYG	Costs		Disc total QALYs	Population[d]	Disc total LYG	Costs		Disc total QALYs	Population[d]	Additional information
				Disc total costs (£)	Price[c]				Disc total costs (£)	Price[c]			
													does not influence the outcomes associated with immunotherapy treatment, and as the ERG base case makes use of the subsequent therapy data observed directly from the CheckMate 067 CSR, the model results are deemed relevant for both subpopulations.
Pembrolizumab for advanced melanoma not previously treated with	TA366 CS Table 4 p. 24 (ID1226 Document B Referenc	VEM	2.74	£83,384	List	1.73	BRAF+	NR	£90,411	List	2.23	BRAF+	Results including PAS for all comparators are reported in a separate Appendix to the
		DAB	3.41	£71,029	List	2.17	BRAF+	NR	£74,267	List	2.15	BRAF+	
		PEMBRO	5.08	£76,689	PAS	3.14	BRAF+	NR	£83,282	PAS	2.96	BRAF+	
		IPI	4.37	£97,873	List	2.69	BRAF+	NR	£95,315	List	2.52	Mixed	

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Appraisal	Document B reference and page number	Intervention	Company base case					ERG preferred case					
			Disc total LYG	Costs		Disc total QALYs	Population[d]	Disc total LYG	Costs		Disc total QALYs	Population[d]	Additional information
				Disc total costs (£)	Price[c]				Disc total costs (£)	Price[c]			
ipilimumab TA366[5]	e 90) and TA366 ERG Report Tables 55, 56 and 57 and 37 p. 117–119[b]												ERG report. Once the relevant PAS are applied to all four drugs, pembrolizumab becomes more expensive than all the comparators and no longer dominates any of them in the company or ERG base
Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma TA319[13]	TA319 Company comments on ACD Table 7 p. 20 and ERG Report Tables 6.19 and 6.20 p.	VEM	2.8401	RED	NA	2.0550	Mixed	NR	£52,346	List	2.1658	Mixed	The ERG considered the manufacturer's base-case ICERs to be highly uncertain and argued that the only reasonable model structure considers first-
		IPI	3.2326	RED	NA	2.2566	Mixed	NR	£57,760	List	2.3527	Mixed	
		DTIC	2.0018	RED	NA	1.4611	Mixed	NR	£19,914	List	1.4611	Mixed	

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Appraisal	Document B reference and page number	Intervention	Company base case					ERG preferred case					
			Disc total LYG	Costs		Disc total QALYs	Population[d]	Disc total LYG	Costs		Disc total QALYs	Population[d]	Additional information
				Disc total costs (£)	Price[c]				Disc total costs (£)	Price[c]			
	122 and p. 123												line treatments only (rather than also second-line treatments, as in the company's model). Exploratory analyses performed by the ERG using alternative assumptions had a 'major' impact on the cost-effectiveness results.
Trametinib in combination with dabrafenib for treating unresectable or metastatic	TA396 CS Table 4 p. 15 (ID1226 Document B Reference 20) and TA396	VEM	2.933	[redacted]	PAS	2.098	BRAF+	3.461	£177,436	List	2.461	BRAF+	The ERG made several changes to the company model, however these had little impact on the QALY estimation for
		DAB	2.933	[redacted]	PAS	2.146	BRAF+	3.461	£166,544	List	2.461	BRAF+	
		DAB + TRA	4.586	[redacted]	PAS	3.443	BRAF+	4.511	£327,467	List	3.255	BRAF+	

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Appraisal	Document B reference and page number	Intervention	Company base case					ERG preferred case					
			Disc total LYG	Costs		Disc total QALYs	Population[d]	Disc total LYG	Costs		Disc total QALYs	Population[d]	Additional information
				Disc total costs (£)	Price[c]				Disc total costs (£)	Price[c]			
melanoma TA396[6]	ERG Report Tables 36 and 37 p. 114–115												DAB + TRA (3.443 versus 3.255).

[a]The ERG-preferred case was unclear from the ERG report. Results from the ERG analysis in a BRAF+ population have been reported in this table as this is the population most relevant to the current decision problem. [b]Discounted LYG were not reported in the ERG report. However, undiscounted LYG values of 4.42, 4.18, 5.83 and 5.06 were reported in the ERG report for VEM, DAB, PEMBRO and IPI respectively. [c]Price: list price of PAS price. PAS price represents true cost to NHS. [d]Population: Mixed includes BRAF-mutated (BRAF+ve) and wild type.

Abbreviations: ACD: appraisal consultation document; CS: company submission; DAB: dabrafenib; DTIC: dacarbazine; ERG: Evidence Review Group; DTIC: dacarbazine; ICER: incremental cost-effectiveness ratio; IPI: ipilimumab; LYG: life years gained; NA: not applicable; NHS: National Health Service; NIVO: nivolumab; NR: not reported; OS: overall survival; PAS: patient access scheme; PEMBRO: pembrolizumab; QALY: quality-adjusted life year; RED: redacted; TRA: trametinib; TTP: time to progression; VEM: vemurafenib.

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Section C: Textual clarifications and additional points

C1. Of the curves within the model, please list those that can sensibly be used for:

- Initial RFS to 50 months
- Extrapolation of RFS from 50 months
- Initial LR to 50 months
- Extrapolation of LR from 50 months
- Initial DR to 30 months
- Extrapolation of DR from 30 months

These lists should not be restricted to the base case and may overlap; e.g., COMBI-AD RFS curves for both RFS to 50 months and extrapolation from 50 months. Please also clearly identify which trial each curve is drawn from as this is not unambiguous within the model.

Response:

The curves that can be sensibly used in the model are those that fit the observed data well and provide clinically plausible estimates after the observed period of the trial.

Please refer to Table C1.1 in the Excel workbook *Novartis Pharmaceuticals ID1226 NICE Clarification Responses Questions Data File.xlsx* for a description of the curves, with the trial each curve is drawn from to avoid any ambiguity. It should also be noted that in our submission, post LR-OS was modelled using the RFS Kaplan Meier Curve adjusted by the calibration ratio and Post DR-OS is not used given our approach to modelling metastatic disease.

C2. On page 48 of the CS Document B the following was noted: *"serious adverse events (SAEs) occurred in 155 patients (36%) in the dabrafenib plus trametinib arm and in 44 patients (10%) in the placebo arm. One fatal SAE (pneumonia) was reported in the dabrafenib plus trametinib arm".* Please clarify:

1. Why patients taking the placebo experience adverse events, especially serious adverse events.
2. Whether these adverse events were due to the placebo substance or due to progression of underlying stage III melanoma disease.
3. Whether there are any other possible explanations for adverse events in the placebo arm.

Response:

1. Patients on the placebo arm had all AEs (including SAEs) recorded during the course of the study, as per protocol definition, "any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product". The only causality recorded was that due to study medication, and [redacted] patients experiencing SAE's in the placebo arm had a causality that was reported as related to study treatment. Therefore, the remaining patients in the placebo arm most likely experienced an SAE due to underlying disease and comorbidities.

2. As per study protocol, matching placebo capsules for dabrafenib (50 mg and 75 mg) and placebo tablets for trametinib (0.5 mg and 2 mg) were provided to the study sites and these

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capsules/tablets contained exactly the same *inactive* ingredients and film coatings as the dabrafenib and trametinib active study treatment. It is therefore unlikely that the AEs experienced by patients in the placebo arm were unique to the placebo substance and it probable that the events in in the placebo arm were due to underlying disease and/or other co-morbidities.

le-Rademacher et al (2017) published a paper where they explored the value of adverse events relatedness to study treatment by analysing data from randomised double-blind placebo-controlled clinical trials across nine oncology trials. They recognised that a high proportion of AEs, including grade 3-5 AEs occur in patients receiving placebo. They observed that: "The main patterns consistently observed ……. include the following: (i) clinician-reported attribution tends to overestimate the rate of AEs related to treatment, (ii) a very high proportion of AEs reported as related to treatment were classified as possibly related, (iii) a significant proportion of AEs in the placebo arm were incorrectly reported as related to treatment……."[1]

Finally, we note that the rates of AEs and SAEs in the placebo arm of the COMBI-AD trial are similar to the rates of AEs and SAEs observed in the placebo arms of other randomised controlled trials for the adjuvant treatment of resected stage III melanoma (EORTC 18071 trial[14] and BRIM8). [15] As such, the occurrence of AEs and SAEs in patients receiving placebo is not unique

3. Other than the explanations given above, Novartis does not have other possible explanations for AEs reported in the placebo arm.

C3. Please provide unredacted copies of the TA396 submission and the accompanying electronic model.

Response:
An unredacted copy of our submission TA396 and economic model has been provided. Please note that all highlighted data within the submission and the associated economic model should be considered confidential in nature, as should any analyses performed by the ERG on this model.

C4. On page 48 of the CS Document B the following was noted: *"As of the primary data cut-off (30th June 2017), a total of 153 deaths had occurred; 60 (14%) in the dabrafenib plus trametinib arm and 93 (22%) in the placebo arm. In both trial arms, the most common cause of death was melanoma (54 patients [12%] in the dabrafenib plus trametinib group and 77 patients [18%] in the placebo group)."*

Of the 12% of patients who took combined therapy with dabrafenib and trametinib and who died due to a fatal recurrence of their melanoma, please confirm whether this is likely to be due to:

[1] le-Rademacher J, Hillman S, Meyers J, et al. Statistical controversies in clinical research: Value of adverse events relatedness to study treatment: analyses of data from randomized double-blind placebo-controlled clinical trials. Annals of Oncology, Volume 28, Issue 6, 1 June 2017, Pages 1183–1190

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1. Underlying disease progression or to 'escape' of the tumour from the suppressive effects of the dabrafenib/trametinib combination
2. Recurrence of melanoma in the same form of the disease that the patients experienced initially? i.e., BRAF V600E mutation

Response:

1. It is difficult to ascertain exactly what occurs in the tumour micro-environment upon cessation of therapy, as this area of science is still largely unknown. Since the majority of these deaths occurred >30 days after the last dose of study medication, it is most likely that the stopping of therapy after one year (per protocol) may allow the disease to progress in some cases.

2. The BRAF mutation is known to be stable, and is generally reported as being present in biopsies taken from patients who have experienced a recurrence. This was confirmed in the 66 relapse samples taken from patients enrolled in the COMBI-AD trial where a BRAF V600E/K mutation was detected in all relapse samples except in 1 secondary primary melanoma.[16]

C5. Long et al., (2017) on page 1819 of their publication state that non-cutaneous cancers were reported in 10 and 4 adjuvant and placebo patients, respectively. This does not appear to tally with the data presented in Table 24 of the CS Document B. Similarly, new primary melanoma in Long et al., (2017) was reported for 11 and 10 adjuvant and placebo patients, respectively. By contrast, Table 24 in the CS Document B implies different numbers. In addition, the text on page 71 of the CS Document B states that 7 and 6 adjuvant and placebo patients, respectively, experienced new primary melanoma without concomitant LR or DR. Please clarify these apparent discrepancies and tabulate all malignancies by category that were reported in each group during the study period.

Response:

Novartis acknowledges the discrepancies. The data used for the primary publication erroneously included cutaneous malignancies (Basel Cell Carcinoma, Squamous Cell Carcinoma and Bowen's Disease) in the non-cutaneous table. Safety reporting was re-run for the generation of the final clinical study report (CSR), which contains the data used in our submission.

The CSR therefore reflects our most accurate and current data and should be used as the source for interpretation and analysis by NICE.

Novartis is currently tabulating the requested listing of all observed malignancies and will send as soon as this listing has been received from the statisticians.

C6. Table 24 of the CS Document B reports the percentages of patients experiencing diarrhoea by grade and treatment. The ERG would like clarification on whether patients who experienced diarrhoea had their treatment stopped due to malabsorption, as the treatments are given orally. Is the diarrhoea side effect transient? If possible, please provide alternative formulations of the drug combination for patients who cannot take an oral formulation and the costs of doing thisResponse:

There were no reported treatment discontinuations due to diarrhoea in the dabrafenib plus trametinib arm. The dose of dabrafenib was reduced or interrupted/delayed in [redacted] of patients

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respectively, and the trametinib dose was reduced or interrupted/delayed in [redacted] of patients respectively.

It should be noted that the diarrhoea AEs were mainly grade [redacted] in nature and considered transient since all events were resolved, following a median [redacted]. In addition, dose modifications due to diarrhoea were not due to malabsorption, but were conducted according to the study protocol dose modification guidelines.[1]

Novartis confirms that there are no alternative formulations available at present for dabrafenib or trametinib.

C7. Please clarify why there is a difference in numbers/percentages (as stated in the table below) between the reported outcomes in the CS Document B and Long et al. (2017) paper?

Location	Outcome	Combination-therapy	Placebo
CS Document B (page 35)	RFS events Disease recurrence or death	166/438 (38%)	248/432 (57%)
Long et al., (2017) (Page 1816)	Disease recurrence	163/438 (37%)	247/432 (57%)

Response:

The difference in reported outcomes between our company submission (Table 12, page 36) and the primary publication for COMBI-AD: Long *et al.* (2017)[17] is due to a difference in the definition of the outcomes being reported.

Table 12 (page 36) of our submission describes the outcome of *RFS events* which are defined as disease recurrence (loco-regional or distant recurrence, or identification of a new primary melanoma) or death (without prior documentation of tumour recurrence).[1] As such, the values of 166/438 (38%) for dabrafenib plus trametinib and 248/432 (57%) for placebo describe the outcome of RFS events.

The values reported in the publication by Long *et al.* (2017)[17] (163/438 [37%] for dabrafenib plus trametinib and 247/432 [57%] for placebo) are for the outcome disease recurrence only.

C8. The ERG note that there were nine missing references cited in the CS Document B that were not listed in the reference pack. The ERG have identified the majority of these from our own sources. The only reference we haven't been able to identify is reference 64: "Novartis. Data on File. Novartis Internal Estimates." Cited in Table 4 in the CS Document B. In addition, we have not found the draft SmPCs. In Appendix C, the company state that 'The draft SmPCs for this indication can be found in the accompanying reference pack to this submission', but the ERG can only see the current SmPCs downloaded from www.medicines.org.uk in the reference packs. Please provide these references and the draft SmPCs.

Response:

Novartis apologise that references were missing from the reference pack, and appreciate the ERG have been able to identify them from their own sources.

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Further to this, please find enclosed:

- Reference 64: Kantar Health Estimates. Novartis internal data on file
- Draft SmPC for the indication under review

References

1. Novartis Pharmaceuticals Ltd. COMBI-AD: A Phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection. Protocol. Data on File. 2013.
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9. Peach H. Presentation at the Melanoma Focus Regional Meeting (Cambridge, 18th May 2018). Available at: https://melanomafocus.com/meetings/regional-meeting-2018/.
10. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016;17:757-767.
11. NICE. NICE TA384: Nivolumab for treating advanced (unresectable or metastatic) melanoma. 2016.
12. NICE. NICE TA400: Nivolumab in combination with ipilimumab for treating advanced melanoma. 2016.
13. NICE. TA319: Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. 2014.
14. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med 2016;375:1845-1855.

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15. Maio M, Lewis K, Demidov L, et al. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2018.
16. Dummer R, Hauschild A, Santinami M, et al. Mutational and immune gene expression profiling at relapse in patients (pts) treated with adjuvant dabrafenib plus trametinib (D + T) or placebo (pbo) in the COMBI-AD trial. ASCO Annual Meeting; 2018. https://meetinglibrary.asco.org/record/163696/abstract.
17. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. NEJM 2017.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

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 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 submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association of Skin Cancer Specialist Nurses**

3. Job title or position	**Nurse clinician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **X** 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):
5a. Brief description of the organisation (including who funds it).	An association of specialist skin cancer nurses. Funding from conference profit and some external non-promotional grants from pharmaceutical companies.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of the treatment is to reduce the risk of patients who have been diagnosed with primary melanoma developing metastatic melanoma .

or prevent progression or disability.)	
7. 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.)	A significant reduction in the number of patients developing metastatic disease when compared to patients having standard of care which is currently no treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Current standard of care is observation with additional scanning for patients at high risk of developing metastases
• Are any clinical guidelines used in the treatment of the	British association of dermatologists NICE Improving outcomes guidance.

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are some differences of opinion about the best method of surveillance but the majority of HCP have a consistent opinion
• What impact would the technology have on the current pathway of care?	There would be more patients having active, adjuvant treatment. But hopefully in the future, fewer people will be having treatment for metastatic disease.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not current standard of care. Hopefully will be
• How does healthcare resource use differ between the technology and current care?	More patients will be having adjuvant treatment and therefore increased pressure on outpatient clinics
• In what clinical setting should the technology be	Specialist centres

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Extra clinic space and likely more staff. Initial training of staff in new technology
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with a previous diagnosis of high risk melanoma
The use of the technology	
13. 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.)	As current standard of care is observation there will be more clinic visits and investigations for the patient with subsequent knock on effect of additional clinic visits, blood tests etc Some side effects may occasionally require occasional admission.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes Yes
15. 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?	Yes
16. 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	Yes , reduction in number of patients developing metastatic disease and therefore overall survival improved

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Currently no adjuvant treatment available
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Drugs are generally well tolerated and side effects relatively straightforward to manage.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important 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?	None known
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	Unable to comment at this time as not used outside clinical trial
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Substantial improvement in relapse free survival and overall survival
- Generally well tolerated
- Out patient treatment
- Quality of life usually maintained
- Reduction in number of patients needing treatment for metastatic disease

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission in July 2018 for the 1st meeting on the NICE appraisal of adjuvant dabrafenib and trametinib in stage III cutaneous malignant melanoma

1. NHS England notes that the median duration of follow-up in the adjuvant dabrafenib plus trametinib (D+T) trial is only [redacted] months and that few patients are at risk after [redacted] months. NHS England notes too that relapses are still occurring at least at 44 months. The dataset is thus immature in terms of observing what the long term difference might be for disease-free survival.
2. NHS England notes that one clinical expert to this appraisal predicts a long term difference in outcomes with adjuvant D+T whereas the ERG's clinical expert considers that this treatment will delay rather than prevent disease recurrence. Although D+T given for advanced disease is rarely curative, there are precedents from other malignancies in which non-curative systemic therapy in the advanced disease setting nevertheless increases the cure rate in early disease post-surgery eg breast cancer, colorectal cancer, non small cell lung cancer. NHS England would therefore consider it unlikely for adjuvant D+T to have no long term survival benefit in melanoma.
3. It is fair to say that adjuvant nivolumab or pembrolizumab are also likely to have long term benefits in melanoma. The same biological plausibility argument points to a greater effect in early disease than in advanced therapy as immunotherapy does appear to cure a modest proportion of melanoma patients with advanced disease. If both adjuvant D+T and adjuvant immunotherapies are recommended by NICE (the latter too has immature data), then it is likely that most fit patients would opt for adjuvant immunotherapy given this biological plausibility argument. The fitness requirements for patients to tolerate these two types of treatment options are broadly the same.
4. NHS England notes that no administration costs for D+T have been included in the economic model. This is incorrect. The NHS England chemotherapy delivery tariff in 2017/18 for oral systemic anti-cancer therapy is coded as SB11Z and should be £120 per cycle (ie every month).
5. NHS England agrees with the ERG that it is reasonable to use a figure of a [redacted] treatment rate for immunotherapy in patients treated with adjuvant D+T (who are in themselves a selected population) who subsequently relapse with a distant recurrence.
6. NHS England considers it reasonable for a relatively high rate of re-treatment with D+T to be assumed to occur in those patients treated with adjuvant D+T. For the 10-15% who progress whilst on adjuvant D+T, further D+T would be inappropriate. For the rest who recur after completion of adjuvant D+T, such patients are likely to be treated with immunotherapy first. By the time further disease progression occurs, further time will have elapsed since completion of adjuvant D + T and it is thus likely that patients would then have a trial of re-treatment with D+T.

Prof Peter Clark

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

July 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

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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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Avinash Gupta**
2. Name of organisation	**The Christie NHS Foundation Trust**

3. Job title or position	**Locum Consultant 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 (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 main aim of this treatment is to reduce the risk of recurrence of melanoma following surgical resection in high risk cases (patients with resected stage III melanoma with BRAF V600 positive mutations), and thus increase the cure rate for this 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.)	I would consider a reduction in the relapse of melanoma, particularly distant relapse of melanoma, to be clinically significant. To quantify what level of reduction is clinically significant is difficult. An EORTC meta-analysis of adjuvant randomised controlled trials in melanoma published in 2018 has demonstrated Relapse Free Survival (RFS) to be a valid surrogate endpoint for Overall Survival (OS) in melanoma patients (although this meta-analysis referred to studies of adjuvant immunotherapy). In this analysis a Hazard Ratio for RFS of ≤0.77 was judged to predict an impact of adjuvant treatment on OS (Suciu et al, J Natl Cancer Inst, 2018). The Hazard Ratio for adjuvant dabrafenib + trametinib vs placebo in the Combi-AD study is 0.47 (95% CI 0.39-0.58).
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is certainly an unmet need. There is a high rate of recurrence with Stage III melanoma, and when it recurs often it is metastatic, having spread to other parts of the body, with devastating consequences. Once melanoma has spread it is generally life-limiting, with median survival of 8-9 months without further treatment. Treatments exist that can control disease and prolong survival, but generally these do not act as a cure, with a median survival of 20-30 months, and are very costly, both in terms of the actual financial cost of both the treatment itself and the cost of managing side effects of treatment, and in terms of the impact on patients' quality of life.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Following resection of high risk melanoma patients are currently monitored for any signs of recurrence with regular clinical review for up to 10 years and regular CT/PET-CT/MRI imaging for up to 5 years. There is no adjuvant therapy currently in routine use for this patient population in the NHS. Interferon-α is currently licensed in the UK as adjuvant therapy for melanoma, but is not standard of care due to relatively low effectiveness and poor tolerance.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The NICE guidelines for assessment and management of malignant melanoma (NG14). The Melanoma Focus 2013 Consensus Paper on Follow-up of High Risk Cutaneous Melanoma in the UK. The British Association of Dermatologists guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined as outlined below. Generally patients are monitored as follows: CT or PET body plus MRI head scans every 6 months for the first 3 years after surgery, then annually in years 4-5, then no further scans unless clinically indicated. For Stage IIIC patients some centres, including the Christie and the Royal Marsden Hospital, now scan every 3 months for the first 1 year after surgery, based on data showing that for these patients, the majority of relapses occur in the first 12 months.
• What impact would the technology have on the current pathway of care?	Suitable patients with Stage III BRAF mutant melanoma will be on active treatment with dabrafenib + trametinib instead of surveillance, for up to 1 year after surgery, with more frequent clinic reviews during this period. Hopefully in the future fewer patients will develop unresectable stage III/Stage IV disease requiring the same treatment for a potentially longer duration.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The treatment (oral dabrafenib + trametinib) is already in use in the NHS, but in the advanced palliative settling, where it is used to control the disease, rather than the adjuvant setting proposed here, where it will be used to increase the likelihood of cure from the disease.
• How does healthcare resource use differ between the technology and current care?	Whilst on adjuvant treatment patients would need to be seen more often in clinic (generally every 4 weeks, rather than every 3 months). They would also need a baseline eye examination, regular echo scans during treatment, to monitor cardiac function, and more regular CT body scans (every 3-4 months in year 1, rather than every 6 months).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Oncology Clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Resources to increase capacity in Specialist Melanoma Clinics (clinic space and staff).
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment will only be effective for patients with resected BRAF mutant melanoma who are at high risk of relapse. In the Combi-AD study this treatment was more effective than placebo across all subgroups of patients treated.
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	The technology will require patients to take tablets daily for up 1 year after surgery and to be reviewed more regularly in clinic. There will be some additional monitoring tests as outlined above. Patients could experience side effects, which may require concomitant medications, although the need for this is generally for short durations. Some patients may experience more significant side effects requiring hospital admission to manage.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Healthcare professionals will need to see patients more regularly in clinic whilst on this treatment, but administering the treatment and managing side effects should not be any more difficult in the adjuvant setting than in the advanced setting as used currently.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will only be eligible for this treatment if their melanoma is found to contain the BRAF mutation (which is routinely tested for currently anyway, for high risk melanoma patients, so is not an additional test to current standard of care). Continuation of treatment will be determined by tolerability and side effects, which is commonly assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events.
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?	Yes. In particular, this technology will result in substantial benefit for patients where it prevents recurrence of melanoma.

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, as it will transform the way we manage high risk BRAF mutant melanoma.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
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?	Side effects of treatment may require a dose reduction or early cessation of adjuvant treatment. Concomitant medication or hospital admission may be needed to manage these side effects, but generally this is only for a short duration.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Relapse Free Survival, Distant Metastasis Free Survival, Overall Survival, Patient Reported Outcome Measures (in particular Quality of life). All of these were measured in the Combi-AD study
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Data on median OS is not yet available, due to the number of deaths so far. Besides, this outcome measure will be confounded by subsequent treatment patients may receive on disease relapse. RFS has been shown to predict for OS in trials of adjuvant immunotherapy in melanoma, as noted above (section 8).
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not in my experience.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. How do data on real-world experience compare with the trial data?	No data outside of clinical trials available in the adjuvant setting.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No issues with equality that I am aware of.
22b. Consider whether these issues are different from issues with current care and why.	N/A.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Adjuvant dabrafenib + trametinib has been shown to significantly reduce the risk of relapse of melanoma in high risk patients.
- This technology is expected to increase the cure rate for melanoma and reduce the need for palliative treatment.
- The treatment is generaly well tolerated, with manageable side effects.
- The experience and facilities to deliver this treatment on the NHS already exist.
- This will be the first approved adjuvant treatment for high risk melanoma patients that has been shown to provide significant clinical benefit.

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

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr. Paul Nathan**
2. Name of organisation	**Mount Vernon Cancer Centre**

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): Trustee of Melanoma Focus
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.)	To reduce the chance of relapse To reduce the chance of death
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.)	Reduction in chance of relapse by more than 10%. Reduction in chance of death by more than 10%
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – major unmet need – no currently approved adequately active adjuvant treatment for patients at significant risk of relapse of melanoma
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?	Stage III patients are on surveillance program (re Melanoma Focus consensus statement https://melanomafocus.com/members/follow-up-position-paper/)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes
• What impact would the technology have on the current pathway of care?	Larger numbers of patients receiving treatment
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – within specialist oncology care

• How does healthcare resource use differ between the technology and current care?	Patients will require to attend clinic every 4/52 during treatment period and receive 3/12 cross sectional imaging (as opposed to 6/12ly on surveillance protocol off treatment).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinic
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increasing numbers of patients in melanoma clinics
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – major benefit
• Do you expect the technology to increase length of life more than current care?	Yes – major benefit.. I expect significant numbers of patients to be cured with adjuvant treatment

• Do you expect the technology to increase health-related quality of life more than current care?	Yes – in comparison to QoL in relapsed disease
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This is only appropriate for stage III melanoma patients whose tumours carry a V600 BRAF mutation
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	Increased number of patients requiring treatment than standard surveillance although those patients for whom a relapse is prevented will not require palliative treatment for stage !V disease

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing needed. Treatment will be planned as per clinical trial protocol for 1 year and will only be stopped if a) unacceptable toxicity despite dose modification b) relapse c) patient preference
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?	Yes as QALY calculation highly insensitive to many important aspects of patient experience
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes – will be the first adjuvant treatment for stage III melanoma with clinically worthwhile proven survival benefit

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?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
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?	Melanoma oncologists are used to managing D+T side effects in the metastatic setting.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – it was randomised vs placebo
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	RFS, OS Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• 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	no

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	equivalent
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Major advance in treatment
- Durable benefit in RFS translates into OS benefit
- Patients will be cured who would otherwise have relapsed and died
-
-

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

Patient expert statement

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

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 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.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Delia Sworm**
2. Are you (please tick all that	☐ a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☐ a patient organisation employee or volunteer? X other (please specify):
3. Name of your nominating organisation	BASCSN
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
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)	**X** 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.)	**X** yes

Title: Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma (ID1226)

Produced by: Warwick Evidence

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Declared competing interests of the authors
None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

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Contributions of authors

Paul Sutcliffe (Associate Professor) and Aileen Clarke (Professor) coordinated the project. Ewen Cummins (Health Economist) and Rhona Johnston (Computer programmer) conducted, reviewed and critiqued the cost-effectiveness evidence and modelling. Martin Connock (Senior Research Fellow) coordinated and conducted the critique of clinical effectiveness evidence. Martin Connock (Senior Research Fellow), Lena Al-Khudairy (Senior Research Fellow) Archik Das (Academic F2 Doctor) and Payagalage Senaratne (Visiting Academic) conducted the critique of clinical effectiveness and critique of statistical analysis. Daniel Gallacher (Resaerch Associate) provided statistical support. Rachel Court (Information Specialist) conducted the critique of the company searches and conducted ERG searches. Aileen Clarke (Professor) and Paul Sutcliffe (Associate Professor) commented on draft versions of the report and formatting of the report. All authors contributed to the writing and formatting of the report.

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF BOXES

Not applicable

DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

ADJ	Adjuvant
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
AUC	Area under the curve
BIC	Bayesian information criterion
C	Censoring
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CR	Competing risk
CS	Company submission
CSR	Complete study report
CT	Computed tomography
DABR	Dabrafenib
DFS	Disease free survival
DMFS	Distant metastasis free survival
DSU	Decision Support Unite
E	Event
ECHO	Echocardiogram
EFU	End of follow-up
EMA	European Medicines Agency
EQ-5D-3L	EuroQol Five Dimensions Three levels
ERG	Evidence Review Group
FDA	Food and Drug Administration
FFR	Freedom from relapse
GEE	Generalised estimation model
GP	General practitioner
HR	Hazard Ratio

HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IC	Information Criteria
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intent to treat
KM	Kaplan-Meier
LOCF	Last Observation Carried Forward
LVEF	Left Ventricular Ejection Fraction
MA	Moving average
MAPK	Mitogen-activated protein kinase
MEKi	Inhibitor of mitogen-activated protein kinase kinase enzymes
MRI	Magnetic resonance imaging
MUGA	Multiple Gated Acquisition
NICE	National Institute for Health and Care Excellence
OffTx	Off treatment
OP	Out-patient
OnTx	On treatment
OS	Overall survival
PAS	Patient access scheme
PBO	Placebo
PEFU	Premature end to follow up
PET	Positron emission tomography
PFS	Progression-free survival
PLAC	Placebo
Post-DR	Post distant recurrence
Post-LR	Post loco regional recurrence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QALYs	Quality Adjusted Life Years
QoL	Quality of life
RAMOS	Registration and Medication Ordering System
RCT	Randomised controlled trial
RFS	Recurrence-free survival

SAE's	Safety adverse events
SD	Standard deviation
SF-6D QoL	Short-form six-dimension quality of life
SPM	New primary melanoma
SR	Systematic Review
STA	Single technology assessment
T4b	Thick and ulcerated primary tumour
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
VAS	Visaula analogue scale
WTP	Willingness to pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's definition of the decision problem matches the population, intervention, and the comparator described in the final NICE scope. The decision sought to estimate the clinical effectiveness and cost-effectiveness of oral adjuvant combination therapy with dabrafenib plus trametinib in the treatment of adult patients who had had complete resection for stage III melanoma carrying a BRAF V600 mutation. The comparator was routine surveillance. The major clinical effectiveness outcomes were recurrence-free survival (RFS), overall survival (OS) and safety. Other outcomes included distant metastasis-free survival and health related quality of life (HRQoL).

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company were derived from a single international randomised placebo-controlled trial (COMBI-AD) undertaken at 169 sites in 26 countries. The study was initiated in early 2013 and study cut-off for the submission was the end of June 2017, at which time the median follow was 2.8 years. Randomisation of patients (438 and 432 to adjuvant and placebo arms, respectively) was stratified according to their *BRAF* mutation status (V600E or V600K) and disease stage (IIIA, IIIB, or IIIC). The study was described as double blind. A 12-month treatment duration was anticipated. The primary outcome was RFS established by study investigators at visits scheduled every 3 months to month 24 and every 6 months thereafter. OS was designated a pre-specified secondary outcome.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Based on the company submission (CS) CONSORT diagram there appeared to be an imbalance between study arms in numbers and timing of patients for whom follow up terminated before study cut off. This imbalance could potentially influence outcome measures, especially those involving time to event analysis such as RFS and OS.

The company's Kaplan Meier (KM) analysis of the primary outcome measure (RFS) clearly demonstrated that combination adjuvant therapy with dabrafenib and trametinib considerably delayed recurrence; for RFS a hazard ratio (HR) of 0.47 (95% CI: 0.39–0.58) was estimated. RFS was a composite outcome encompassing death (from melanoma or other cause) recurrence

(local and/or distant), a new primary melanoma (SPM), and censoring with ongoing follow up or with premature follow up ended (PEFU). There was some imbalance in the numbers and timing of the latter censorings. These multiple components of RFS occur at different times. In response to the opinion expressed by an expert consulted by the company that some competing risk (CR) type of analysis should have been undertaken, the ERG conducted a CR analysis of RFS in which PEFU and SPM were considered as a CR. The results indicated that the difference between arms in restricted mean RFS to 41 months estimated by KM analysis of 9.44 months (95% CI: 7.36 – 11.52) represented a modest overestimate of approximately 11% relative to that estimated using the CR analysis (8.35 months: 95% CI: 6.61 – 10.08). Similarly, for the specified secondary outcome of OS, the company's KM analysis yielded a difference between arms in restricted mean survival to 42 months of 2.31 months (95% CI: 0.96 – 3.66) an approximate 21% overestimate relative to CR analysis (1.83 months, 95% CI: 0.27 – 5.05). It should be noted that the company did not employ the COMBI-AD OS analysis in its economic analysis. There was no difference between arms in quality of life measures (EQ-5D-3L) undertaken in the COMBI-AD study. The ERG expressed concerns regarding safety outcomes recorded in COMBI-AD and other studies of dabrafenib and trametinib. The ERG was concerned that a trial in a different population (patients with BRAF status undetermined) was used in the economic model in order to extrapolate the short term observed RFS outcome in COMBI-AD; this use has assumed an "equivalence" between a trial with mixed BRAF population and a trial with an exclusively BRAF+ population; there appears to be some inconsistency of approach between clinical and cost effectiveness considerations. Given such an assumption it would appear logical to have conducted a network meta-analysis comparing clinical effectiveness reported from various alternative adjuvant treatments. No indirect treatment comparisons were undertaken in the CS.

The ERG is in agreement with the company over the costs of hospitalisation for the treatment of common, non-severe side effects such as pyrexia, but feel that costs for more potentially life-threatening adverse events, such as haemorrhage and uncommon, and potentially serious non-life-threatening effects such as uveitis are difficult to predict in a non-trial setting. Certain side effects such as impaired glycemic control, may impact on primary care services, as opposed to hospital costs, while others such as diarrhoea which affect the absorption of the drug may reduce compliance, which in itself is difficult to predict with certainty. The ERG also feel that the absence of non-oral formulations of dabrafenib/trametinib could limit its overall marketability. Furthermore, whilst the company has acknowledged the costs of mandatory baseline and serial monitoring of cardiac function for patients on treatment, the ERG feel that these costs may have

underestimated the true monitoring requirements, as the onset or recovery of left ventricular function from cardiomyopathy may post-date the treatment period. It was also felt that routine dermatology input from the onset of treatment would be essential to monitor for recurrence or progression of underlying melanoma or onset of novel skin malignancies. Those with recurrences are likely to require additional BRAF testing to determine whether or not the current treatment is successful or if alternative adjuvant treatment strategies may be required. Last of all, with a number of adverse events taking place in the placebo arm, for which there remains doubt as to the aetiology, whether from the placebo substance itself or progression of underlying patient comorbidities, the ERG had concerns regarding the chemical composition of the placebo. The ERG therefore feels that in an indefinite proportion of cases, it may have been difficult to decipher whether adverse events in the treatment arm were also due to progression of the underlying disease or due to dabrafenib or trametinib itself.

1.4 Summary of cost effectiveness submitted evidence by the company

The company builds a de novo cohort markov model with a 1 month cycle, a 50 year horizon and the following health states:

- All patients start in RFS, events for which are either loco-regional recurrence (LR), distant recurrence (DR) or death. Treatments costs, monitoring costs, quality of life values and the like are applied to patients in the RFS health state for each cycle of the model.
- Those who have an LR move into the LR health state, with their RFS (post-LR RFS) then being modelled, the events for which are also either another loco-regional recurrence (LR), a distant recurrence (DR) or death. Treatments costs, monitoring costs, quality of life values and the like are applied to patients experiencing an LR recurrence event for each cycle of the model.
- Those who have a DR, whether this is an RFS event or a LR-RFS event, are not really modelled. These patients simply have a total cost and a total QALY applied to them, derived from TA366 and TA396. The DR health state is an absorbing health state, much like death.

The model structure is consequently unusual because the cost effectiveness estimate is not reliant upon any modelled OS, despite it being anticipated that OS will differ between the arms.

The model is segmented into two periods. Up to 50 months which corresponded with the longest follow-up during COMBI-AD, and 50 to 600 months.

- For RFS up to 50 months the company applies arm specific log-logistic (U) cure parameterised curves based upon COMBI-AD data
- For RFS from 50 months the company applies common probabilities of events derived from a company parameterisation of the placebo arm of the EORTC 18071 trial of adjuvant ipilimumab versus placebo
- For post-LR RFS up to 50 months the company applies the same curves as for RFS up to 50 months, but qualified by a 2.53 hazard ratio
- For post-LR RFS from 50 months the company applies the same common probabilities of events as applied for RFS from 50 months, but with a greater proportion of these events being deaths.

General population mortality risks are also applied.

COMBI-AD EQ-5D-3L data is analysed to give quality of life values of 0.854 for patients receiving dabrafenib+tramatinib, 0.869 for all other patients in RFS amd 0.836 for LR. The regression also yields an estimate of 0.792 for DR, but this is not applied in the model. Quality of life values subsequent to baseline are age weighted by UK norms.

The mean drug use is based upon the minimum number of whole packs of dabrafenib and the minimum number of whole packs of trametinib that could have been prescribed that are consistent with each COMBI-AD patient's cumulative dose. This results in estimated means of [redacted] packs of dabrafenib and [redacted] packs of trametinib. Prescribing costs of £13.90 are also included.

Monitoring costs are differentiated between the arms during the 1st year, with monthly OP visits and six-monthly ECHO and MUGA cardiac monitoring for those receiving dabrafenib+trametinib compared to quarterly visits and no additional cardiac monitoring for those who have ceased dabrafenib+trametinib and those in the placebo arm.

Incident LR patients are mainly assumed to be resected, with some additional visit costs. Incident DR patients are estimated to accrue a further 3.23 QALYs at a total cost of £143k, based upon the model outputs given in the CSs to TA366: pembrolizumab for unresectable or stage IV melanoma

and TA396: dabrafenib+trametinib for unresectable or stage IV melanoma weighted [redacted]. SAEs that resulted in hospitalisations are costed.

Including the dabrafenib PAS and the trametinib PAS the company estimates the medication and administration costs of dabrafenib+trametinib will be [redacted]. There are quite large cost off sets from avoiding DR of [redacted], with total net costs being [redacted]. While not directly contributing to the cost effectiveness estimate the model estimates that mean survival without adjuvant therapy of 15.0 years will be increased by [redacted] years by dabrafenib+trametinib. There is a corresponding gain of [redacted] QALYs which result in a cost effectiveness estimate of £20,039 per QALY. The probabilistic modelling estimate of £20,037 per QALY is aligned with this.

The company presents a range of sensitivity analyses and scenario analyses, all of which suggest that dabrafenib+trametinib is cost effective.

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

The company model structure and base case is unusual for three main reasons:

- It fits parameterised curves to the head-to-head trial data but does not use these for any extrapolation. Instead, extrapolation from month 50 applies common risks to both the dabrafenib+trametinib arm and the placebo arm, based upon the placebo arm of the EORTC 18071 trial. There are concerns about the generalisability of the EORTC 18071 trial population to the BRAF+ve patients of COMBI-AD. The method also essentially freezes the proportionate OS gain at the 50 month value, with survival in the placebo arm being around 80% of survival in the dabrafenib+trametinib arm from month 50 to month 600.
- When patients have a distant recurrence these patients are not modelled explicitly. Instead, total costs and total QALYs are taken from CS to NICE STAs of treatments for metastatic disease. NICE STAs of treatments for metastatic disease have typically been viewed as satisfying End of Life criteria and the total costs that are applied are large compared to the total QALYs that accrue. As a consequence, the treatments that NICE has approved as valuable due to End of Life become fairly disastrous from a cost effectiveness viewpoint when their costs and QALYs are appended to the current model. There is an argument for valuing these costs and QALYs at the End of Life willingness to pay threshold.

- Related to the above bullet, while the model does fit an OS curve to the post-DR patients this does not affect the cost effectiveness estimates and is more for validation purposes. During COMBI-AD there was a noticeably larger number of non-melanoma deaths in the placebo arm than in the dabrafenib+trametinib arm, which might argue for a competing risks analysis. But because the modelled OS does not affect the cost effectiveness estimate, it is not obvious how this could be taken into account within the economics.

The company rejects a number of parameterisations of the COMBI-AD RFS data because the dabrafenib+trametinib curve falls below the placebo curve. For a number of curves this does not occur until well into extrapolation, and is minimal to the point of being inconsequential when it does. The company has not properly justified why these curves should be rejected. In the opinion of the ERG they should be considered within the economics.

The main uncertainty is around which curves should be applied and to what extent they should be extrapolated. The company position is that the COMBI-AD log-logistic (U) cure model curves should be used to 50 months but should not be used for extrapolation, with extrapolation being based upon data from the EORTC 18071 trial instead. The ERG notes the differences in populations between COMBI-AD and EORTC 18071. The ERG sees more merit in using parameterised curves derived from COMBI-AD for extrapolation. This also permits the duration of benefit from dabrafenib+trametinib over placebo to be explored.

ERG expert opinion suggests that dabrafenib+trametinib may postpone recurrences but are less likely to avoid them altogether, meaning that in the longer term the proportion who are cured will converge with that of the placebo arm. This argues for the COMBI-AD log-logistic (R) cure model curves over the COMBI-AD log-logistic (U) cure model curves. It can be noted that the AIC for the (U) model may show some superiority, but the BICs are virtually identical for the two models. Convergence of cure rates further argues for the ERG COMBI-AD competing risks model curves, with an additional argument in their favour being that both a company adviser and the ERG are of the opinion that a competing risks analysis is necessary due to the COMBI-AD data definitions. Convergence of cure rates further argues that these curves should be used for extrapolation. Clearly, if the proportion who are cured by dabrafenib+trametinib tends to converge with that of placebo the cost effectiveness of dabrafenib+trametinib worsens somewhat.

While the calculation of the calibrating hazard ratio for post-LR events has intuitive appeal, it suggests that more than 90% of those with a 1st recurrence will experience a 2nd recurrence within 50 months. No external data has been provided to support this, though it can be noted that the majority of 1st recurrences are anticipated to be distant recurrences.

The proportion on treatment is applied in the quality of life calculations. Data supplied at clarification suggests that a higher proportion of dabrafenib+trametinib patients should be modelled as being on treatment, but this only marginally worsens the cost effectiveness estimate. Of more concern is data supplied at clarification which states that for quite a large proportion of dabrafenib+trametinib patients time to treatment discontinuation was censored at day 364 and end of trial. If these patients continued to receive dabrafenib+trametinib beyond day 364 this could affect costs quite considerably. It would help if the company could clarify what number of patients received any dabrafenib+trametinib after day 364 and what number of patients had a dabrafenib+trametinib prescription beyond day 364.

There is uncertainty about drug wastage during COMBI-AD. The company method is likely to underestimate this, as it applies the minimum number of packs that are consistent with individual patients' cumulative doses. Prescriptions at times other than 4-weekly, dose interruptions, dose escalations and dose reduction are all likely to increase wastage. The ERG estimates are based upon company data supplied at clarification, though these may overestimate wastage.

Only SAE hospitalisation costs have been included. There is evidence of higher adverse events, more prophylactic medication of adverse events and more active medication of adverse events in the dabrafenib+trametinib arm. The medication costs may be minor, but any increase in OP or GP visits would be more serious. But these costs would have to rise significantly to have a major effect upon the cost effectiveness estimate. Differentiating quality of life values for RFS by arm appears to have some effect, which may suggest that the company base case has not entirely taken into account the quality of life effects of adverse events.

The company assumes a high proportion of stage IV patients will receive dabrafenib+trametinib for their stage IV disease. The costs of dabrafenib+trametinib treatment at stage IV are very large, so avoiding these costs improves the cost effectiveness estimate. ERG expert opinion suggests that a somewhat lower proportion of stage IV patients will receive dabrafenib+trametinib, and

that some will receive nivolumab+ipilimumab. The ERG proportions worsens the cost effectiveness estimate.

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

1.6.1 Strengths

The ERG considers the overall quality of the company's systematic review to be reasonable. Following systematic review, the clinical effectiveness evidence submitted were derived from a single well-conducted international randomised placebo-controlled trial (COMBI-AD) undertaken at 169 sites in 26 countries. The ERG considers that the baseline demographic characteristics of patients recruited in the COMBI-AD trial were comparable to those of the relevant patients in the UK. The company present the results from this trial investigating the effectiveness of daily oral adjuvant therapy combining dabrafenib and trametinib in the treatment of patients after complete surgical resection. No other comparable adjuvant studies in this population have been identified. The COMBI-AD trial is directly relevant to the decision problem. The study demonstrated a clear and substantial delay in RFS resulting from combination therapy. There was also an apparent effect benefitting OS, although data were rather immature for both outcomes (median follow up 2.8 years) especially for OS.

From a cost-effectiveness perspective, the CS is well-written and clear. Very few points required clarification, which was limited to requesting additional data and analyses. The company electronic model is a model of good documentation. This aspect cannot be praised enough. Given the complexity of the model, it has been an enormous help to the ERG. The company was also notably helpful clarifying some aspects of the model prior to formal clarification.

1.6.2 Weaknesses and areas of uncertainty

There was some numerical and timing imbalance between study arms in patients ending follow up before study cut off that may influence effectiveness estimates. The company and the ERG therefore both conducted a CR analysis. The ERG analysis suggested that the company's KM analysis may over estimate the benfit of dabrafenib/trametinib adjuvant therapy by approximately 11% and 21% (for RFS and OS, respectively). Because follow up was insufficient however one of the major uncertainties is whether the therapy merely delays disease recurrence, so that recurrence in the intervention arm eventually 'catches up' with that in the control arm, or whether

a proportion of patients receiving adjuvant therapy do not experience a recurrence that they would have done and a proportion are "cured".

For the cost effectiveness analysis the company used data from a trial (EO 18071 RCT) undertaken in a different population (patients with BRAF status undetermined) in order to extrapolate from observed COMBI-AD RFS. This assumed equivalence between the mixed BRAF population and COMBI-AD (a trial with an exclusively BRAF+ population) and is open to question because of potential non comparability between the two populations. This issue could have been explored further in the conpamny's clinical effectiveness section investigating the possibility of using other adjuvant trials with unknown BRAF status to be explored for extrapolation.

Lastly, the ERG has some reservations about the company's approach to treatment safety and associated costs of adverse events and monitoring, and consider that these may have been somewhat underestimated. Further weaknesses and areas of uncertainty in the economics are summarised in section 1.2 above.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG presents three sets of analyses:

- Using the company log-logistic (U) cure model
- Using the company log-logistic (R) cure model
- Using the ERG competing risks model, with a common placebo risk from month 256 when the curves come together.

The company log-logistic (U) suggests that dabrafenib+trametinib will permanently cure a larger proportion of patients. Both the company log-logistic (R) and the ERG competing risks suggest that dabrafenib+trametinib will postpone recurrences but that in the medium to long term the dabrafenib+trametinib cure rate will converge with that of placebo, which the ERG finds more persuasive.

The ERG has made two minor corrections to the company model structure. The ERG has also revised the company model along the following lines.

- Assume that those who have received dabrafenib+trametinib require the same monitoring requirement as those remaining on dabrafenib+trametinib

- Assume an additional quarterly OP appointment for dabrafenib+trametinib to account for dermatological monitoring
- Apply the treatment proportions that appear to be implied by the company responses at clarification
- Revise the dabrafenib+trametinib drug costs to be based upon the company answer to clarification question A3, further qualifying prescription costs accordingly
- Revise the proportion of DR patients who receive pembrolizumab from [redacted] to reflect expert opinion and the probable costs and effects of nivolumab+ipilimumab
- Using the base case set of assumptions when fitting the model outputs at calibration to the post-LR COMBI-AD OS KM curve.

The ERG undertook a range of scenario analyses.

- SA01: Applying the EQ-5D regression that splits on treatment by arm and off treatment by arm
- SA02: Varying the intercept term of the EQ-5D regressions by ±25% for both the base case regression and the regression that splits on treatment by arm and off treatment by arm, this resulting in approximately a ±0.1 change in the quality of life values that are applied
- SA03: Extending the monitoring requirement for dabrafenib+trametinib by 50%
- SA04: Varying the proportion of LR events that require resection from 10% to 0% and to 20%
- SA05: Deriving the balance between LR, DR and death events in the post-LR modelling from the same source as for the RFS balance between events: EORTC 18071
- SA06: Valuing the health benefits of the DR treatments at the end of life WTP of £50k/QALY
- SA07: EORTC extrapolation from month 50 for RFS in the dabrafenib+trametinib arm, RFS in the placebo arm, Post-LR RFS in the dabrafenib+trametinib arm and Post-LR RFS in the placebo arm.

The ERGs revised analyses and ICERs are as follows:

	L-Log (U)	L-Log (R)	ERG CR
Base case	£20,701	£62,853	£46,161
SA01: EQ-5D RFS split by arm	£21,734	£70,752	£49,492
SA02a: EQ-5D intercept -25%	£24,134	£72,018	£53,061
SA02b: EQ-5D intercept +25%	£18,134	£55,790	£40,873
SA02c: SA01 + EQ-5D intercept -25%	£25,697	£83,032	£57,814
SA02d: SA01 + EQ-5D intercept +25%	£18,830	£61,636	£43,264
SA03: DABR monitoring +50%	£21,929	£65,675	£48,347
SA04a: LR resection 0%	£21,329	£63,847	£46,954
SA04b: LR resection 20%	£20,073	£61,859	£45,369
SA05: LR events balance EORTC 18071	£20,764	£63,716	£46,530
SA06: DR costs and benefits reflect EoL	£24,980	£61,487	£46,589
SA07: EORTC extrapolation	£26,258	£30,866	£27,432

The scenario that extrapolates from month 50 to month 600 using the EORTC placebo data rather than the arm specifc COMBI-AD data result in quite similar ICERs almost regardless of which COMBI-AD parameterisation is used for up to month 50. This is because applying common risks to each arm from 50 to month 600 effectively freezes the benefits to be as they were at month 50. The EORTC extrapolation results in survival in the placebo arm being around 80-85% that of survival in the dabrafenib+placebo arm for month 50 to month 600.

More fully accounting for SAEs and possibly AEs that did not require hospitalisation but did require medication and possibly additional appointments would probably increase costs more in the dabrafenib+trametinib arm than in the placebo arm. But given the modelled large net cost for dabrafenib+trametinib, any SAE costs would have to be quite large to have much effect on the cost effectiveness estimate. There is the suggestion, as shown in SA01, that explicitly accounting for the different SAE profiles by arm would worsen the cost effectiveness estimate.

If patients were prescribed dabrafenib or trametinib beyond day 364 of the COMBI-AD trial either the clinical data does not particularly reflect the anticipated license or costs could be somewhat higher in the dabrafenib+trametinib arm. Either would worsen the cost effectiveness estimate.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

On pages 15-21, the company describes the underlying health condition with emphasis on its diagnosis, staging, epidemiology, morbidity and mortality.

Malignant melanoma is a highly aggressive and potentially lethal form of cancer which arises from mutated melanocytes, which are the pigment producing cells which usually colonise the basal epidermal layer of the skin during embryonal development.[1] The incidence of the disease has continued to rise in recent years.[2]

Staging of the disease, as accredited by NICE, is most commonly derived from the American Joint Committee on Cancer (AJCC) classification, which is essential to guide management strategies and for determining prognosis. The first part of staging is using the Tumour, Node, Metastasis system, which takes into account the size, ulceration status/mitoses, the degree of lymph node spread and the presence of distant cutaneous / subcutaneous or other visceral metastases.[3] The second part of staging stratifies patients to AJCC Stage 1 – IV, whereby stages I – IIC represent local disease based on the thickness of the tumour and the presence or absence of ulceration of the primary tumour, AJCC stage III represents micro / macroscopic disease involving lymph nodes as confirmed by sentinel lymph node biopsy or completion lymphadenectomy, and AJCC stage IV represents disease with any evidence of distant metastases.[3, 4]

The CS acknowledged a new 8th edition of the classification from January 2018 and considered that it is likely to represent a shift in the classification of patients from Stage II melanoma to Stage III melanoma. The company also highlighted the addition of a new subgroup in Stage III disease (Stage IIID). However, they continued to focus on the 7th edition definitions as these provided the basis for the COMBI-AD trial, the main randomised control trial relevant to their decision problem. The new features required for classification to AJCC Stage IIID are a thick and ulcerated primary tumour (T4b), and either ≥4 tumour-involved regional nodes (N3a or N3b) or ≥2 tumour-involved nodes and evidence of microsatellite, satellite, or in-transit metastases (N3c). Stage IIID has an estimated 5 year survival of 32% which is significantly worse that that compared for stage IIIC which is 69%.[5] Despite a lack of consensus regarding the shift of patients from stage II to Stage III, the ERG were in agreement with the company to abide by the staging of the 7th edition as the focus of the proposed treatment remains on surgically resected

disease with prior evidence of lymph node involvement and further sub classification of stage IIID is unlikely to affect OS of Stage III patients as a group and would have been included in the study as potential participants. Nevertheless, it is likely that over time, availability of adjuvant treatment options will be stratified further according to sub-categories of Stage III disease and for AJCC Stage IIC (a group for whom prognosis is deemed worse than Stage IIIB), as the UK continues to adopt the new AJCC 8th Editionn staging guidelines.

Approximately 40-650% of cutaneous melanomas harbour mutations in BRAF. Molecular alterations in this pivotal oncogene result in the constitutive activation of key components of the mitogen-activated kinase (MAPK) pathway, which results in uncontrolled tumour growth, proliferation and survival. These mutations occur most commonly in exon 15 at codon 600 (BRAFV600), of which 75% are characterised by the substitution of the amino acid valine by glutamic acid at residue 600 (BRAFV600E). A less frequent mutation BRAFV600K involves the substitution of valine by lysine in 10-30% of BRAFV600 melanomas.[6] Patients with BRAFV600E and BRAFV600K positive completely resected Stage III melanoma were the subjects included in the COMBI-AD trial of adjuvant therapy. The mutation was detected by genetic testing of the primary melanoma or lymph node tissue using a central reference laboratory.[2]

We note that the regulatory approval was granted by the US Food and Drug Administration for the first time on April 30 2018 to Dabrafenib and Tremetinib in combination, based on the findings of the COMBI-AD trial for the treatment of BRAFV600E or BRAFV600K melanoma with evidence of lymph node involvement following complete resection.[7] Previously approval was acquired for BRAF-mutant metastatic melanoma only, based on the findings of the BREAK-3 trial.[6, 8] This approval was granted after the company's current submission to NICE. In Europe, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for Dabrafenib (applied by GlaxoSmithKline) on 27 June 2013[9] and Trametinib (by Novartis Europharm Ltd.) on 23 February 2017[10] for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. These positive recommendations were subsequently approved by the European Medicines Agency, which granted a marketing authorisation valid throughout the European Union for Dabrafenib on 26 August 2013[11] and Trametinib on 30 June 2014.[12]

2.2 Critique of company's overview of current service provision

On pages 21-24, the company provides an overview of the current UK guidelines for the treatment pathway of resected AJCC stage III melanoma and proposes the positioning of Dabrafenib and Trametinib in the adjuvant setting. They appraise a series of clinical guidelines for the management of stage III melanoma and describe the NICE guidelines which recommend clinical follow-up with imaging for stage III disease following complete resection with completion lymphadenectomy, at three-monthly intervals for the first three years following resection and then at six-monthly intervals for the subsequent two years. Adjuvant radiotherapy may be considered for Stage IIIB or IIIC melanoma if the risk of local recurrence is estimated to outweigh the risk of significant adverse events. Surveillance imaging is advised during follow-up and computerised tomography (CT) scans are advised to aid staging in the initial stages.[4]

The ERG was in agreement with the company that there are currently no recommended medical or systemic treatments for AJCC Stage III melanoma, regardless of the genetic subtype, in the adjuvant setting, following surgical excision. Similarly, the ERG's clinical advisor confirmed that there is no adjuvant treatment options for stage IIC patients who are at high risk of disease recurrence. Patients are offered three monthly surveillance consultations usually shared between Plastic surgery and Medical oncology with six-monthly CT scans for chest, abdomen and pelvis. A brain MRI may or may not also be required. Hence, the ERG considers that this conservative method of clinical surveillance alone, was thus deemed a fair comparator against Dabrafenib and Trametinib therapy in the context of this appraisal, as depicted in Figure 4 on page 23 of the CS.

In the view of the ERG the company's overview of the current service provision was adequate. The ERG note that the company recommend treatment for 12 months. The mean duration of exposure to Dabrafenib and Trametinib in the trial was less than this with means of 8.2 and 8.3 months respectively (CS table 19 on pg. 50). The ERG suggest that in practice, the average treatment duration may be < 12 months since the presence of serious adverse effects and other factors will compromise treatment compliance.

The ERG also considered that a number of additional measures will be required to follow up patients treated with Dabrafenib and Trametinib for routine monitoring of adverse effects. The FDA label[13] suggests that Dabrafenib causes a risk of cardiomyopathy, defined as a reduction in the Left Ventricular Ejection Fraction (LVEF) by ≥10%, hence all patients who take the medication are likely to need baseline and possibly subsequent serial echo-cardiography.

Although the CS does take into account the cost implications of 3-monthly Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA) scanning during the 12-month treatment phase, the ERG found that the cost implications of this had not been taken into consideration following completion of treatment with Dabrafenib and Trametinib in the original CS. The ERG's clinical advisor stated that scans will be carried out by a cardiologist and there will be cost implications depending on the frequency of these scans.

These concerns were raised on the basis that cardiomyopathy occurred in 6% (12/206) of patients receiving combined therapy in the COMBI-d study compared to 2.9% (6/207) receiving Dabrafenib alone. Although the majority of patients taking one or both of these agents recovered from cardiomyopathy, the ERG felt it would be prudent to continue serial monitoring of cardiac function up and until the recovery and normalisation of left ventricular function. It is also worth noting that from the COMBI-d study, in patients receiving single-agent Dabrafenib, development of cardiomyopathy resulted in dose interruption (2.4%), dose reduction (0.5%), or discontinuation (1.0%).[7, 14] Hence the ERG did not feel it was appropriate for the company's model to assume that those who discontinued treatment prematurely were to require the same follow-up and monitoring as the placebo group, as stated on page 96 of the CS.

Additionally concerns were raised because multiple clinical trials in the past had associated Dabrafenib with an increased risk of non-melanoma skin cancers.[14, 15] There was also a risk of melanoma relapse, as seen with fatal consequences in 12% of patients who were in the combined treatment arm in the COMBI-AD trial.[2] In view of these findings, the ERG were in agreement with the company that patients treated with Dabrafenib and Trametinib would likely require rigorous follow up to monitor for recurrence of melanoma or the development of new cutaneous malignancies both during and post treatment. The ERG were satisfied with the methods by which the cost implications for CT and PET scanning had been taken into account, but felt that rapid access to dermatologists in addition to oncologists would be mandatory during the first 12 months of treatment and beyond in order to monitor and appropriately manage benign and malignant cutaneous toxicity in a timely manner. Hence, the ERG felt that the model on page 96, with its simplifying assumption of outpatient visits to a medical oncologist alone, was inadequate. The FDA label proposed a minimum follow up duration of 6 months post treatment[13] but the ERG consider that post treatment follow up period, may be required for a longer period.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company summarised the decision problem in Table 1 of the CS (pg. 9-10 of document B).

3.1 Population

The CS population matches that in the NICE final scope: adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.

3.2 Intervention

The CS intervention matches that in the NICE final scope: adjuvant treatment of dabrafenib plus trametinib. The intervention was presented within the full anticipated marketing authorisations for both drugs (dabrafenib plus trametinib) for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. This conforms to the anticipated marketing authorisation.

3.3 Comparators

The CS comparator matches that in the NICE final scope and is consistent with trial evidence submitted.

3.4 Outcomes

The CS outcomes match those in the NICE final scope and are appropriate to the decision problem. The CS primary outcome was investigator assessed RFS. In addition to the outcomes considered in the NICE scope, the CS included freedom from relapse defined as *"the interval from randomisation to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death"*. Concomitant medications and post-reoccurrence therapies were recorded.

3.5 Other relevant factors

Dabrafenib plus trametinib does not currently have a UK marketing authorisation for the adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection. The CS states that there is a pending marketing authorisation application that was made to the EMA. The FDA has recently (30th April 2018) approved the dabrafenib plus trametinib for adjuvant treatment of melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company employed standard systematic review methods: literature search, study selection, data extraction and synthesis.

The ERG's appraisal of the CS systematic review of clinical effectiveness is summarised in Table 1. The literature searches (CS Appendix D, Table D.4.1) were conducted in October 2017 and yielded to 115 potentially relevant records. The eligibility criteria of the CS was broader than the scope in terms of population, comparators and outcomes. One trial was included (COMBI-AD) as relevant to the decision problem.[2, 16] Study selection process and data extraction were carried out appropriately. Overall, the ERG considers that the quality of the company's systematic review was reasonable and that the chance of systematic error in the systematic review was low.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Although eligibility criteria were broader than the scope, they covered the review scope.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes (Table D.6.1, Appendix D)
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.1 Searches

Comprehensive searches in an appropriate set of bibliographic databases were undertaken on 16–17th October 2017, using relevant search terms. In addition, searches of references of included studies, trials registers, relevant conferences, regulatory and HTA agencies were undertaken and are well reported.

4.1.2 Inclusion criteria

Eligibility criteria for study selection are summarised in of CS appendix D Table D.3.1. and are summarised by the ERG in Table 2.

Table 2: Study selection criteria

Domain	Inclusion criteria	ERG comment
Population	Patients with advanced stage III melanoma with a BRAF mutation or resectable stage IV melanoma	Meets the decision problem. However, extended to include stage IV melanoma as this treatment is currently licensed for use in this group
Intervention	Dabrafenib in combination with trametinib	-
Comparator(s)	Surveillance/watchful, waiting/best supportive care, Interferon alpha, Ipilimumab, Nivolumab, Pembrolizumab, Vemurafenib, Cobimetinib, Chemotherapy treatments, Placebo	Meets the decision problem but included additional licensed pharmacological treatments of a later disease stage to ensure that all studies were captured including those that may have included patients at an earlier disease stage
Outcomes	Relapse-free survival, Freedom from relapse, Disease-free survival, Progression-free survival, Distant metastases-free survival, Recurrence-free survival, Adverse events, Quality of life	Meets the decision problem but included additional relevant outcomes (FFR, DFS, PFS, and RFS)
Study design(s)	RCTs Systematic reviews Indirect treatment comparisons Prospective, comparative non-RCTs (e.g. cohort studies and case control studies)	-

	Prospective single-arm observational studies (case series studies)	

The CS PRISMA diagram (Table D.3.2, pg. 11 of the CS Appendix D) itemises the identification of 3054 publications from searches, the exclusion of 2383 for specified reasons and the final inclusion of one study reported in two records.[2, 16] The ERG consider the study selection to have been transparent. The ERG notes that the number of trials reported in the PRISMA diagram matches the number of trials reported in the CS, page 26.

4.1.3 Critique of data extraction

The ERG has cross checked the data presented in the CS against that in the Trial Report and study publication.[2, 17] Only minor typographical errors were detected. The ERG considers the data presented were accurate and relevant. There was a lack of transparency regarding clinical effectiveness data extraction methods. In addition, number of reviewers involved, data extraction forms used, and how disagreements were resolved were all not clearly described in the CS.

4.1.4 Quality assessment

The company's assessment of study quality of the included RCT (CS B pg. 34 and CS Appendix D, Table D.6.1, pg. 30) is summarised in Table 3 together with the ERG's independent assessment. The ERG largely agrees with the company's assessment except with respect to potential bias from the imbalance in numbers of drop-outs between the two arms, and the fact that some important outcomes were investigator-assessed. Other adjuvant therapy RCTs have assigned such outcomes to an Independent Review Committee masked to treatment assignments.[18, 19]

Overall, the ERG considers the quality and assessment of the trial to be reasonable.

Table 3: Quality assessment of included study

NICE Checklist Item	Quality assessment judgment in CS	ERG judgement – rational
Was randomisation carried out appropriately?	Yes - Central randomisation using a randomisation schedule generated by the GlaxoSmithKline Biostatistical Department. Patients were randomised 1:1 to either treatment or placebo, with stratification according to BRAF mutation status (V600E or V600K) and disease stage (IIA, IIB or IIC). Eligible patients who has been entered in RAMOS, an interactive voice response system, were assigned a randomisation number.	Yes
Was the concealment of treatment allocation adequate?	Yes – Interactive voice system (RAMOS). Eligible subjects were given a unique subject number and had to have been entered into RAMOS to obtain the blinded treatment assignment. Matching placebo capsules for dabrafenib (50 and 75 mg) and trametinib (0.5 mg and 2.0 mg) provided to sites by Novartis. Placebo capsules/tablets contained same inactive ingredients and film coatings as the dabrafenib and trametinib study treatment.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes - There were no differences in baseline characteristics between groups.	Yes
Were the care providers,	Yes - Study treatment double-blinded: Novartis, study personnel (including investigator) and	Yes

participants and outcome assessors blind to treatment allocation?	patient did not know treatment assignment. Blinding was maintained until all analyses were performed.	
Were there any unexpected imbalances in drop-outs between groups?	No - There were imbalances between the groups in terms of drop outs, but these were not unexpected considering the comparator was placebo. Dabrafenib plus trametinib: 60 died and 47 withdrew (31 withdrew consent, 11 lost to follow-up, 5 at investigator discretion); 331 patients still in follow-up. Placebo: 93 died and 62 withdrew (40 withdrew consent, 18 lost to follow-up, 4 at investigator discretion); 277 patients still in follow-up. Authors highlighted an imbalance between the two groups in types of therapy administered after recurrence, which could impact OS outcomes.	Yes- There was some imbalance between the two groups with respect to the types of therapy that were administered after recurrence which could have had an effect on OS. outcomes. This is acknowledged in the CS.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No - All outcomes pre-specified in the full-text publication were reported.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate	Yes - Efficacy analyses conducted on ITT population; safety analyses conducted on all patients who had received at least one dose of a study drug. The last LOCF method was used to account for missing data.	Yes – but the ERG could not locate the text on the LOCF method.

methods used to account for missing data?		
Also consider whether the authors of the study publication declared any conflicts of interest.	Yes - All conflicts of interest were declared. The trial was sponsored by GlaxoSmithKline and Novartis	Yes

4.1.5 Evidence Synthesis

In the CS systematic review of clinical effectiveness, one RCT (Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma, NCT01682083 [COMBI-AD]) is presented in tabular, graphical and narrative form. As only one trial was identified, no meta-analysis was conducted and no indirect treatment comparison was undertaken. This is consistent with NICE and CS scopes, each of which specify the population as BRAF positive, since no other trials in exclusively BRAF positive patients have been identified. However, the ERG note that for economic modelling of extrapolation of recurrence free survival the company used data from the placebo arm of the EO18071 trial in which participants' BRAF status was not determined.[19] Therefore, the CS has assumed an "equivalence" between a trial with mixed BRAF population and a trial with exclusively BRAF+ population. Given this assumption it might appear logical to conduct a network meta-analysis comparing multiple adjuvant treatments.

In summary, the ERG considers the quality of the company's systematic review to be reasonable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Overview

Evidence for the clinical effectiveness on dabrafenib and trametinib is presented from a single RCT.[2, 16] The COMBI-AD trial was a phase III double-blind, international, multi-centre, placebo controlled RCT sponsored by GlaxoSmithKline and the company. Summary details of the trial were provided in the CS pg. 27 – 30. The trial was reported in two peer reviewed records [2, 16] and

a confidential CSR summary which have been submitted to the ERG. The COMBI-AD trial was relevant to the company's decision problem in terms of population, intervention, comparator and outcomes (see section 3 for comparison to the NICE decision problem).

Conduct of the trial

The trial was designed to investigate dabrafenib in combination with trametinib in the adjuvant treatment of melanoma after surgical resection. Oral intake of 150 mg of dabrafenib (twice a day) plus 2 mg of tramerinib (once a day) or of placebo was assigned randomly in a 1:1 ratio for a double blind controlled period of 12 months. Participants, investigators and site personnel (Novartis) were blinded to treatment allocations. However, the investigator/treating physician could un-blind treatment assignment in case of emergency. The trial protocol states that details of un-blinding were provided in the CS. Details of un-blinding were not described in the CS. Treatments given daily for 12 months, the first dose (150 mg of Dabrafenib and 2.0 mg of Trametinib or placebo) was administered in the morning at the same time every day. The second dose of treatment (150 mg of Dabrafenib or placebo) was to be administered 12 hours after the first dose. Treatments were taken orally with approximately 200 mL of water under fasting conditions either 1 hour before or 2 hours after a meal. Participants were enrolled between January 2013 and December 2014 and the clinical cut-off was 30th June 2017. The conduct of the trial was clearly presented though details of un-blinding were not clear.

Selection of participants

The CS reported the key inclusion criteria in Table 8 page 28 and Appendix L; in summary these were patients aged ≥ 18 years, and had undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma, which carried BRAF V600E or V600K mutations. Patients had not undergone previous systemic anticancer treatment or radiotherapy for melanoma, had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). Patients with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were also eligible. The ERG noted that CS Table 8 (pg. 28) did not mention the requirement for BRAF mutations. A number of exclusion criteria were listed under 'Exceptions' in the CS Appendix L page 141. The trial records[2] stated additional exclusion

criteria regarding which the CS was unclear. The ERG clinical advisor considers the selection of participants acceptable.

Consort diagram

A flow-chart of participants through the COMBI-AD trial was presented in Table D.5.1 of the CS Appendix D: 870 patients were randomised, 438 were assigned to receive combination therapy (435 received drug) and 432 were assigned to receive placebo. Three patients did not receive treatment in the intervention arm.

[redacted]. The ERG noted a typographical error in the CONSORT diagram where it is stated that there were 453 patients instead of 435 in the treatment group and 342 instead of 432 in the placebo group. CS page 34 provides information about numbers of patients who fully completed the planned dosage schedules.

Follow-up

Follow-up visits occurred every 3 months for the first 24 months and every 6 months thereafter. Follow- up frequency was similar to NICE guidance for melanoma follow-up care.[20] The ERG has some concern that since imaging and examination to detect disease recurrence were only performed every 3 months during the first 24 months and then every 6 months until disease recurrence or the completion of the trial, (as stated on pg. 49 of the CS), the accuracy of the true relapse free survival may have been somewhat limited. Patients who discontinued the study treatment were followed for disease recurrence every 3 months after the end of treatment until 24 months and every 6 months thereafter until study completion, withdrawal or death. At the time of cut-off (30th of June 2017), follow-up was still occurring in 331 patients (76%) in the combination-therapy group and 277 (64%) in the placebo group. Median follow-up was [redacted] in the treatment group and [redacted] in the placebo. Scheduled doses were completed by 272/435 (63%) of patients for dabrafenib while 163 (37%) discontinued treatment due to either adverse events (108 patients), or disease recurrence (23 patients) or other reasons (32 patients). At the time of cut-off (30th of June 2017) scheduled doses were completed by 277/435 (64%) of patients for trametinib while 158 (36%) discontinued treatment due to either adverse events (104 patients), or disease recurrence (23 patients) or other reasons (31 patients). At the time of cut-off (30th of June 2017) scheduled doses were completed by 227/432 (53%) of patients for placebo while 205 (47%) discontinued treatment due either to adverse events (12

patients), or disease recurrence (175 patients) or other reasons (18 patients). The ERG clinical advisor queried why the dose completion as some paients may have moved to single agent therapy. The proportions completing scheduled doses at the time of cut-off were higher in the treatment group than in the placebo group, largely because recurrences of melanoma occurred more frequently as a reason to discontinue treatment in the placebo group (175 vs. 23). The main reasons for discontinuing treatment in the dabrafenib+trametinib arm were adverse events rather than recurrence (104 trametinib and 108 dabrafenib vs. 12 placebo).

Withdrawals and discontinuation of follow up

Overall, 47 patients (11%) in the combination group and 62 patients (14%) in the placebo group withdrew from the study. In the treatment group, the most common reasons for withdrawal were withdrawal of consent (31 patients); loss to follow-up (11 patients) and investigator discretion (5 patients). In the placebo group the most common reasons for withdrawal were withdrawal of consent (40 patients); loss to follow-up (18 patients) and investigator discretion (4 patients).

Duration of dose exposure

CS table 19 pg. 50 provides some information about treatment duration. The median exposure for dabrafenib and trametinib was 11 months ([redacted]) while it was less for placebo (median 10 months; [redacted]). The CSR states that [redacted] The median ([redacted]) daily dose of dabrafenib and trametinib received by patients was 283.85 mg [redacted] and 1.97 mg [redacted] respectively. Placebo median ([redacted]) daily dose was 299.55 mg ([redacted]) for dabrafenib and 2 mg ([redacted]) for trametinib. Complete compliance with the planned 12 month dosage schedule would result in mean daily dosages of 300 mg of dabrafenib and 2 mg of trametinib. A higher proportion of patients with any dose interruption were in the treatment arm ([redacted]) in comparison to the placebo group [redacted]. Some of the patients were counted multiple times if they had multiple interruptions for the same reason. The main reason for dose interruption in the treatment group was adverse events [redacted] while non-compliance was the main reason in the placebo group

[redacted] The ERG clinical advisor questioned the non-compliance rate in the placebo as tablets were identical to intervention side effects were potentially less. Document B pg. 24 of the CS summarises discontinuation rates. At the time of cut-off (30th June 2017) 37% of pateints had discontinued treatment with dabrafenib, 36% with trametinib and 47% discontinued placebo.

Baseline characteristics

Baseline characteristics were presented in the CS, Table 9, pg. 31 for the ITT population. There were no meaningful differences at baseline in demographics or disease characteristics between dabrafenib+trametinib and placebo groups. The ERG noted a typographical error in sex n (%) in the CS Table. This Table does not provide information on distribution of patients by country, however elsewhere the CS states that 13 UK centres were included and that these recruited 86 patients split [redacted] between adjuvant and placebo arms. The ERG clinical advisor considers that the baseline demographic characteristics of patients recruited in the COMBI-AD trial are comparable to patients in the UK. The ERG compared the baseline characteristics Table 4 of COMBI-AD patients to the two studies recommended by the company's clinical experts for the RFS extrapolation.[19, 21, 22] EORTC 18071 included only stage III patients. However, the treatment duration in AVAST-M was similar to COMBI-AD. The crucial difference between trials was that BRAF status of patients was not stated in EORTC 18071. Therefore the company assumed an "equivilance" for BRAF status between EORTC 18071 and COMBI-AD and chose the placebo arm for RFS extrapolation (discussed later in 4.5.2 Weaknesses and areas of uncertainty).

Table 4: Characteristics of COMBI-AD patients at baseline vs AVAST- M[23, 24] vs EORTC 18071[21]

Variable	COMBI-AD		AVAST-M [23, 24]		EORTC 18071[21]	
	Dabrafenib + Trametinib	Placebo	Bevacizumab	Observation	Ipilimumab	Placebo
Length of study (median FU)	2. 8 years		6 years		5.3 years	
Treatment duration	1 year		1 year		3 years	

N	438	432	671	672	475	476
Age (yrs)	50 (18–89)	51 (20–85)	56 (18–87)	55 (19–88)	51 (20–84)	52 (18–78)
Male (%)	[redacted]	[redacted]	377 (56)	376 (56)	296 (62.3)	293 (61.6)
Female (%)	[redacted]	[redacted]	294 (44)	296 (44)	179 (37.7)	183 (38.4)
AJCC stage						
IIB	-	-	103 (15%)	109 (16%)	-	-
IIC	-	-	84 (13%)	72 (11%)	-	-
IIIA	83 (19)	71 (16)	104 (15%)	95 (14%)	98 (20.6)	88 (18.5)
IIIB	169 (39)	187 (43)	242 (36%)	253 (38%)	213 (44.8)	207 (43.5)
IIIC	181 (41)	166 (38)	138 (21%)	143 (21%)	164 (34.5)	181 (38)
III unspecified	5 (1)	8 (2)	-	-	-	-
***BRAF* status established (%)**	438 (100)	432 (100)	299 (45)	346 (51)	-	-
Wild type	-	-	173/299 (58)	181/346 (52)	-	-
V600 mutant	-	-	126/299 (42)	165/346 (48)	-	-
V600E	397 (91)	395 (91)			-	-
V600K	41 (9)	37 (9)			-	-
Outcomes						
RFS / DFI	Primary		2ndry		Primary	
OS	2ndry		Primary		2ndry	
DMFS	2ndry		2ndry		2ndry	
FFR	2ndry		-		-	

Outcome selection

The outcomes reported in the CS encompassed those in the final scope together with additional outcomes not mentioned in the scope. The majority of outcomes were clearly pre-specified in the trial protocol and are summarised in Table 5. There was no evidence of outcome reporting bias.

Table 5: Summary of outcome measures presented in the CS

CS outcome	Definition	Pre-specified	In line with NICE scope
Primary outcome:			
Investigator assessed RFS	Recurrence-free survival	Yes – in the study protocol	Yes
Secondary outcomes:			
DMFS	Distant metastasis free survival	Yes – in the study protocol	Yes
OS	Overall survival	Yes – in the study protocol	Yes
FFR	Freedom from relapse	Yes – in the study protocol	No but relevant
Safety (AEs)	Safety adverse events	Yes – in the study protocol	Yes
Exploratory outcomes:			
HRQoL	Health-related quality of life	Unable to identify	Yes
Outcome ranking unavailable:			
Concomitant medications	-	Unable to identify	No
Post-recurrence therapies	-	Unable to identify	No

Safety (adverse events)

The ERG was satisfied that the adverse events noted from the COMBI-AD trial were all reported accurately in the CS. The CS has reported all of the common and serious adverse effects which are referenced in the FDA label.[13]

Whilst the ERG were satisfied with the company's acknowledgment for the resource implications of the most serious adverse effects requiring hospitalisation, most notably from pyrexia, the ERG considered that the company may have underestimated resources required for follow up for echocardiography and monitoring of cutaneous side effects with outpatient dermatology appointments.

Description and critique of the company's approach to trial statistics

The CS statistical approach to the COMBI-AD trial is summarised in CS Table 10.

The sample size calculation appeared to be correct; the ERG repeated the calculation based on the hazard rates provided, and obtained almost identical estimates. The ERG notes that the sample size was based on an analysis assuming exponential hazards in both trial arms, yet the results were then produced using a Pike's Estimator to estimate HRs, rather than fitting an exponential model in order to estimate the HR. It is unclear why the sample size was not consistent with the analysis method, but the ERG do not believe this to be a concern.
The ERG are unclear of the reasoning behind the choice of the Pike Estimator to estimate HRs. The company state that the Pike Estimator is more efficient in terms of mean square error than the more commonly used Cox model. The ERG were unable to validate this claim.

The Pike Estimator yields a HR, it is therefore assuming proportional hazards (PH), which were (not formally) verified by the company. Departure from the PH assumption suggests that the HR estimate may be inaccurate. Similarly the log-rank test performs best when PH are present, suggesting that the p-values may misrepresent the data.

An interactive voice activated system was used for treatment allocation; patients were stratified according to their *BRAF* mutation status (V600E or V600K) and disease stage (IIIA, IIIB, or IIIC). The ERG note there was no stratification by geographic region. There was no mention of block size and so the ERG assume a simple random sequence was created according to prespecified strata. Given this and considering the international nature and size of the trial it is likely the allocation sequence was safe from discovery and hence satisfactory. OS, as the key secondary end point, was to be tested in a hierarchical manner only if the primary end point met the criteria for significance. The ERG judged this approach appropriate, however, it is unclear to the ERG if it was applied only to OS and no other secondary outcome. The ERG believe the hierarchical testing should have been applied to all secondary outcomes.

Randomisation was between 31 January 2013 and 11 December 2014. The data cutoff date for the primary analysis was (June 30, 2017) and seems in line with the amended protocol, though not the original. The ERG note that the Protocol amendment states ([redacted] information) an anticipated median follow up of 3.3 years when doing the primary RFS analysis; the actual median follow up was 2.8 years.[2]

Data from the trial are reported for the ITT population (primary and secondary outcomes but not patient reported outcomes), subgroups for the primary outcome (RFS) and a summary of safety analysis. The trial was expected to provide a power of more than 90% based on the enrolment of 870 participants. One of the assumptions for sample size calculation (CS document B, pg. 33) was to have a dropout rate of 5% for the placebo group and 15% for the combination group. The drop-out rate in the intervention group was less than 15% while drop-out rate was at 14% in the placebo group. The latter may have reduced trial power.

Subgroup analyses

The CS states that pre-planned subgroup analyses were undertaken on the primary outcome RFS [redacted]. The subgroup analyses for the primary outcome included mutation status, gender, age at screening, race, region and nodal metastatic mass and primary tumor ulceration. Details are listed in CS Figure 11 page 47 and Appendix E and were pre-specified in the protocol. However, the CS conducted additional subgroup analysis (number of nodal metastases) for the primary outcome that was not pre-specified in the protocol. The treatment effect estimates across subgroups were similar to the overall population except for V600K, Asian ethnicity and some regions (Asia/Pac, South America and Australia and New Zealand) where statistical significance was no longer present. It should be noted that the confidence intervnals across some subgroups such as stage IIIA, presence/absences of micrometastasis, and USA and Canada group were wide.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No meta-analysis or indirect comparison was undertaken.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No meta-analysis or indirect comparison was undertaken.

4.5 Summary and critique of results

4.5.1 Effectiveness

The ERG considers the quality of the company's systematic review to be reasonable. Following systematic review, the clinical effectiveness evidence submitted derived from a single well conducted international randomised placebo-controlled trial (COMBI-AD) undertaken at 169

sites in 26 countries. The ERG considers that the baseline demographic characteristics of patients recruited in the COMBI-AD trial are comparable to those of the relevant patients in the UK.

4.5.2 Weaknesses and areas of uncertainty

There were differential numbers and timing of patients dropping out in the COMBI-AD trial intervention and control arms and therefore of patients censored in the analysis of different arms of the trial. Following the suggestion by an expert consulted by the company, the ERG therefore conducted a CR analysis which indicated that relapse free survival estimates might represent an overestimate of approximately 11%. For the cost effectiveness analysis the company used data from a trial undertaken in a different population (patients with BRAF status undetermined) in order to extrapolate from observed RFS. This assumed equivalence between the mixed BRAF population and COMBI-AD (a trial with an exclusively BRAF+ population) and is open to question because of potential non comparability between the two poulations. The Company chose the Pike Estimator to estimate HRs. Although the ERG are unclear of the rationale for this choice.

Premature end to follow up (PEFU)

The CS CONSORT diagram (CS Appendix pg. 29) states that, 47 and 62 of live participants in adjuvant and placebo arms respectively ended follow up before study closure. The ERG used data provided in clarification (question A8) to investigate the timing of PEFU in the two study arms. The results are summarised in Figure 1. The imbalance seen in numbers and timing between arms may potentially influence estimates of outcomes, especially those involving time to event analyses.

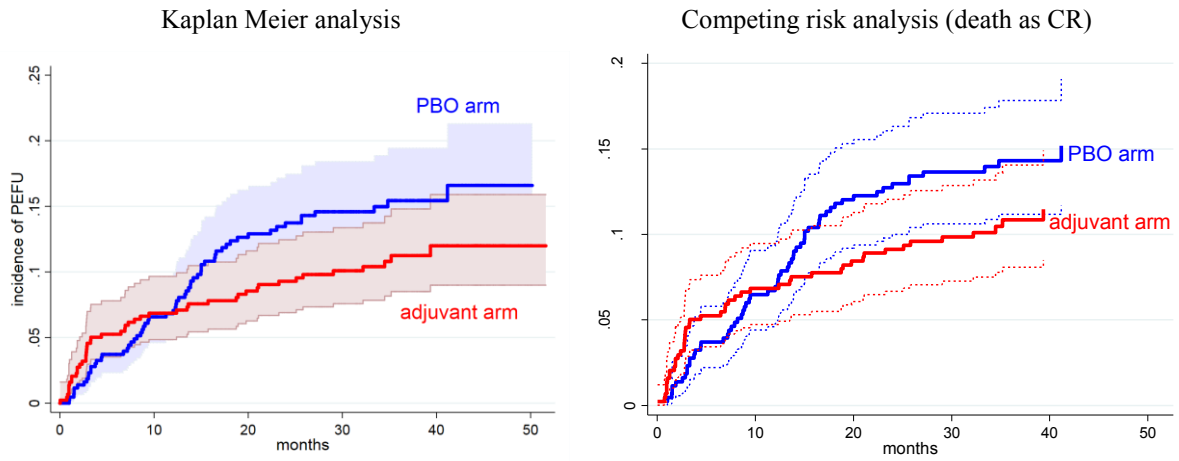
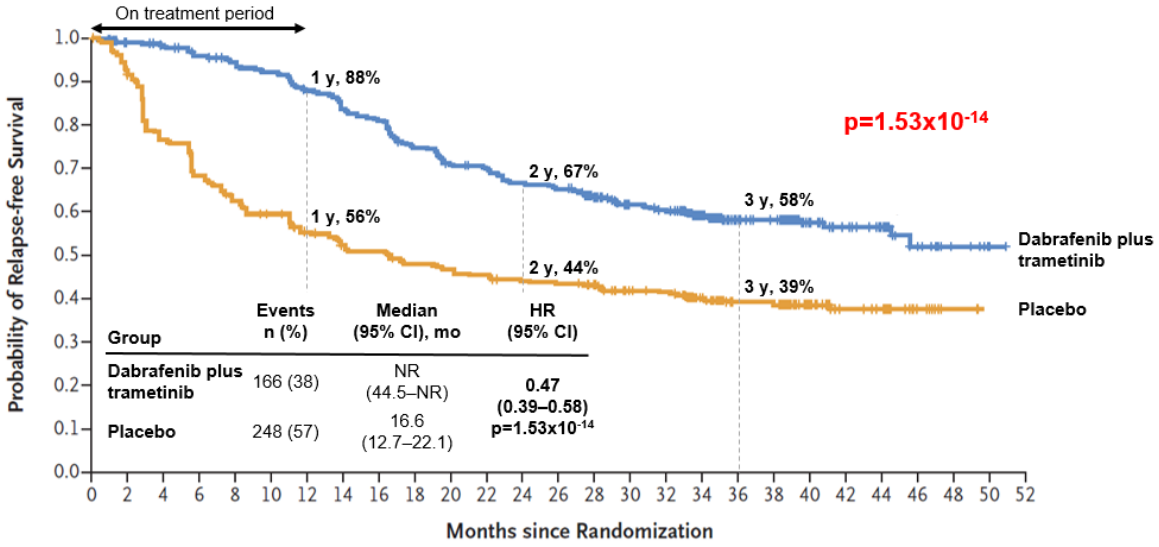


Figure 1: Premature end of follow up (PEFU) in COMBI-AD

Primary outcome, recurrence free survival (RFS)

The primary outcome in COMBI-AD was recurrence free survival (RFS), a composite outcome measure. RFS was defined as the time from randomisation to disease recurrence or death from any cause. Analysis was based on the ITT population (CS Table 10).



No. at Risk

Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

RFS results were presented in the form of a Kaplan-Meier (KM) analysis (CS Figure 6, shown above), a HR estimate (0.47; 95% CI: 0.39–0.58), and a stratified logrank P value (<0.001) for the comparison of adjuvant versus placebo treatment. Median RFS was 16.6 months (95% CI: 12.7–

22.1 months) in the placebo arm and not reached in the adjuvant arm. There is clear evidence that adjuvant treatment delays recurrence.

RFS events encompassed multiple types: "occurrence of loco-regional recurrence only; distant recurrence only; both local and distant recurrence; identification of a new primary melanoma; or occurrence of death from any cause without prior documentation of tumour recurrence. This latter could be further subdivided as attributable to melanoma, to non-melanoma or to unknown cause. The breakdown of events and censorings according to type are summarised in Table 6 which is based on CS Table 12.

Table 6: Events and censorings in the RMS KM analysis shown in CS Figure 6

	Adjuvant (N 438)	Placebo (N 432)
Total events	166	248
Events as deaths	3	1
Total events not as deaths	163	247
Events not as deaths: a] Loco-regional recurrence only	54	107
Events not as deaths: b] Distant- recurrence only	96	126
Events not as deaths: c] Loco & distant recurrence	7	7
Events not as deaths: d] New primary melanoma	6	7
Total censorings	272	184
Censoring due to no recurrence or death & follow up ongoing	[redacted]	[redacted]
Censorings due to no recurrence or death & follow up ended	[redacted]	[redacted]

Two types of censored patients were detailed in CS Table 12: Censored "follow up ongoing" was defined in Table 12 footnote as "*Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from the study by the data cut-off for the primary analysis (30th June 2017)*". Censored "follow up ended" was defined as "*Patients censored with follow-up ended are the remaining censored patients*". The ERG interpret these latter patients to be those who did not experience recurrence or death (any cause) and whose follow up terminated before the study cut off (30th June 2017). According to the CONSORT diagram, possible reasons (other than death) for not being in follow up at the study cut off included: loss to follow up, withdrawal from the study, and investigator discretion.

In the CS cost effectiveness section (3.3.1 pg. 71) a further KM analysis of "RFS" is presented (CS Figure 13); this was used in the economic analysis on the basis of clinical advice that new primary melanoma (SPM), in the absence of observed recurrence, should not be considered a recurrence event and should instead be censored. This reduced the total events to 160 and 241 in adjuvant and placebo arms respectively and increased the censorings to 278 (adjuvant) and 191 (placebo). The analysis does not correspond to any reported in the clinical effectiveness section and appears to have been introduced specifically for economic modelling. In clarification (question A12) the company supplied the following statistics for the Figure 13 analysis: HR 0.47 (95% CI, 0.38–0.57) P<0.001, these numbers are almost indistinguishable from the RFS analysis of Figure 6. In this additional RFS analysis patients could follow one of several pathways as summarised in Table 7. Although the composite RFS outcome may be appropriate as an overall estimate of clinical effectiveness, it is less well suited to the company's model design for economic analysis (CS Figure 12); indeed untangling the various strands of the composite outcome poses problems that appear to contribute to the considerable complexity of the economic model.

Table 7: ERG interpretation of possible patient pathways for RFS in KM analysis Figure 13

Patient pathway		KM designation (Figure 13)	Adjuvant N	Placebo N
A	Not experience death or recurrence, follow up ongoing at end of study	Censored at last time of follow up	[redacted]	[redacted]
B	Experience recurrence	Event at time of recurrence	157	240
C	Death prior to recurrence detection	Event at time of death	3	1
D	Development of a new primary melanoma	Censored at time of detection	6	7
E	Follow up ended before end of study and before recurrence or death (PEFU)	Censored at time of PEFU	[redacted]	[redacted]

The ERG note that an expert consulted by the company remarked: "what I would expect to have happened would be some CR type of analysis and actually model those recurrence events separately".[25] Competing risk analysis is an alternative approach sometimes used in circumstances where multiple outcomes are recorded (as in COMBI-AD), and offers an alternative estimate of the incidence of an event of particular interest to that from KM analysis. A

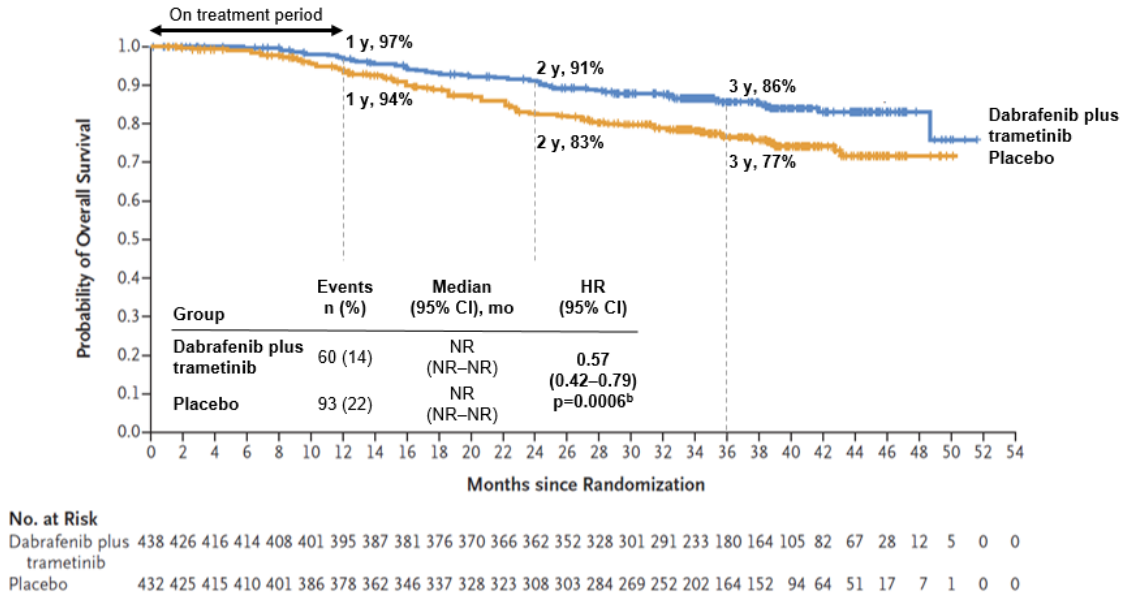
CR / event is one that will preclude occurrence of the event of particular interest (here recurrence / death). The CS reports that 47 and 62 patients in the intervention and placebo arms ended follow up before study close (CONSORT diagram, Appendix D); amongst these, [redacted] and [redacted] did not experience either all-cause death or recurrence (path E in Table 7). These patients thus experience a CR for the event of interest. PEFU (pathway E) contributed more to censoring in the placebo arm than the adjuvant arm. Such potential inequalities between arms in PEFU might influence the KM estimate i.e. the "true measure of treatment benefit". Similarly, patients censored for a new primary melanoma are precluded thereafter from experiencing a recurrence event and so represent a CR for recurrence. Thus, with reference to Table 7 censorings in pathways D and E represent CRs / events since when they occur they preclude observation of the event of interest. For these reasons the ERG requested that the company undertake the CR analysis of RFS suggested by one of the company's consulted experts. The results were provided in the company clarification response and are described below (section 4.6). The ERG's analysis suggests that the CR approach will deliver a reduction in the gain from adjuvant over placebo in restricted mean survival from 41 months by approximately 11% compared to a KM analysis.

For pathway C (death from any cause counted as a recurrence) the underlying assumption appears to be that death was actually preceded by a recurrence but that this was not detected (possibly due to gaps between monitoring times), hence such deaths may be legitimately recorded as RFS-like events. If the death is directly related to melanoma this seems reasonable. However, if the death is not from melanoma assuming that it was preceded by recurrence does not seem sensible. Only 3 and 1 patients in the adjuvant and placebo arms respectively followed pathway C.

Specified secondary outcomes; Overall survival (OS)

CS Table 8 specified the following secondary outcomes: OS, distant metastasis free survival (DMFS, defined in section 2.3.1), and safety. These are described and critiqued in the following section.

The OS results from COMBI-AD were not employed in the company's economic analysis.



OS was defined as the time from randomisation to death from any cause in the ITT population. The results were presented in the form of a KM analysis (CS Figure 7, shown above), a HR estimate (0.57; 95% CI: 0.42–0.79), and a stratified logrank P value (0.0006) for the comparison of adjuvant versus placebo treatment. Median survival was not reached in either arm. There were 60 and 93 events, respectively, in adjuvant and placebo arms. Table 8 summarises the breakdown of events and censorings.

Table 8: Events and Censorings in the OS KM analysis shown in CS Figure 7

	Adjuvant (N 438)	Placebo (N 432)
Events	60	93
Total censorings	378	339
Censorings due no death by the end of follow up	331	277
Censorings for PEFU before death occurred	47	62

There is numerical imbalance between arms in the censorings due to PEFU. Because PEFU will preclude observation of a death event before end of study the ERG requested information during clarification (question A5) that would allow CR analysis to be done; the results of the ERG CR analysis (section 4.6), suggest that a KM analysis may overestimate the gain from adjuvant over placebo in restricted mean survival to 41 months by approximately 21%. There was also imbalance between arms in the numbers of patients who died from non-melanoma or unknown causes (16 placebo, 6 adjuvant). The higher rate in the placebo arm may be suggestive of poorer

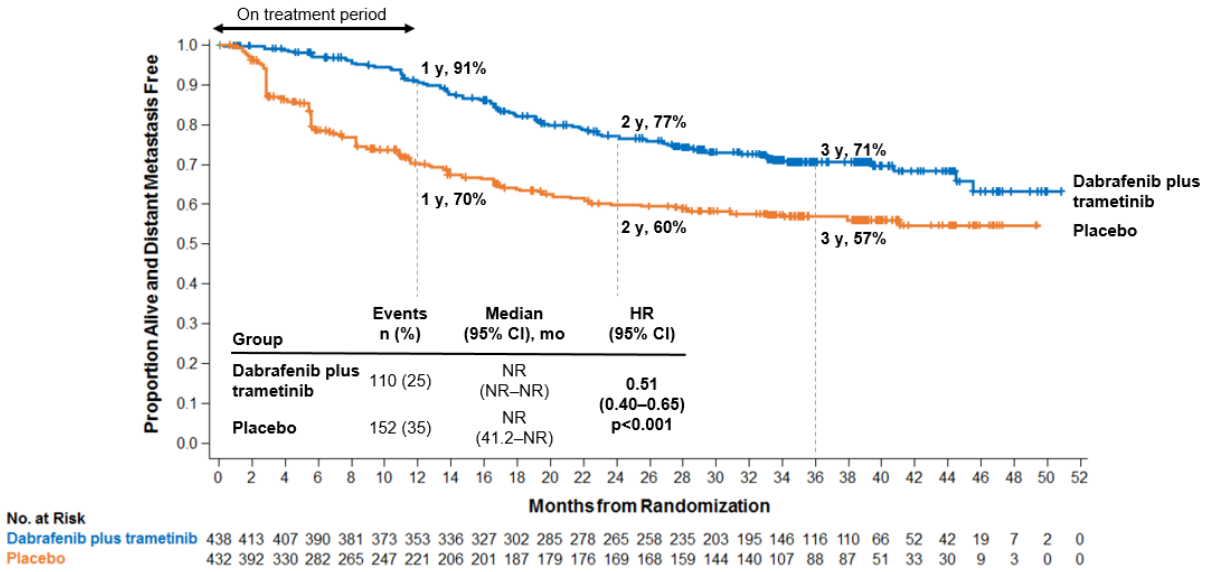
health at baseline amongst placebo patients compared to adjuvant patients or differences in post-recurrence treatments between arms. The OS experienced by patients in each arm of the trial is likely influenced by post-recurrence treatments received (and whether patients experience subsequent recurrence(s) after a first recurrence). Should such treatments differ between arms this may introduce bias in the comparison of adjuvant versus placebo. It may be that this is a reason why the results for OS from COMBI-AD have not been made use of in the company's economic model.

Specified secondary outcomes: Distant metastasis free survival (DMFS)

DMFS was defined as "the interval from randomisation to the date of first distant metastasis or date of death, whichever occurred first" (CS pg. 39). The results were presented in the form of a KM analysis (CS Figure 8, shown below), a HR estimate (0.51; 95% CI: 0.40–0.65), and a stratified logrank P value (<0.001) for the comparison of adjuvant versus placebo treatment. Median survival was not reached in either arm. The breakdown of events and censorings are summarised in Table 9.

Table 9: Events and Censorings in the DMFS KM analysis shown in CS Figure 8

	Adjuvant (N 438)	Placebo (N 432)
Total Events	110	152
Distant metastasis relapse events	[redacted]	[redacted]
Died	[redacted]	[redacted]
Total censorings	[redacted]	[redacted]
Censorings due no DMFS follow up ongoing	[redacted]	[redacted]
Censorings no DMFS follow up ended	[redacted]	[redacted]
*Assumed typo in CS Table 14, corrected 105 to 150		

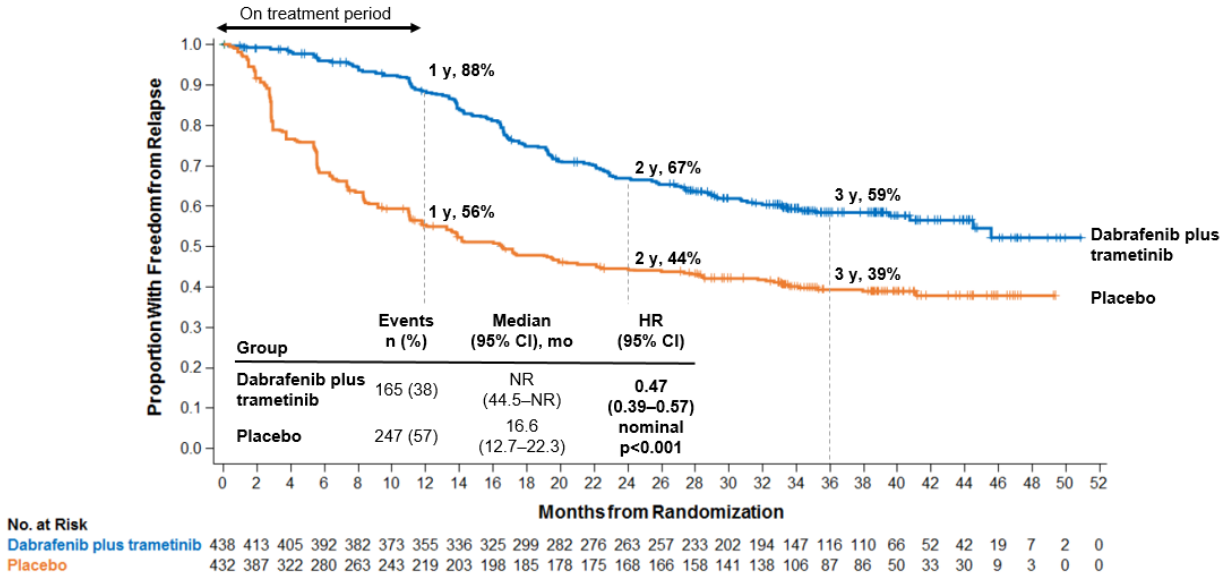


As with the company's KM analysis of RMS and OS there is some imbalance between arms in the numbers of patients experiencing PEFU; these preclude the subsequent observation of DMFS and may be regarded as a competing event.

Unspecified secondary outcomes, exploratory and other reported outcomes

Freedom from relapse (FFR)

FFR was defined as the interval from randomisation to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death. The results were presented in CS Figure 9 (shown below) and correspond to that presented by Long et al 2017 as Figure S3.[2] The reported HR was 0.47 (95% CI: 0.39–0.57) and the stratified logrank P value (<0.001). The median in placebo arm 16.6 months (95% CI: 12.7–22.3 months) and was not reached in the adjuvant arm.



FFR and RFS as presented in CS Figures 6 and 13 can be viewed as alternative but related methods to explore time to recurrence. A summary of the outcomes categorised as events or censorings in the three analyses is summarised in Table 10. The total numbers of events and censorings by trial arm are summarised in Table 11 according to analysis. Any of these might provide information for building the economic model although in the company base case the company selected the unpre-specified analysis shown in the CS Figure 13.

Table 10: Categories of outcome considered as censorings or as events in analyses presented in the CS

Recurrence ADJ PBO	SPM ADJ PBO	Death Melanoma ADJ PBO	Death "other" ADJ PBO	FUP ongoing ADJ PBO	FUP ended ADJ PBO
157 240	6 7	2 0	1 1	229 149	[redacted]

Table 11: Numbers of events (E) and censorings (C) according to analysis

Trial arm	RFS analysis Figure 6	RFS analysis Figure 13	FFR analysis Figure 9
PBO ARM	E 248 C 184	E 241 C 191	E 247 C 185
ADJUVANT ARM	E 166 C 272	E 160 C 278	E 165 C 273

In summary the ERG have some concerns that the numbers of patients experiencing PEFU and therefore available to experience the outcomes of interest varies between the intervention and

control arms of the COMBI-AD trial and that this may affect the overarching findings, diminishing the benefits accruing as a result of dabrafenib/trametinib combination therapy.

Patient reported outcomes

The HRQoL outcomes in the CS were obtained from the EQ-5D-3L. The ERGs clinical advisor proposed alternative HRQoL tools, such as the EORTC-QLQ-C30[26] and PRO-CTCAE,[27] since they more sensitive to patients in this population and toxicity. Results were presented in CS Table 16 and Figure 10 (CS pg. 43) showing, the mean utility scores with SD and the number of participants providing data for each arm at baseline (*n* = [redacted] adjuvant, *n* = [redacted]) and for each assessment time point (every 3 months to 2 years and then every 6 months to 54 months). [redacted] Final assessment was conducted at [redacted] in the treatment group and [redacted] in the placebo group. Overall, there were no significant improvements in reported HRQoL scores in the trial as measured using the EQ-5D-3L, but there are questions raised about whether it adequately considers toxicity in this patient population.

4.5.3 Safety

While the ERG was in agreement with the inclusion of the costs of hospitalisation due to common side effects such as pyrexia, there were concerns that costs for additional severe side effects such as haemorrhage or relatively minor side effects such as hyperglycaemia, uveitis or diarrhoea could have potentially been underestimated as they are very difficult to predict in a non-trial setting and are thus ill-defined and unrestricted.

Concerns regarding haemorrhage were raised on the basis that in the COMBI-d study haemorrhagic events took place in 19% of patients taking Dabrafenib and Trametinib combined (40/209) compared with 15% (32/211) of patients receiving Dabrafenib alone. Gastrointestinal bleeding occurred in 6% (12/209) of patients receiving combination therapy compared with 3% (6/211) of patients receiving Trametinib alone. Fatal intracranial haemorrhage occurred in 1.4% (3/209) patients receiving combined therapy compared with none in those taking Dabrafenib alone.[14] Furthermore, 2/93 patients from the BRF113928 study which tested Dabrafenib and Trametinib on non-small-cell lung cancer, suffered fatal haemorrhagic events – including retroperitoneal haemorrhage and subarachnoid haemorrhage. It is thus clear that there is a small

risk of fatal haemorrhage with Dabrafenib and that the risk of haemorrhage increases when it is combined with Trametinib.[28] Additionally, the ERG felt that Dabrafenib and Trametinib may impair glycemic control of diabetic patients in a primary care setting, which may have additional cost implications for their hypoglycaemic medication, which would optimally be managed by the General Practitioner / Community diabetic clinics and not in the hospital setting. 27% (4/15) of patients with a history of diabetes in COMBI-d receiving Dabrafenib with Trametinib and 13% (2/16) of patients with a history of diabetes receiving single-agent Dabrafenib required an upregulation of hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia based on laboratory values occurred in 5% (11/208) and 0.5% (1/208) of patients receiving Dabrafenib with Trametinib respectively, compared with 4.3% (9/209) for Grade 3 hyperglycemia and no patients with Grade 4 hyperglycemia for patients receiving single-agent Dabrafenib.[14]

An additional side effect flagged up by the FDA label was uveitis, which is stated to have occurred in 1% (6/586) of patients receiving Dabrafenib across multiple clinical trials and in 2% (9/559) of patients receiving Dabrafenib with Trametinib across randomized melanoma trials.[7] The ERG was of the view that additional costs are likely to be required for routine opthalmological monitoring which were not clarified in the initial CS report. However, in clarification question B12 it was stated that ophthalmological monitoring would not be carried out routinely and referral for ophthalmic assessments would only be undertaken if patients were to become symptomatic. The cost-implications of this are difficult to predict and uncertain in nature. Other side effects mentioned in the FDA label which did not appear to affect any patients in the COMBI-AD trial included Glucose-6-phosphate-dehydrogenase deficiency and embryo-foetal toxicity.[7]

Whilst the ERG was in agreement with the company that many of the less severe side effects such as pyrexia can be alleviated by self-treatment measures, the ERG was concerned that side effects which may potentially be responsible for malabsorption of the drugs, such as diarrhoea, stated on Table 24 on page 56 of the CS, to have taken place with grade 1 severity in 115 of the patients on the treatment arm, may preclude further compliance and efficacy of the treatment. Reassuringly in clarification question C6 it was confirmed that there were no reported discontinuations of treatment due to diarrhoea which was mainly transient with [redacted]. However it is difficult to predict whether this will hold as true in the clinical setting as it did in the trial setting. This is an important consideration for any of the adverse effects reported. It was also confirmed that no dose modifications due to diarrhoea were due to malabsorption. However,

the ERG considers that for the future it might be advisable to consider alternative formulations of the treatment for those who cannot take oral formulations. Novartis have however confirmed that no alternative formulations are currently available.

Furthermore, in acknowledgment of the fact that 12% of patients died due to melanoma and that a new primary melanoma was reported in 11 patients from the Dabrafenib plus Trametinib group the ERG felt it would be important to classify whether or not these incidences of melanoma were BRAF V600 positive. It was confirmed that a BRAF V600E/K mutation was detected in all relapse samples except in 1 secondary primary melanoma. The company also stated that since the majority of deaths occurred >30 days following the last dose of the study treatment, it remains possible that the disease may progress following cessation of treatment following the one year treatment protocol. This raises doubts as to whether 12 months is likely to remain an adequate treatment duration in the clinical setting, a timeframe which may expand in the future as more clinical evidence arises. This may require additional costs for BRAF testing and may modify the treatment plan for the patients affected.

As an aside, the ERG initially requested further clarification as to why patients in the placebo arm suffered from side effects, especially serious side effects. It was not known whether these effects were due to the placebo substance, progression of the underlying stage III melanoma or whether or not any alternative explanations could be offered. In response, the company confirmed that any adverse event including serious adverse events were defined as “any untoward medical occurrence in a subject or clinical investigation subject, temporarily associated with the use of a medicinal produce, whether or not considered related to the medicinal product”. In clarification question C2 it was stated that [redacted] patients experiencing SAE’s in the placebo arm had a causality that was reported as related to the study treatment and that the remaining patients in the placebo arm were assumed to have most likely experienced an SAE due to underlying disease comorbidities, a proposition which was backed by our clinical expert. On that basis the ERG had serious reservation regarding the safety, chemical composition and pharmacodynamics of the placebo substance, as one would traditionally expect it to be inert. Further clarification as to why the remaining patients on the placebo arm, who supposedly suffered SAEs owing to underlying disease and comorbidities may have helped identified which adverse effects in the treatment arm were directly related to Dabrafenib and Trametinib products and which due to underlying disease.

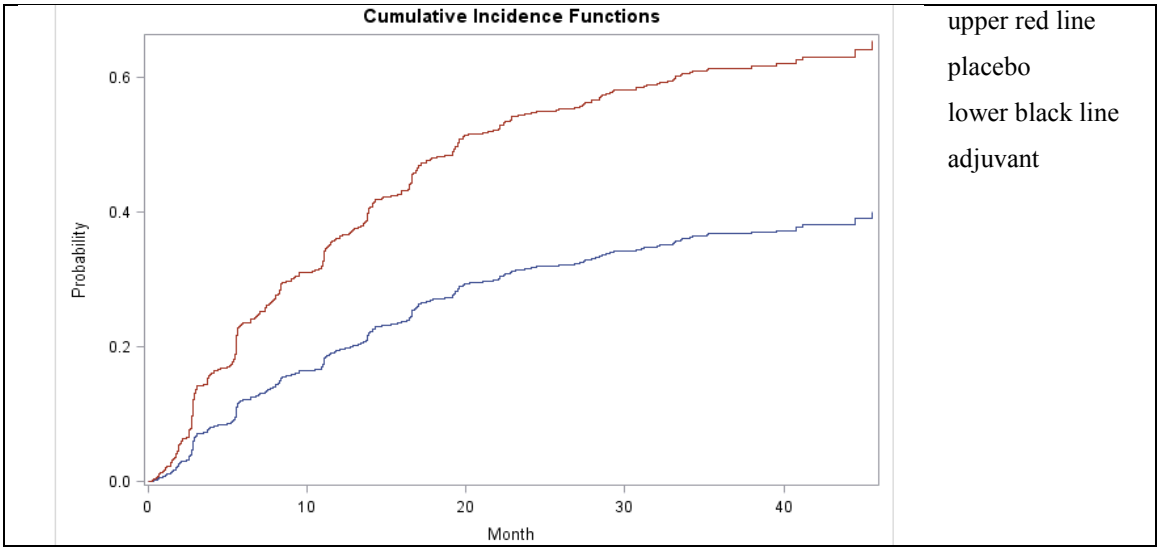
4.6 Additional work on clinical effectiveness undertaken by the ERG

RFS competing risk analyses

In a clarification response (question A1) the company supplied CR analyses for RFS. These employed semi parametric models that encompassed various assumptions. The potential advantage of the approach is that covariates may be included in the analyses. Table 12 summarises the results. These were expressed in terms of cumulative incidence plots and as HRs, the latter being very similar to those reported for the non-parametric KM analysis.

Table 12: Summary of the results of the company's RFS competing risk analysis

	Dabrafenib + Trametinib	Placebo
	(N=438)	(N=432)
Number (percentage) of subjects		
Event of interest: Relapse* + Death under disease	158 (36.1%)	239 (55.3%)
Competing risks:	15 (3.4%)	16 (3.7%)
Death from any cause other than melanoma without relapse	1 (0.2%)	1 (0.2%)
Patients with a new primary melanoma	7 (1.6%)	8 (1.9%)
Loss to follow up without relapse	7 (1.6%)	7 (1.6%)
Hazard Ratio from cause-specific hazard model		
Estimate	0.463	
95% CI	(0.379, 0.567)	
P-value	<.0001	
Hazard Ratio from subdistribution hazard model		
Estimate	0.474	
95% CI	(0.390, 0.577)	
P-value	<.0001	



Analyses were based on a small number of patients experiencing CRs in the analyses (15 and 16 in adjuvant arm and placebo arms respectively). SPM was counted as a competing event. There is small discrepancy in SPM numbers relative to CS. The ERG's intention in requesting the analysis was that follow up which terminated before the study cut off without a recurrence or death from any cause (numbering [redacted] patients in the adjuvant and placebo arms in CS Table 12 respectively) would be counted in the CR analysis. However the company only included "Loss to follow up without relapse" as a CR.

ERG CR analysis of RFS

The company supplied data in clarification (question A4) that allowed the ERG to undertake a more complete CR analysis. This was done because temporal and numerical imbalances between arms in "follow up ended" might influence the non-parametric estimate of difference between arms in the KM analysis. The primary purpose was to explore the difference in restricted mean RFS between arms delivered by the two non-parametric analyses, KM and CR. Patients experiencing "Follow up ended" ([redacted] people respectively in adjuvant and placebo arms) were treated as experiencing CRs following Graham et al. 2013.[29] SPM (affecting 6 and 7 patients in adjuvant and placebo arms respectively) was also considered a CR. Figure 2 summarises RFS incidence in each arm according to method of analysis. The area between adjuvant and placebo arms to a given time point represents the months of restricted mean recurrence free survival. This was estimated to 41 months since this was the longest follow up common across analyses and arms. Because CR analysis yields fewer recurrence events than KM analysis, the months of restricted mean recurrence free survival (to 41 months) is greater (32.15

(95% CI 31.07 – 33.24) and 23.81 (95% CI 31.07 – 33.24) in adjuvant and placebo arms using the CR analysis and 31.05 (95% CI 29.78 – 32.32) and 21.61 (95% CI 19.97 – 23.26) in adjuvant and placebo arms using KM analysis. The gain from adjuvant over placebo according KM restricted mean recurrence free survival was 9.44 months (95% CI: 7.36 – 11.52) and by CR analysis was 8.35 months (95% CI: 6.61 – 10.08), representing a modest overestimate by KM analysis of approximately 11%. The corresponding gain from adjuvant using the KM RFS depicted in CS Figure 13 rather than CS Figure 6 was 9.36 (95% CI: 7.28 – 11.45) months.

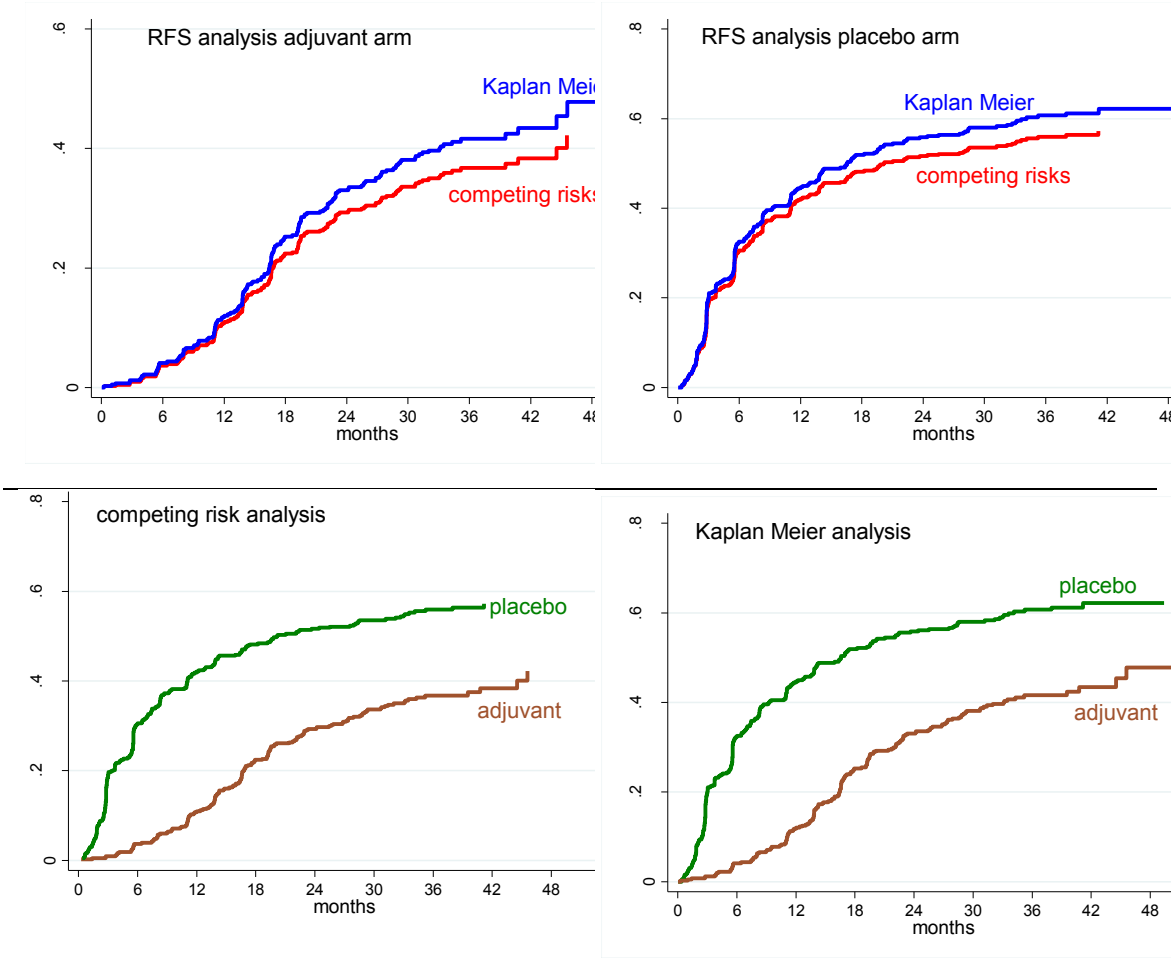


Figure 2: Kaplan Meier and competing risk analysis of RFS

ERG competing risk analysis of overall survival

The ERG undertook CR and KM analyses of OS using data supplied in clarification (question A8). Figure 3 summarises incidence of all cause death in each arm according to method of analysis. The area between adjuvant and placebo arms to a given time point represents the restricted mean survival. This was estimated to 42 months since this was the longest follow up

common across analyses and arms. The gain from adjuvant therapy according to KM restricted mean survival was 2.31 months (95% CI: 0.96 – 3.66) and according to the CR analysis was 1.83 months (95% CI: 0.27 – 5.05), representing a modest overestimate when using the KM analysis of approximately 21%.

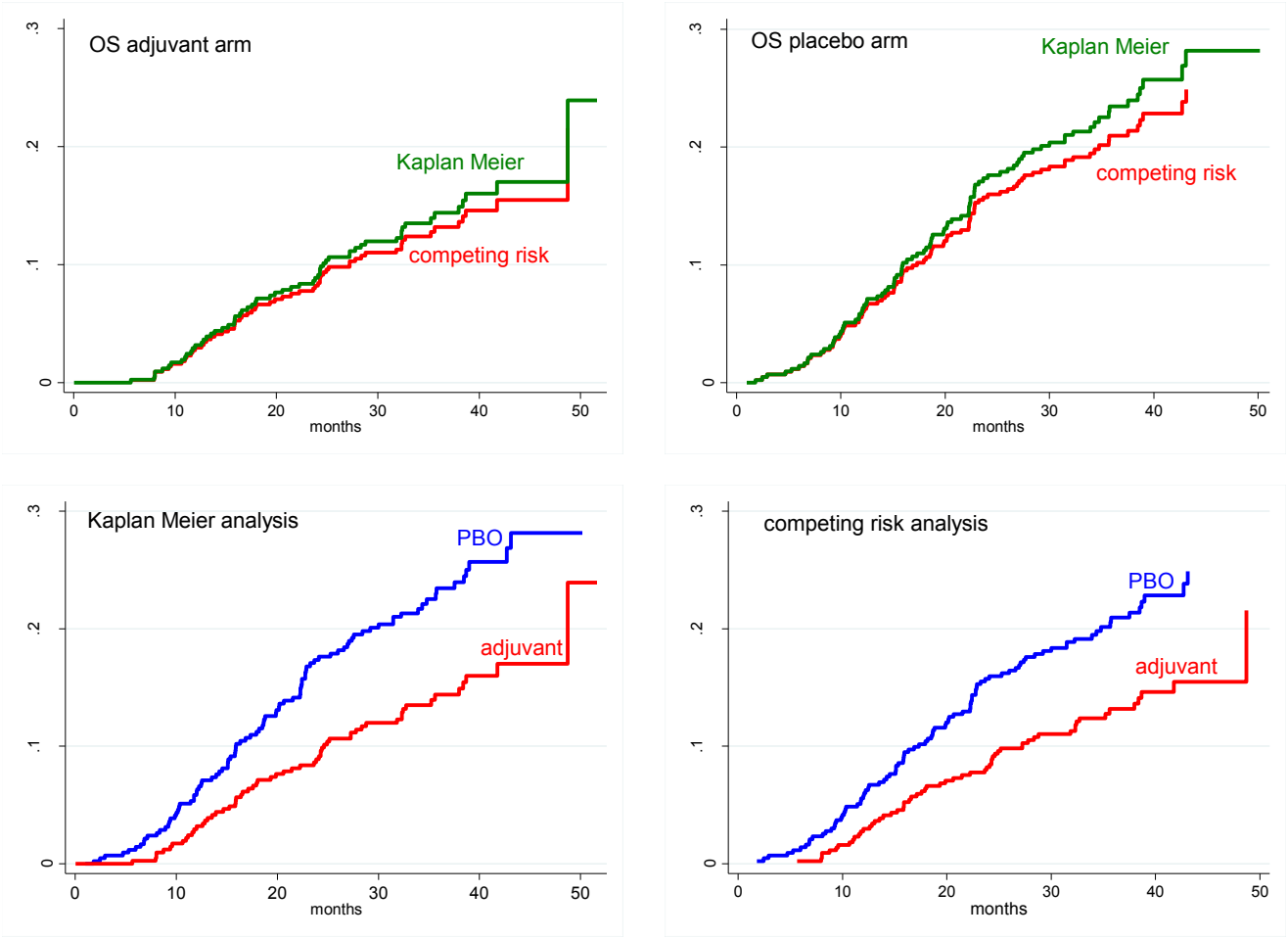


Figure 3: Kaplan Meier and competing risk analysis of OS

Parametric modelling of RFS

For the base case economic analysis the company explored many distributions to model the observed trial data for RFS (CS Figure 13, CS pg. 72-74); these assumed that the same class of distribution should apply for both arms and thereby conforms to NICE DSU advice.[30] These were not used for extrapolation to a life time horizon. A generalised F distribution provided the best fit according to AIC BIC testing but did not provide a good visual fit. A loglogistic model was selected (CS Figure 15) on the basis of low AIC BIC scores, combined with good visual fit and clinical opinion on clinical plausibility. Several models might provide a reasonable visual fit and

which of these is selected will have a small effect on the economic model output when not used for extrapolation. For extrapolation to a life time horizon (50 years) the company employed external data, sourced from an adjuvant RCT comparing ipilimumab versus intravenous placebo.

The company's choice of model for Figure 13 was made on basis of the three criteria: a] AIC BIC score, b] visual fit, c] clinical plausibility. The models explored by the company all incorporated treatment as an indicator. The ERG doubt that this is obligatory especially when the observed KM plots differ substantially in shape; the ERG found no evidence to support an assumption of proportional hazards Appendix A (pg. 143) The selected model exhibited a good visual fit to the KM plot (Figure 15) and relative to most other models a low AIC BIC scores (3708.5 and 3737.0), and it was considered clinically plausible. The ERG explored standard parametric models and flexible parametric models with and without treatment as an indicator. With treatment as indicator these generated low IC scores but relatively poor visual fits compared to the company selected model. With models fitted separately to each arm (treatment not an indicator) flexible parametric models generated visual fits as good as those of those of company selected model; AIC BIC values were low (Appendix B pg. 145), but cannot be compared with those from models using treatment as an indicator. Table 13 and Figure 4 summarise similarities and differences between the company selected model and flexible models.

Table 13: Comparison of the company's RFS models and flexible parametric models

Criterion	Company selected model	Flexible parametric model
Visual fit	good	equivalent or better
IC	AIC 3708.5, BIC 3737.0	PBO AIC 795.1, BIC 811.5 ADJ AIC 1209.4, BIC 1225.7
Clinical plausibility during observation time	yes	yes
Clinical plausibility in extrapolation	no	yes

In extrapolation to a life time horizon, the company's chosen model for the observed period produces a clinically implausible almost complete cessation of events after the maximum observation time. According to the company's 50 year prediction (pg. 83) using external data, the adjuvant and placebo arms reach between 16% (placebo) and 25% (adjuvant) without failure of RFS. The flexible parametric modes reach 11% and 18%, respectively, at 50 years.

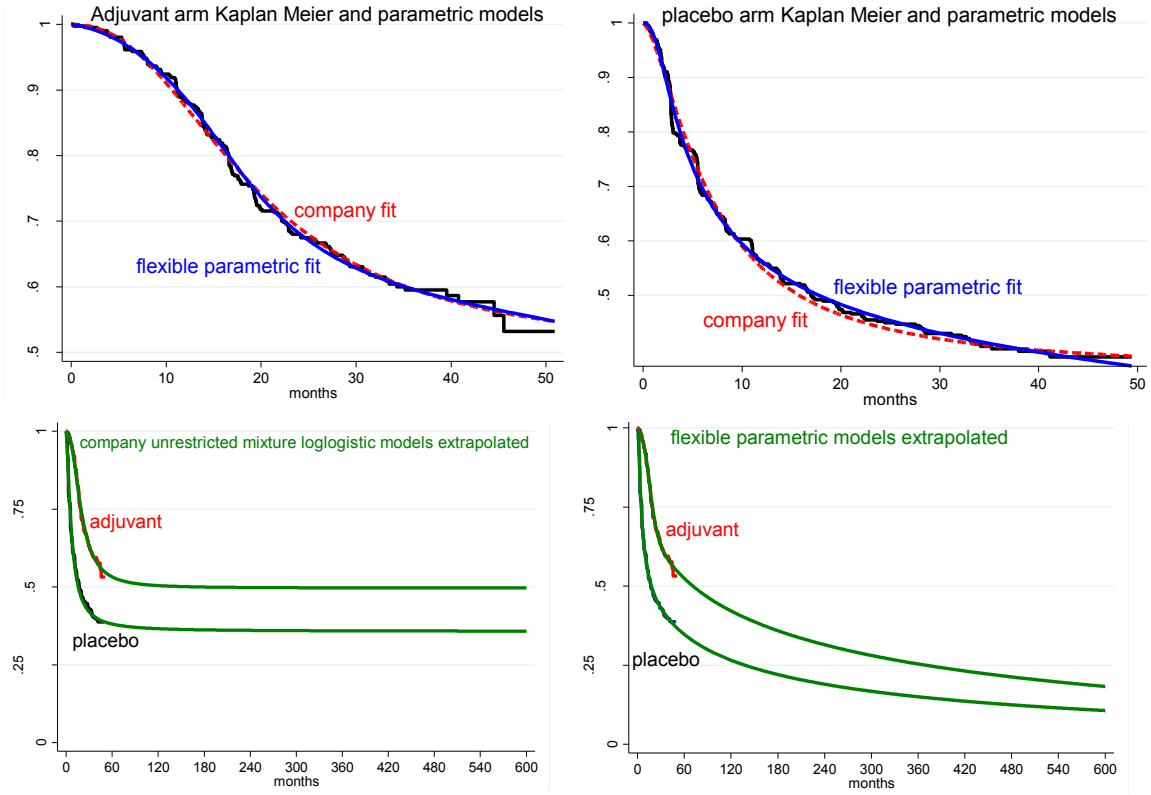


Figure 4: Kaplan Meier analysis and parametric models of RFS compared

Figure 5 summarises the results using the Machin et al. 2006 tests for goodness of fit of parametric models and compares the company's selected models with flexible models.[31] In this test the long dashed line with slope one and intercept zero represents a perfect fit to the KM data; the better the model fit the closer the model scatter points, and the closer will the regression line through them (short dashed lines), be to the perfect fit line. According to this test the flexible models perform at least as well as the company's selected model. The ERG considers that the flexible models may provide plausible candidates for use in extrapolation in the economic modelling.

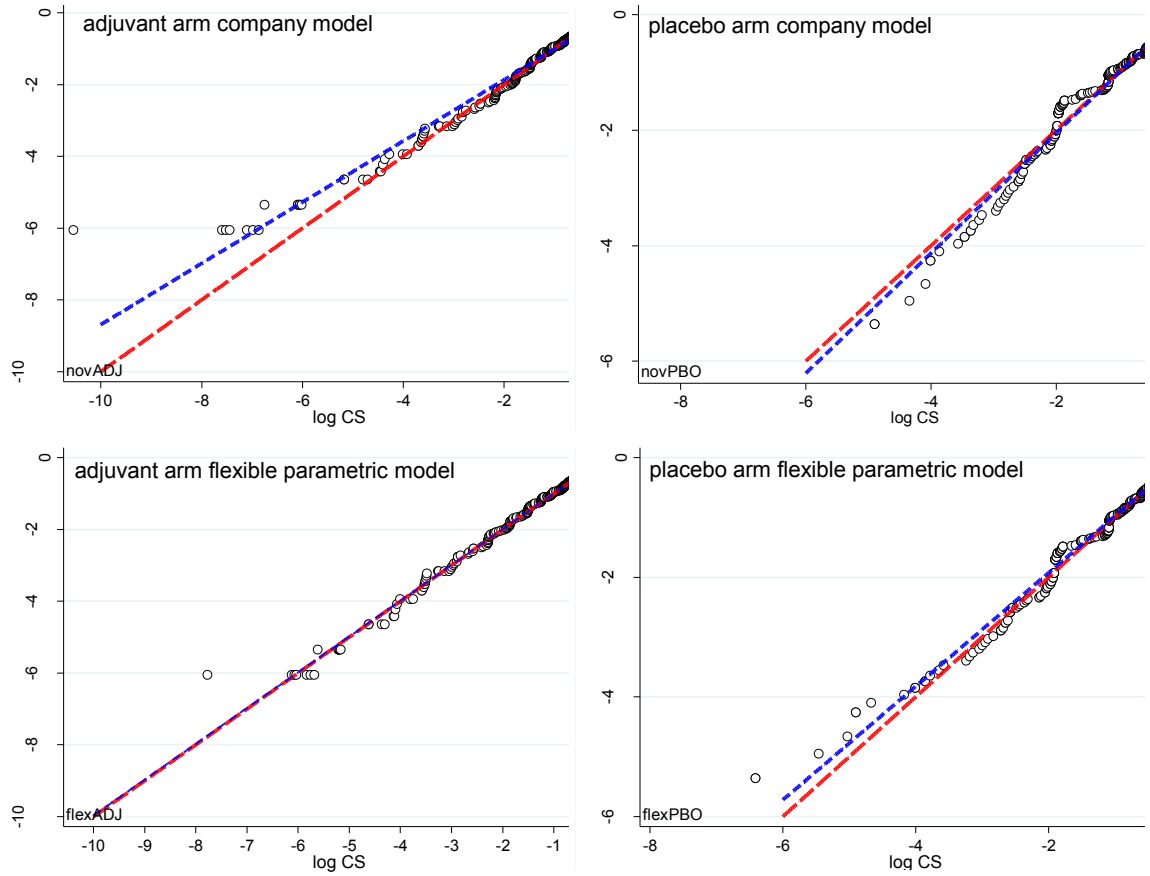


Figure 5: Machin et al. test of fit for parametric models of RFS

Extrapolation of RFS to life time horizon

In extrapolating beyond the observed RFS in COMBI-AD the CS has employed external data in a complex procedure comprising: a] the selection of an external evidence source (in this case the placebo (PBO) arm of the EO RCT 18071); b] Reconstruction of "pseudo" IPD from the external data source; c] fitting of multiple parametric models to a life time horizon; d] selection of plausible models; e] use of clinical expert advice concerning the most suitable plausible model to use in the economic base case; f] the application of data from the selected model to both the PBO and adjuvant arms of the COMBI-AD RFS model.

The method appears somewhat indirect and rather cumbersome and performs poorly on the principle of parsimony.[32] In the ERG's judgement the adopted procedure encounters several problems including those outlined below.

i) A justification for using the placebo arm of EO-18071 included its considerable similarity to the KM plot for the COMBI-AD placebo arm (CS Figure 16) and availability of follow up to ~78 months. The selection of only EO-18071 appears to have excluded exploration of other external sources. Indeed, the ERG notes that the company's clinical experts (quoted in CS REF 57) also suggested the use of the AVAST-M trial for extrapolation.[25] The ERG reconstructed the KM for disease free survival in AVAST-M using the latest available results (Figure 6).[23, 24] One year and five year rates correspond closely to the published rates of 70% and 45%. The hazard associated with flexible parametric model for AVAST-M is provided in Appendix C (pg. 146).

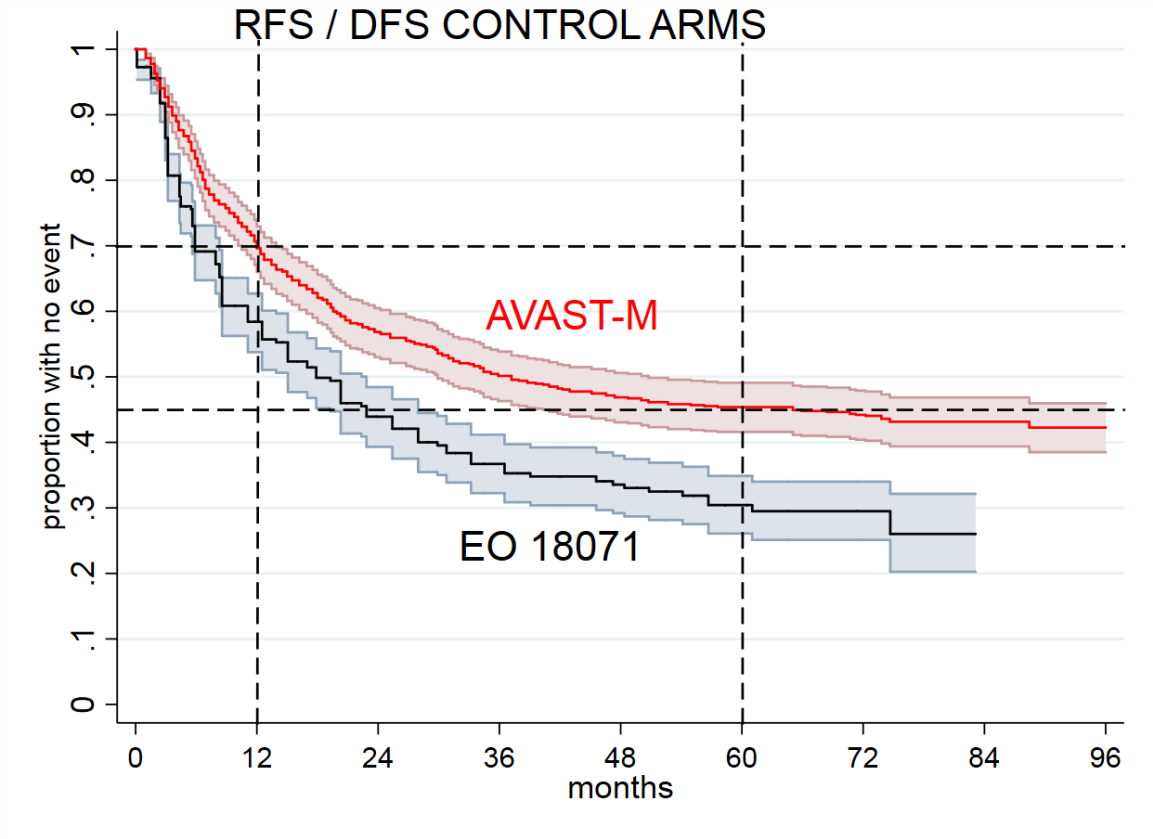


Figure 6: KM plot for DFS in AVAST-M and for RFS in EO 18071

It is clear that the experience of control participants in AVAST-M and in EO-18071 differs and that choice of external data source will likely influence the extrapolation. There are many potential reasons why AVAST-M DFS, EO 18071 and COMBI-AD RFS may be similar or different to each other including known or unknown differences in populations or treatments, losses to follow up influencing censoring times, criteria defining an event (e.g., inclusion or exclusion of SPM), monitoring frequency and local practice in different countries. A potential

advantage of AVAST-M over EO 18071 is that the trial was conducted in UK patients, while EO 18071 was an international study (99 centers in 19 countries in 3 continents) likely to have recruited few UK patients (COMBI-AD enrolled only [redacted] UK placebo arm patients). In the ERG's opinion extrapolation using AVAST-M would be more likely to be generalizable to the UK. Furthermore, AVAST-M is a larger (1347 participants) and longer study (to 8 years); the control arm received "observation" and would likely reflect the current UK alternative to a licenced treatment with adjuvant. The most noticeable difference between trial populations, other than BRAF status was the inclusion of 16% and 11% stage IIB and IIA patients in AVAST-M (Table 14).

Table 14: Percentages of stage III patients in three adjuvant trials

	AVAST-M		EO 18071[21]		COMBI-AD	
	observation		placebo		placebo	
IIB	109	16%	0		0	
IIC	72	11%	0		0	
IIIA	95	14%	98	20.6%	71	16%
IIIB	253	38%	182	38.2%	187	43%
IIIC	143	21%	196	41.2%	166	38%
III unknown					8	2%

ii) The ERG notes several potentially relevant differences between the COMBI-AD and EO-18071 trials. Of first importance is the fact that the studies were undertaken in different populations; all participants in COMBI-AD were BRAF+ whereas the proportion of BRAF+ in EO 18071 is unknown and probably <50%. This seems relevant in view of the CS statement that BRAF V600 mutations drive disease progression (e.g., CS Table 2). However in describing the use of EO 18071, CS states that "the exact prognostic role of BRAF V600 mutations in melanoma remains uncertain" (pg. 75), and "in the absence of evidence to suggest that there would be a difference in outcomes for patients in the adjuvant setting, it is assumed that outcomes in the EORTC 18071 trial would be similar irrespective of BRAF status". To the ERG it seems odd to justify an assumption on the basis of no evidence. Similarly to the ERG it would appear odd to have conducted an adjuvant trial in BRAF+ patients (i.e. COMBI-AD) under an assumption that BRAF status has no direct relevance for recurrence outcomes. Furthermore, if this assumption is accepted then the ERG would expect other adjuvant trials with unknown BRAF status to be explored for extrapolation. Secondly the ERG notes the CS remarks (pg. 21) that due to its

significant toxicity ipilimumab has an uncertain risk-benefit ratio; this suggests that withdrawals and incomplete follow up patterns may likely differ between COMBO-AD and EO 18071 and exert a curve-changing influence on RFS analysis.

iii) The company used clinical expert advice in deciding the most suitable parametric model of the EO 18071 trial PBO arm to use for extrapolation. According to Jackson et al. 2016[33] the elicitation of expert opinion on beliefs about survival extrapolation is rare in the use of external data (no example was found in the Jackson study). Details of how expert opinion(s) were elicited by the company were not provided.[25] Although the use of external data is sometimes used in extrapolation of survival analyses[33] the ERG find this particular application unusual in that usually large population surveys or registries are the source for external data rather than another small scale RCT. Jackson et al. discuss the potential and the challenges of such procedures.[33]

A further alternative to the RFS extrapolation undertaken by the company is to employ the CR analysis of RFS described above rather than the company's KM analysis shown in CS Figure 13. Figure 7 summarises two similar extrapolations of this type undertaken by the ERG. Both employ the company's generalised F model of the placebo arm of the EO 18071 trial; in one, the extrapolation follows from week 41 of the CR non-parametric plot and in the other, from week 41 of flexible parametric fits to the CR analysis.

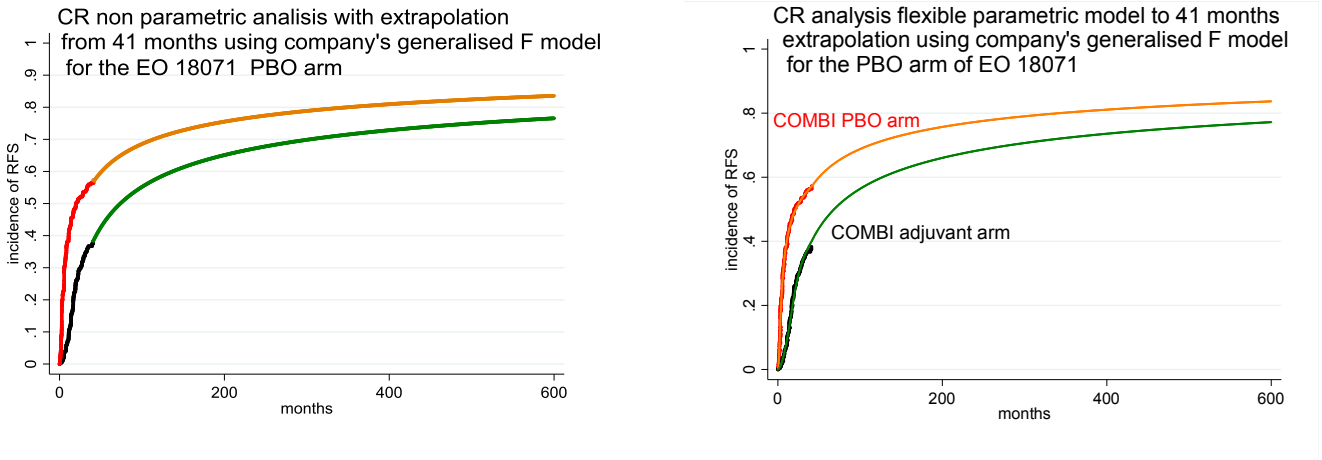


Figure 7: CR analysis of RFS; extrapolations to 50 years

It should be noted that the extrapolations indicated in Figure 7 deliver considerably less advantage of adjuvant over placebo than the company's extrapolation depicted in CS Figure 22 B.

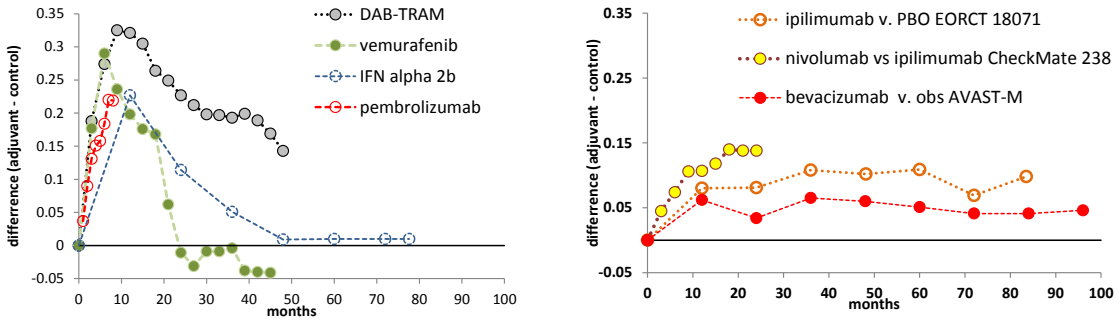
In summary, the company has introduced multiple options for modelling RFS and its extension to a life time horizon. The variety of possible options includes basing models on KM or CR analyses, employing COMBI-AD observed data only or combining this with an external source or external sources and splitting such mixed sources at various time zones. In the foregoing section the ERG has explored a few options not addressed in the CS. In the following cost effectiveness section many options are examined and their economic impact is assessed.

4.7 Overview of clinical effectiveness

4.7.1 Delay in recurrence and or cure from recurrence

The ERG interpret "cure from recurrence" to mean a permanent delay in recurrence. Adjuvant treatment may have no effect on recurrence, it may only temporarily delay it, it may temporarily delay it in some patients and permanently delay in others (i.e. cure), or it may only cure in selected patients.

Unfortunately, ascertaining the pattern of recurrence is not well served by the composite outcome (RFS) employed in most adjuvant trials. Figure 8 looks at the RFS difference between adjuvant and control versus time in a number of adjuvant trials.



Sources: Vemurafenib, Maio et al. 2018[34];IFN alpha 2b, Cameron et al. 2001[35]; pembrolizumab, Eggermont et al. 2018[36]; CheckMate 238, Weber J et al. 2017[37]; AVAST-M Corrie et al. 2018[23, 24]; EORCT 18071, Eggermont et al. 2016[21].

Figure 8: Difference between aduvant and controls RFS vs. Time in adjuvant trials

Two fairly distinct patterns are discernible: a] a large initial increase that decays to zero during the trial follow up (vemurafenib[34] and IFN alpha 2b trials[35]) indicative of only a delay in

recurrence, or the trajectory appears to be heading to zero but follow up is too short to know for sure (DAB-TRAM), or follow up is insufficient to see a pattern[36]; b] a less impressive initial increase which appears to be sustained for appreciable follow up (EORCT 18071) and AVAST-M, or for which follow up was too short to know about longer term recurrence

[redacted]

[redacted]. There was insufficient time for the ERG to extend this analysis to further melanoma adjuvant trials.

4.8 Conclusions of the clinical effectiveness section

The company present the results from a single placebo-controlled RCT (COMBI-AD) investigating the effectiveness of daily oral adjuvant therapy combining dabrafenib and trametinib in the treatment of patients after complete surgical resection of BRAF + melanoma. No other comparable adjuvant studies in this population have been identified. The COMBI-AD trial is directly relevant to the decision problem. The study demonstrated a clear and substantial delay in RFS resulting from combination therapy. There was also an apparent effect benefitting OS; the data were rather immature for both outcomes (median follow-up 2.8 years) but especially for OS. There was some numerical and timing imbalance between study arms in patients ending follow up before study cut off that may influence effectiveness estimates. Competing risk analysis suggests that the company's KM analysis may over estimate adjuvant benefit (by approximately 11% and 21% for RFS and OS, respectively). Because follow up was insufficient the major uncertainty is whether the therapy merely delays disease recurrence, so that recurrence incidence in the intervention arm eventually catches up that in the control arm, or whether a proportion of patients receiving adjuvant do not experience recurrence that they would have done had they only received surveillance (a proportion are "cured"). The ERG is concerned that the company has turned to data from a study in a different population (undetermined BRAF status) in attempting to model clinical effectiveness beyond that observed in COMBI-AD. The ERG has some reservations about the company's approach to treatment safety and associated costs of adverse events and monitoring, and consider these may have been somewhat underestimated.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost-effectiveness evidence

The CS (Appendices G, H and I) provides detailed reports of three systematic reviews (SRs), aimed at identifying; a) any relevant cost-effectiveness studies previously published in patients (aged over 13 years) with advanced stage III or resectable stage IV melanoma, as part of an SR with a wider scope than the decision problem for this submission; b) relevant HRQoL data in patients with stage III melanoma, following complete resection; c) cost and resource use data associated with the treatment of stage III melanoma, following complete resection.

5.1.1 Search strategy

Broad searches combining terms for cost-effectiveness and melanoma were undertaken between 2nd November and 6th November 2017. A range of sources were searched, the majority of which were appropriate. The searches incorporated a suitable combination of search terms relevant to the broad scope of this wider SR, which included several other interventions/comparators. Additional searches were undertaken to improve the comprehensiveness of the search.

A separate search for HRQoL studies was conducted on 2nd November 2017. A range of sources were searched, the majority of which again were appropriate. Search terms combined melanoma terms with a number of general HRQoL terms and terms for specific utility measures, aimed at achieving a reasonable balance between sensitivity and precision.

A third search for cost and resource use, restricted to literature published after 1990, was undertaken between 2nd and 3rd November 2017. A range of sources were searched, the majority of which were appropriate. The database searches include a range of terms for resource use, but terms for cost are not included. This may have resulted in some cost studies being missed. Additional searches were undertaken to improve the comprehensiveness of the search.

5.1.2 Inclusion criteria

Eligibility criteria for study selection are provided in CS appendix G Table G.3.1. (cost-effectiveness SR), CS appendix H Table H.3.1 (HRQoL SR) and CS appendix I Table I.3.1 (cost and resource use SR).

5.1.3 Included studies

No studies were included in the cost-effectiveness systematic review, one study (reported in two publications by Middleton et al.)[38, 39] was included in the HRQoL systematic review and three studies (reported in six publications) were included in the cost and resource use systematic review.[40-45] Lists of studies excluded after full-text review and reasons for exclusion are provided.

5.1.4 Conclusions

The company correctly identifies a the quality of life studies by Middleton et al, funded by Bristol-Myers Squibb, which used standard gamble among 155 members of the UK and Australian general public to estimate quality of life values for patients with resected high risk melanoma. This resulted in means of 0.890 for adjuvant therapy with no toxicities, 0.855 for no treatment and 0.620 for recurrence. Interestingly, the values for the UK subgroup were consistently lower then those of the Australian subgroup, with 0.840 for adjuvant therapy with no toxicities, 0.837 for no treatment and 0.581 for recurrence. The values for recurrence are considerably lower than those estimated by the company from COMBI-AD EQ-5D-3L data.

The main issue is that the exclusion criteria are too severe. They exclude a number of studies which could provide context, and cause all the previous NICE assessments' quality of life values to be excluded as well as the results of those of Batty et al (2012).[46]

Batty et al[a] (2012) in an ESMO poster presentation analyse SF-36 data from the MDX010-20 trial of ipilumab for advanced melanoma, 599 patients with 1,157 SF-36 observations.[46] They derive quality of life values by applying the SF-6D algorithm (see Table 15). The authors compare predicting quality of life values by progression status with time to death. The mean quality of life values of 0.640 for pre-progression and 0.619 for post progression are compared with the 0.80 and 0.52 of Beusterien et al.[47] But time to death showed a lower Root Mean Square Error (0.450 vs 0.118) and higher R^2 (0.389 vs 0.080).

[a] From BresMed, which the ERG assumes means that the study was supported by Bristol Myers Squibb

Table 15: Batty et al [46] quality of life values

Survival (days)	N	SF-6D QoL	SD
≥ 180	418	0.655	0.108
120-179	96	0.608	0.107
90-119	61	0.598	0.112
60-89	59	0.572	0.098
30-59	68	0.538	0.101
<30	34	0.505	0.135

The authors conclude that modelling survival rather than progression status may result in more accurate QALY estimates. This may suggest that the company should have explored time to death in its analyses of COMBI-AD EQ-5D data and/or structured the model to consider OS.

The previous NICE assessments are in unresectable or metastatic melanoma. The company model does not really include this as a health state. The CS for the STA of dabrafenib for treating unresectable advanced of metastatic BRAF V600+ve melanoma [TA321][48] estimated quality of life values from the BREAK-3 trial EQ-5D data [8] of 0.767 for progression free survival and 0.677 for post progression survival. These are reported as being "*similar*" to the values reported in Beusterien et al.,[47] which have apparently informed previous NICE appraisals.

The pembrolizumab STAs (Table 16), TA357[49] and TA366[50] found time to death to be a better predictor of EQ-5D quality of life than progression and the ERG also preferred this method of modelling, but retained a coefficient for progression. This could argue for explicitly modelling post-DR survival to take this into account. It could also argue for post-LR survival taking this into account.

Table 16: Quality of life by time to death: Pembrolizumab STAs

Indication	Unresectable stage III or stage IV	
Patients	Mixture	BRAF +ve
Time to death	Keynote-002	Keynote-006
>360		0.82
270-360	0.77	0.71
180-270		0.66
90-180	0.62	0.66
30-90	0.52	0.57
<30	0.42	0.33
PFS		0.80
PPS		0.70

The values from the pembrolizumab STAs appear to be broadly in line with those of Batty et al, though with quality of life declining more steeply during the last month of survival.

Some STAs such as that of dabrafenib+trametinib for BRAF+ve unresectable or metastatic melanoma [TA396][51] have included terminal care costs, the terminal care cost for TA396 being £7,287. Again, this could argue for explicitly modelling post-DR survival to take this more explicitly into account. It could also argue for post-LR survival taking this into account in the current modelling. But the company base case estimates that only a small percentage of patients die from the post-LR health state and it seems unlikely to much affect results.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Summarise and critique the cost effectiveness evidence submitted by the company (headings 5.2.1 to 5.2.11 are suggested headings). It is noted that the ERG may prefer NOT to combine the summary and critique of the submitted economic evidence and instead report summary and critique sections separately.

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The model compares adjuvant dabrafenib + trametinib treatment with no adjuvant treatment.
Patient group	As per NICE scope. "*People with completely resected, stage III melanoma with BRAF V600 positive mutations*".	In part. The 1st 50 months of the company base case are based upon data from the main trial, COMBI-AD, which is specific to the patient group of the scope. After 50 months the company base case extrapolates using data from the placebo arm of the EORTC 18071 trial of adjuvant ipilimumab after stage III rescection.[21] This is not specific to BRAF+ve patients.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes. Cost-utility.
Time horizon	Sufficient to capture differences in costs and outcomes	50 years. This is effectively a lifetime horizon given the COMBI-AD median baseline age of 50 and that general mortality risks are also applied in the model.
Synthesis of evidence on outcomes	Systematic review	No. COMBI-AD provides direct head-to-head evidence.
Outcome measure	Quality adjusted life years	Yes.

Health states for QALY	Described using a standardised and validated instrument	The COMBI-AD quality of life data is EQ-5D-3L.
Benefit valuation	Time-trade off or standard gamble	Unknown. The company only states that COMBI-AD EQ-5D-3L is consistent with the NICE reference case, but does not state whether it is valued using the usual UK social tariff.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Unknown. The company only states that COMBI-AD EQ-5D-3L is consistent with the NICE reference case, but does not state whether it is valued using the usual UK social tariff.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes. An issue arises due to the company model not modelling patients when they progress to stage IV. It applies the total cost and QALYs from previous NICE assessments of stage IV treatments. But NICE assesments of treatments for stage IV have typically judged end of life to apply. As a consequence, despite being approved by NICE as a valuable treatment for stage IV, the stage IV treatments in the current model are really rather bad unless valued at the end of life threshold of £50k/QALY.
Probabilistic modelling	Probabilistic modelling	Yes.

Sensitivity analysis		A range of univariate sensitivity analyses and scenario analyses are presented by the company.

5.2.2 Model structure

The company employs a cohort markov model (see Figure 9) with a 1 month cycles and the following health states:

- All patients start in Recurrence Free Survival (RFS), events for which are either loco-regional recurrence (LR), distant recurrence (DR) or death. Treatments costs, monitoring costs, quality of life values and the like are applied to patients in the RFS health state for each cycle of the model.
- Those who have an LR move into the LR health state, with their Recurrence Free Survival (LR-RFS) then being modelled, the events for which are also either another loco-regional recurrence (LR), a distant recurrence (DR) or death. Treatments costs, monitoring costs, quality of life values and the like are applied to patients experiencing an LR recurrence event for each cycle of the model.
- Those who have a DR, whether this is an RFS event or a LR-RFS event, are not really modelled. These patients simply have a total cost and a total QALY applied to them, derived from TA366 and TA396. The DR health state is an absorbing health state, much like death.

The model structure is consequently unusual because the cost effectiveness estimate is not reliant upon any modelled OS, despite it being anticipated that OS will differ between the arms.

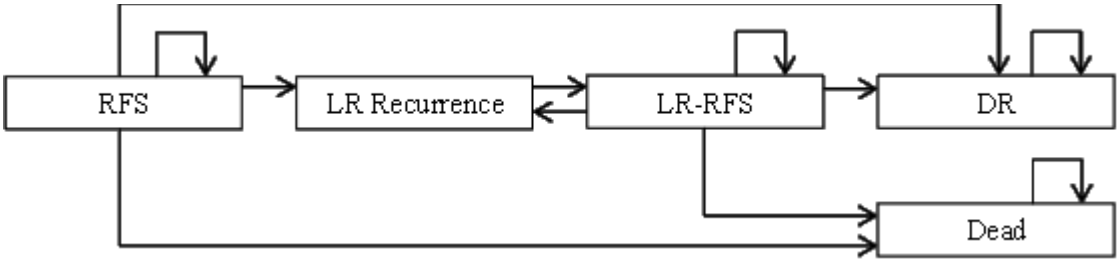


Figure 9: Model structure

The model is segmented into two main periods:

- Segment 1: the 1st 50 months, corresponding to the maximum follow-up during COMBI-AD
- Segment 2: subsequent to the 1st 50 months

Typically the curve that is applied during Segment 1 of the model differs from the curve that is applied in Segment 2 of the model, as does the splitting of events into LR, DR and Deaths. Note that the model permits the cut-point between Segment 1 and Segment 2 to be at any point. It is not limited to being at 50 months.

For RFS:

- Segment 1:
  - Arm specific RFS curves derived from COMBI-AD Kaplan Meier data: Log-likelihood-U-Cure
  - Arm specific splitting of events into LR, DR and Death from COMBI-AD data of 34:64:1.9 for dabrafenib+trametinib and 44:55:0.4 for placebo.
- Segment 2:
  - Common to both arms an RFS curve derived from the placebo arm of EORTC 18071[21] reconstructed Kaplan Meier data: Generalised-F curve
  - Common to both arms splitting of events into LR, DR and Death from the placebo arm of EORTC 18071[21] of 35:62:3.

Given the model structure chosen by the company a problem arises. COMBI-AD only recorded 1st recurrences so cannot provide a post-LR RFS curve.

- For Segment 1 the company assumes that the shape of the LR-RFS curve will be the same as that of the placebo RFS curve, but with a hazard ratio applied to best fit the post-LR modelled survival over 50 months with the COMBI-AD post-LR OS Kaplan Meier data. The hazard ratio of 2.53 is derived in the model by:
  - setting all patients to start in the LR-RFS health state,
  - assuming that LR-RFS curve follows the COMBI-AD placebo RFS Kaplan Meier curve, qualified by the hazard ratio,
  - assuming that the LR-RFS events split between LR, DR and deaths is 32:63:5 based upon the White et al[52] study of 2,505 patients with melanoma with resected regional lymph node metastasis,
  - assuming that the DR-OS curve follows the COMBI-AD placebo DR-OS Kaplan Meier curve, and
  - varying the hazard ratio to minimise the sum of squares difference between the modelled LR-OS and the COMBI-AD placebo LR-OS Kaplan Meier curve.

For the post-LR RFS curve this results in:

- Segment 1:
  - Common to both arms the same curve as the placebo RFS Segment 1 curve derived from COMBI-AD Kaplan Meier data with the probability of events increased by a 2.53 hazard ratio: Log-likelihood-U-Cure
  - Common to both arms splitting of events into LR, DR and Death based upon the White et al.[52] study of 32:63:5.
- Segment 2:
  - Common to both arms the same curve as the RFS Segment 2 curve derived from placebo arm of EORTC 18071[21] reconstructed Kaplan Meier data: Generalised-F curve
  - Common to both arms splitting of events into LR, DR and Death based upon the White et al. study[52] of 32:63:5.

5.2.3 Population

The model uses a number of data sources (Table ***17***) for the different elements of the model. Only the parameterised RFS curves that are applied for the 1st 50 months of the model can be unambiguously described as applying to BRAF V600+ve patients who when at stage III had their disease resected.

Table 17: Population data sources within the model

	Segment 1: 1st 50 months	Segment 2: After the 1st 50 months
RFS	COMBI-AD arm specific RFS parameterised curves. COMBI-AD arm specific balance between LR, DR and deaths events.	EORTC 18071[21] placebo arm parameterised curve. EORTC 18071[21] placebo arm balance between LR, DR and deaths events, common to both arms.
LR	COMBI-AD placebo arm RFS parameterised curve. US registry data split between LR, DR and deaths events, common to both arms.	EORTC 18071[21] placebo arm parameterised curve. US registry data split between LR, DR and deaths events, common to both arms.
DR	Total costs and QALYs for DR are applied to DR incident patients. These are drawn from TA366: Pembrolizumab for advanced melanoma not previously treated with ipilimumab, and	

	TA396: Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma. The DR OS curves do not affect the ICER.

5.2.4 Interventions and comparators

The company compares adjuvant treatment of dabrafenib+trametinib with no adjuvant treatment.

5.2.5 Perspective, time horizon and discounting

The time horizon is 50 years, which with the application of general population mortality risks within the model and a baseline age of 50 years is effectively a lifetime horizon.

The perspective and discounting are as per the NICE methods guide.

5.2.6 Treatment effectiveness and extrapolation

RFS events

As summarised above, the company applies parameterised curves from COMBI-AD for the 1st 50 months of the model, then applies common risks to each arm derived from the placebo arm of the EORTC trial. The split between events during the 1st 50 months is based upon arm specific rates in the COMBI-AD trial, 34:64:1.9 for dabrafenib+trametinib and 44:55:0.4 for placebo, with a common split thereafter drawn from EORTC 18071[21] data of 35:62:3. The raw curves are as below in Figure 10.

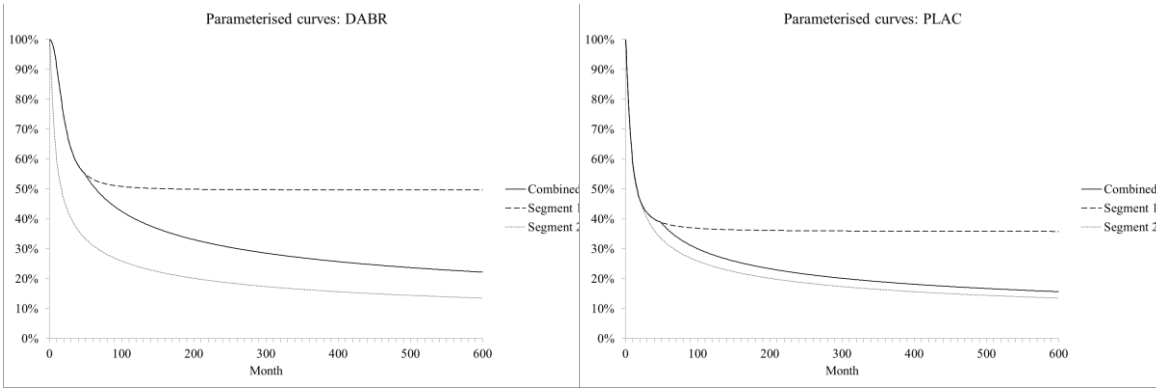


Figure 10: RFS curves for Segment 1 and Segment 2, and their combination

Due to falling risks through time, the company overlays general population mortality risks onto the above which causes the dabrafenib+trametinib RFS curve and the placebo RFS curve (Figure 11) to start to converge more noticeably from around month 200 and to fall to zero by month 600.

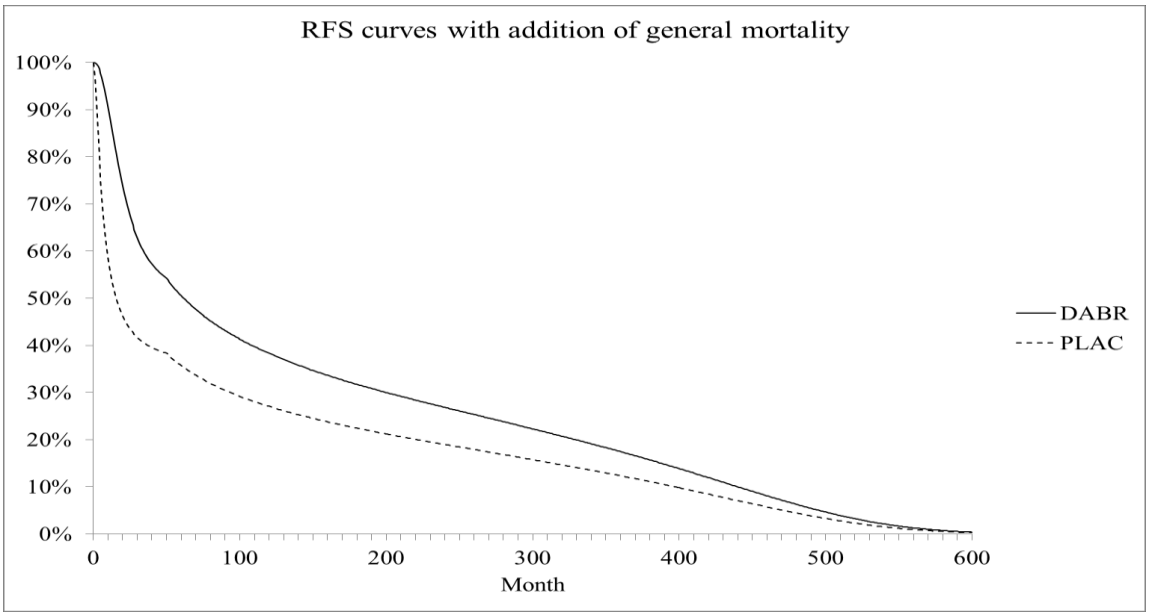


Figure 11: RFS curves with addition of general mortality

Post-LR events

As summarised above, the company assumes that the post-LR RFS curve to 50 months is the same shape as placebo RFS curve derived from COMBI-AD but conditioned by a hazard ratio of 2.53. Extrapolation from 50 months applies the same common risks to each arm derived from the placebo arm of the EORTC trial as are applied for RFS. The only difference is that the split between LR, DR and death for post-LR is 32:63:5. The raw curves are presented in Figure 12.

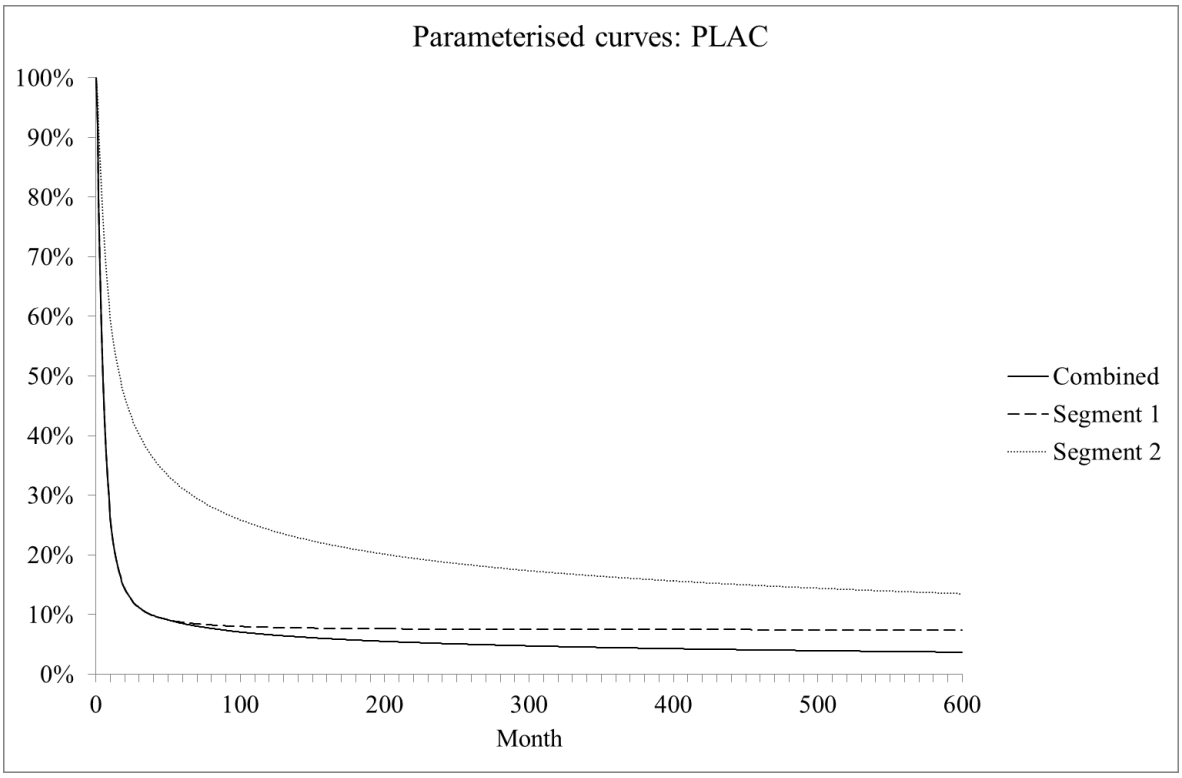


Figure 12: Post-LR curves for Segment 1 and Segment 2, and their combination

Again, due to falling risks through time the company overlays general population mortality risks onto the above. But this is less important for the post-LR RFS curve due to the vast majority of patients being modelled as progressing within 5 years.

Post-DR

Post DR is not modelled but is rather derived from the model estimates reported for TA366: Pembrolizumab for advanced melanoma not previously treated with ipilimumab, and TA396: Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (Table 18). These are combined [redacted] based upon the proportion of 1st line treatments post DR in COMBI-AD.

Table 18: Post DR Costs and QALYs

	Weight	QALYs	Costs
TA366	[redacted]	2.96	£83k
TA396	[redacted]	[redacted]	[redacted]
Weighted		3.23	£143k

An additional £519 treatment initiation cost is applied, based upon a requirement for an OP appointment plus a CT scan, split between CT and PET-CT.

5.2.7 Health related quality of life

The company analyses the COMBI-AD EQ-5D-3L data using a generalised estimation model (GEE) with an identity link function, normal error term distribution, and exchangeable correlation structure with model covariates for baseline EQ-5D utility index value and health state at assessment (Table 19), with the health states being:

- RFS while receiving adjuvant dabrafenib+trametinib,
- RFS off treatment, this also including receipt of adjuvant placebo and treated as the reference health state for the analysis,
- LR, and
- DR.

This resulted in the following coefficients, and quality of life values for the model when applied to a pooled baseline value of 0.863.

Table 19: COMBI-AD EQ-5D-3L analysis

	Coef.	p-value	QoL
Intercept	0.3729	<0.0001	..
Baseline EQ-5D	0.5753	<0.0001	..
RFS on DABR	-0.0154	0.007	0.854
RFS other	..	..	0.869
LR	-0.0336	0.009	0.836
DR	-0.0773	<0.0001	0.792

In the light of previous ERG reports in the area, the company further weights the quality of life values by age based upon the regression of Ara et al.[53]

There is no additional allowance for adverse events as the company suggests that their effect will have been picked up in the COMBI-AD EQ-5D-3L data. There is some evidence for this in the lower value for the RFS on dabratenib+trametinib health state.

5.2.8 Resources and costs

Adjuvant drug and prescribing costs

The mean drug use is based upon the minimum number of whole packs of dabrafenib and the minimum number of whole packs of trametinib that could have been prescribed that are consistent with each COMBI-AD patient's cumulative dose. This results in estimated means of [redacted] packs of dabrafenib and [redacted] packs of trametinib.

Prescribing costs of £13.90 are applied to each pack, based upon an 12 minutes of pharmacist time. Given the total costs in the dabrafenib+trametinib arm and the net costs relative to placebo, results are not sensitive to prescribing costs.

Monitoring costs

Monitoring is based upon a consensus among UK melanoma clinicians as reported in Larkin et al.[54] with CT scans being split between CT and PET-CT scans. Additional outpatients visits and cardiac monitoring are applied to those receiving dabrafenib+trametinib treatment. Those who have ceased dabrafenib+trametinib treatment are assumed to have the same monitoring requirement as placebo. Unit costs for each element are drawn from 2016-17 NHS reference costs (see Table 20).[55]

Table 20: Annual monitoring, annual costs and monthly costs

	Yr1						
	DABR		PLAC				
	OnTx	OffTx	..	Yrs 2&3	Yrs4&5	Yrs6+	Cost
OP visit	12	4	4	4	2	1	£161
CT scan	1	1	1	1	0.5	..	£121
PET-CT scan	1	1	1	1	0.5	..	£595
MRI brain	2	2	2	2	1	..	£142
ECHO	2	..	..	..	..	..	£70
MUGA	2	..	..	..	..	..	£294
Annual cost	£3,663	£1,645	£1,645	£1,645	£822	£161	
Monthly cost	£305	£137	£137	£137	£69	£13	

SAE costs

Only SAEs that resulted in hospitalisations were costed (Table 21). These were split into pyrexia hospitalisations and all other SAE hospitalisations, these being costed using NHS reference costs of an elective inpatient stay for fever of unknown origin (WJ07A, WJ07B, WH07C, WJ07D) for pyrexia and the mean elective inpatient stay for the other SAE hospitalisations.

Table 21: SAE hospitalisation costs: elective IP costs

	DABR	PLAC	Cost
Pyrexia	[redacted]	[redacted]	£1,548
Other SAEs	[redacted]	[redacted]	£3,789
Total cost	£693	£199	

Post-LR costs

The company applies one off treatment costs for incident LR patients, with patients requiring an OP visit and a CT scan. Clinical opinion indicates that 90% will be resected which is costed at £1,816 based upon NHS reference costs: Elective Inpatient HRG JC42A Intermediate Skin Procedures. The company states that the remaining 10% are assumed to be treated with either pembrolizumab, 70%, or dabrafenib+trametinib, 30%, at an average medication, administration and SAE cost of £68,887. The ERG has not been able to cross check this latter cost, but results are relatively insensitive to the Post-LR costs, with higher costs slightly improving the cost effectiveness estimate.

5.2.9 Cost effectiveness results

The company base case estimates the following disaggregate undiscounted life years, recurrences and discounted QALYs (Table 22).

Table 22: Company deterministic base case patient outcome estimates

	DABR	PLAC	Net
Life years (undisc.)			
RFS	[redacted]	8.84	[redacted]
LR	[redacted]	1.12	[redacted]
DR	[redacted]	5.04	[redacted]
Total	[redacted]	15.00	[redacted]
Recurrences			
LR	[redacted]	0.51	[redacted]
DR	[redacted]	0.75	[redacted]
Total	[redacted]	1.27	[redacted]
QALYs (disc.)			
RFS	[redacted]	4.87	[redacted]
LR	[redacted]	0.61	[redacted]
DR	[redacted]	2.17	[redacted]
Total	[redacted]	7.66	[redacted]

The main survival gains occur in RFS. While the dabrafenib+trametinib arm is estimated to result in less time spent in DR it should be recalled that this is largely an artefact of the model and does not affect the total discounted QALYs. As would be expected given model inputs the total number of both types of recurrence are lower in the dabrafenib+trametinib arm, though in both arms on average all patients experience at least one recurrence. Due to fewer recurrences in the dabrafenib+trametinib arm, with these recurrences also tending to occur later, the total QALYs associated with LR and DR are lower in the dabrafenib+trametinib arm than in the placebo arm. But the greater amount of time spent in RFS in the dabrafenib+trametinib arm results in a reasonably large overall total QALY gain from dabrafenib+trametinib compared to placebo.
The company base case estimates the following disaggregate discounted costs, see Table 23.

Table 23: Company deterministic base case cost estimates

	DABR	PLAC	Net
RFS			
Meds + Admin	[redacted]	£0	[redacted]
FU+Monitoring	[redacted]	£3,456	[redacted]
LR			
Recurrence	[redacted]	£4,056	[redacted]
FU+Monitoring	[redacted]	£714	[redacted]
DR			
Recurrence	[redacted]	£349	[redacted]
One-Off costs	[redacted]	£95,890	[redacted]
AEs (mainly RFS)	[redacted]	£289	[redacted]
Total	[redacted]	£104,755	[redacted]

The costs of medication and administration for RFS in the dabrafenib+trametinib arm are substantial. But there are reasonably large cost offsets in the costs of DR.

The company base case deterministic estimates result in an ICER of £20,039 per QALY, as presented in Table 24.

Table 24: Company deterministic base case cost estimates

	LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.00	7.66	£104,755	
Net	[redacted]	[redacted]	[redacted]	£20,039

The probabilistic modelling results are in line with those of the deterministic analysis, with a central ICER of £20,037 per QALY.

[redacted]

Figure 13: [redacted]

5.2.10 Sensitivity analyses

The company provides a range of univariate sensitivity analyses. These vary the variable concerned by ±25% of the base case value. This is with the exception of the sensitivity analysis for the QoL value in LR which varies it by the 95% CI. The variables explored cover:

- The HR for RFS after 50 months, varied by arm, base case HR=1.00 (0.75-1.25) for both arms
- The proportion of RFS events that are deaths up to 50 months, varied by arm, base case 1.9% (1.4%-2.3%) for DABR and 0.4% (0.3%-0.5%) for PLAC
- The proportion of RFS events that are deaths after 50 months, varied by arm, base case 3.1% (2.3%-3.9%) for both arms. The HR applied to RFS events for LR vs RFS, base case 2.53 (1.90-3.16) for both arms
- The QoL for LR, base case 0.836 (0.810-0.862)
- The QoL for RFS on treatment compared to RFS off treatment, base case 0.854 (0.850-0.858) for DABR
- The QoL for RFS off treatment compared to perfect health, varied by arm, base case 0.854 (0.821-0.887) for DABR and 0.869 (0.837-0.902) for PLAC
- The total discounted cost of DR, [redacted] for those receiving targetted thereapy and £83k (£62k-£104k) for those receiving immunotherapy

- The total discounted QALYs of DR, base case [redacted] for those receiving targetted thereapy and base case 3.0 (2.2-3.7) for those receiving immunotherapy
- The unit costs of adverse events of £3,781 (£2,836-£4,726) and £1,548 (£1,161-£1,935)
- The various input unit costs.

The company reports the results for the 10 variables found to have the largest effect upon the ICER, presented in Table 25. Where the variables are varied by arm the submission does not state whether the sensitivity analysis is a univariate sensitivity analysis, or multivariate varying both arms simultaneously. The tornado diagram for the following sensitivity analyses is presented as figure 30 (pg. 120) of CS Document B.

Table 25: Company sensitivity analyses: ICERs

	ICER	
Variable	Lower	Higher
Expected discounted cost of DR	£22,574	£17,504
Hazard for RFS after 50 months	£17,825	£22,239
HR applied to RFS events for LR vs RFS	£22,204	£18,882
Expected discounted QALYs after DR	£18,951	£21,259
Disutility for RFS on treatment vs off treatment	£18,991	£21,209
LR as a % of all RFS events	£19,331	£20,790
Follow-up and monitoring costs	£19,562	£20,516
Acute treatment of LR recurrence costs	£20,288	£19,789
Deaths as a % of all RFS events	£20,141	£19,936
Utility value in LR	£19,938	£20,140

The company provides a range of scenario analyses including:

- Alternative time horizons, which if reduced from the base case 50 years to 20 years worsens the ICER from £20,039 per QALY to £24,684 per QALY.
- Using the COMBI-AD Kaplan Meier curves for RFS to 50 months rather than the log-logistic worsens the ICER from £20,039 per QALY to £22,651 per QALY.
- The curves that are applied:
    - Varying the cut-off point for the 1st segment of the RFS curve between around 40 months to 52 months compared to a base case of 50 months, with earlier cut-offs slightly improving the ICER.

  - Alertnative parametric forms for the EORTC 18071[21] data as applied for the 2nd segment of the RFS curve from 50 months improves the ICER by a reasonable margin in some cases, to between £12,748 per QALY and £19,203 per QALY, as outlined in greater detail in table 52 (pg. 123) of Document B of the CS. The Generalised-F distribution of the base case is the most pessimistic of those presented by the company.
  - Extrapolating RFS using COMBI-AD parameterised curves rather than the EORTC 18071[21] Generalised-F of the base case improves the ICER by a reasonable margin in some cases, to between £3,464 per QALY and £13,860 per QALY, as outlined in greater detail in table 53 (pg. 124) of Document B of the submission. The company estimated a total of 39 curves, but the electronic model and scenario analyses only apply 17 of these due to the company judging 22 of these to provide implausible extrapolations.
  - Varying the calibrating hazard ratio for death from LR compared to the RFS placebo from the base case value of 2.53 to between 1.5 and 4.5 revised the ICER from £20,039 per QALY to between £24,548 per QALY and £17,822 per QALY.
- The balance between types of events that is assumed
  - Assuming different balances between the RFS events of death, LR and DR derived from COMBI-AD rather than EORTC 18071[21] during extrapolation beyond 50 months has minimal impact upon results. Note that in common with the base case, these scenario analyses appear to assume the same distribution between the events for both arms.
  - Assuming different balances between the LR events of death, LR and DR has minimal impact upon results. Note that these scenario analyses also recalibrated the hazzrd ratio for death from LR compared to the RFS placebo so that the LR OS matched that of the COMBI-AD placebo post LR OS.
  - Assuming patients cannot experience a 2nd LR has minimal effect upon the ICER.
- Assuming the same quality of life for LR as RFS has minimal impact upon the ICER, as does assuming there is no treatment related decrement. Not applying an age related decrement improves the ICER from £20,039 per QALY to £18,767 per QALY.
- Assuming no pack wastage for dabrafenib or for trametinib slightly improves the ICER from £20,039 per QALY to £19,253 per QALY

The company reports that the COMBI-AD trial showed a consistent treatment effect across all pre-specified subgroups so did not explore subgroups further in the economics.

5.2.11 Model validation and face validity check

Post-DR OS

The model applied total QALYs and costs from TA366 and TA396 for incident DR patients. As a consequence, the model does not really estimate post-DR OS. But as a cross check the company derived TA366 and TA396 model OS curves can be compared with each other and the COMBI-AD post-DR KM OS curves (Figure 14).

Figure 14: [redacted]

There may be some suggestion of the COMBI-AD post-DR OS curve for placebo lying slightly above the COMBI-AD post-DR OS curve for dabrafenib+trametinib, but Figure 23 of Document B (pg. 85) outlines that there is not a statistically significant difference between these.

The ERG has not managed to source the values for TA366, but the values for TA396 appear to be broadly in line with those for dabrafenib+trametinib in Figure 36 of the CS to TA396. There is a generally reasonably good correspondence between these curves, the curve when they are pooled [redacted] and the post-DR OS curves of COMBI-AD.

Given the above, the OS of the model that is implied when the weighted TA366 and TA396 curves are used for post-DR survival is presented.

Model outputs: OS

The company base suggests the following OS (Figure 15).

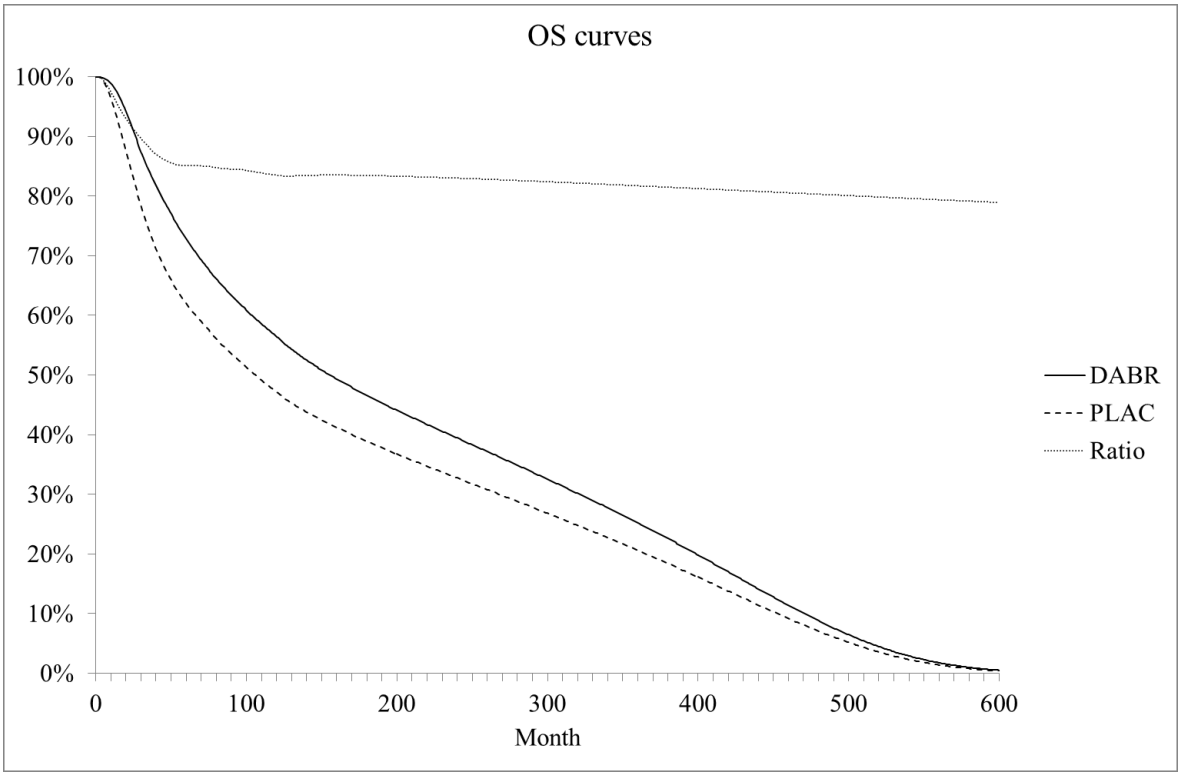


Figure 15: Model OS curves

It is estimated that a smaller proportion of placebo patients survive over the 50 year time horizon of the model compared to adjuvant dabrafenib+trametinib patients. The initial gain in OS over the course of COMBI-AD is estimated to be broadly maintained over the time horizon of the model, due to the model applying common risks thereafter.

Model outputs: Post-LR recurrences and OS

The data within White et al.[52] corresponds with that of the company model in terms of the balance between LR:DR:Death events. The company applies this balance to the post-LR health state.

Perhaps as interestingly, this data was from 2,505 patients referred to the US Duke University Melanoma Clinic between 1970 to 1998 data with "histologic confirmation of regional lymph node metastasis before clinical evidence of distant metastasis and with documentation of full lymph node dissection". White et al also noted that "Experimental adjuvant specific active immunotherapy was received by 95% of patients at some time during their course of treatment. This therapy was offered to highrisk (> 1mm thick primary or stage 2) patients rendered disease-free by surgery and consisted predominantly of vaccination with irradiated, cultured allogeneic or autologous melanoma cells". The median age of 49 years in White et al is aligned with the 50 years in COMBI-AD.

OS rates were estimated as 43% at 5 years, 35% at 10 years, 28% at 15 years, and 23% at 20 years. The authors note that for the RFS and OS curves: "Both curves appeared to plateau at approximately 20%, with no first recurrences after 21 years. Further, although greater than 90% of deaths before 10 years were attributable to melanoma or its treatment, most deaths after 15 years were unrelated to melanoma.". This may call into question the reasonableness of assuming a constant proportion of events being deaths, and indeed of modelling recurrences and melanoma deaths among those who have not had a 1st recurrence after 10-15 years.

Figure 1 of White et al provides both the RFS and the OS curve out to 25 years. Digitising this yields the following (see Figure 16), which can be compared with the corresponding output of the model for the placebo arm.

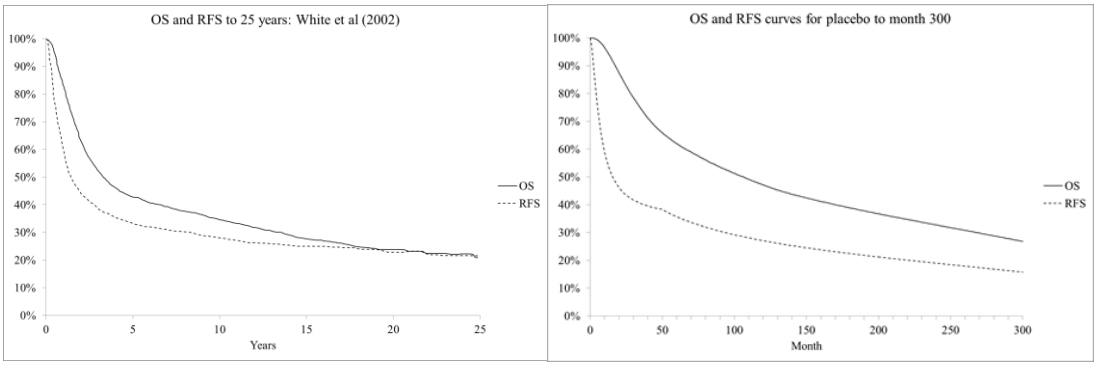


Figure 16: White et al compared to model output

The company model suggests that the OS and RFS curves do not come together, whereas the data from White et al suggests that they do. The White et al RFS curve also clearly plateaus and

converges with the OS curve between year 15 and year 20, which gives support to ERG expert opinion that RFS events are unusual after 15 years and deaths from melanoma among those who have not had a recurrence by year 15 are rare.

The difference in populations between White et al and COMBI-AD argues for caution in drawing too many conclusions for current purposes and a direct correspondence would not be anticipated. But some of the differences such as both BRAF+ve and BRAF-ve and experimental adjuvant treatment might if anything suggest that the curves of White et al might be expected to be slightly superior to the placebo arm of COMBI-AD. To the ERG it seems reasonable to expect that the placebo arm of COMBI-AD may not be all that much different from White et al, and at a minimum that there would be a similar pattern of convergence.

5.3 ERG cross check and critique

5.3.1 Base case results

Due to having to fit post-LR curves to newly incident patients in each cycle, the company model is quite complicated. The ERG has rebuilt a reasonable part of this and has not found any major errors to date. But the ERG has not fully rebuilt the company model. It will do so before the 1st AC.

5.3.2 Data Inputs: Correspondence between written submission and sources cited

Balance between types of RFS events during EORTC 18071

The company states that it extracts the following data for EORTC 18071[21] for the split between RFS events among the placebo patients N=476: RFS events N=323, local or regional events N=114 (35.3%), distant metastases events N=199 (61.6%) and deaths N=10 (3.1%).

The ERG has been able to source RFS events N=323 and local or regional events N=114 (35.3%), but distant recurrences and melanoma deaths are reported together, N=204 (63.2%), with only deaths from another cause or an unknown cause being reported separately, N=5 (1.5%).

It appears that the company may simply have assumed that the number of melanoma deaths will have been the same as the number of deaths from other causes. But this has surprisingly little

effect upon cost effectiveness estimates. Applying a rate of 1.5% worsens the company base case ICER from £20,039 per QALY to £20,082 per QALY, while a rate of 4.6% improves it to £19,995 per QALY.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

Balance between events in RFS: Minor issue

There is a minor error which causes the balance between LR:DR in RFS recurrences during Segment 2 to be based upon the balance during Segment 1. Correcting this marginally improves the company base case ICER from £20,039 per QALY to £19,725 per QALY.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Choice of RFS parameterised curves

The company rejects a number of parameterised curves on the basis of their visual fit to the Kaplan Meier curves. In the opinion of the ERG the following curves have the best visual fits, though this list could be expanded to include others with a visual fit to the dabrafenib+trametinib KM curve that is not all that much worse. The visual fit of the parameterised curves to the placebo KM curve is generally better and is good for a greater number of curves than those listed below (see Table 26). The visual fit of all the parameterised curve to the COMBI-AD Kaplan Meier curves is presented in appendix N of the submission. The table below presents the information criteria, whether the parameterised curves cross over, when this happens and the degree of cross over. It also presented the difference in the area under the dabrafenib+trametinib curve in months compared to that of the placebo curve, Δ AUC. Where the curves cross the Δ AUC is presented to the point of the curves crossing, so can be seen as synonymous with the Δ AUC if the dabrafenib+trametinib curve is assumed to follow the placebo curve from the point at which they touch.

Table 26: Parameterised forms with a good visual fit to COMBI-AD RFS data

			Cross over		Δ AUC	
	AIC	BIC	Month	Degree	50mth	Lifetime
Log-Logistic (U) Mixture	3708.5	3737.0	..	..	11.2	87.6
Log-Normal (R) Mixture	3713.8	3737.5	100	Major	11.1	13.7
Log-Logistic (R) Mixture	3716.4	3740.2	324	Minimal	11.2	18.0
Gen. Gamma (U) Mixture	3704.2	3742.2	..	..	11.1	135.2

Log-Normal (U) Mixture	3715.1	3743.7	217	Minimal	11.0	16.7
Gen. Gamma (R) Mixture	3715.8	3744.3	101	Major	11.1	13.7
Weibull (U) Mixture	3730.9	3759.4	..	..	11.0	103.8
Gompertz (U) Mixture	3748.8	3777.3	..	..	11.0	121.4
ERG flexible fit			..	..	11.0	74.3
ERG flexible fit competing risks			256	Moderate	10.7	22.9

The information criteria are not that dissimilar between most of the company curves. The log-logistic (U) mixture and the general gamma (U) mixture have the lowest. While the Weibull (U) mixture and the Gompertz (U) mixture have a good visual fit, their information criteria are that bit above the others, and given space and time constraints the ERG has not considered them further.

The ERG curves are also presented. But due to the parameterisations being fitted separately to each arm their information criteria are not comparable to the information criteria of the company curves. In the visual fits that follow, the Kaplan Meier curves are the raw data from COMBI-AD. This is with the exception of the ERG flexible fit competing risks model which is fitted to the competing risks non-parametric curves.

Given the goodness of visual fit, the difference in the areas under the curves is virtually identical at 11 months for all the parameterisations to 50 months. The company suggests that the COMBI-AD parameterised curves should only be applied to 50 months. The curves when extrapolated diverge quite noticeably.

The company rejects a number of curves due to them crossing. Whether this is a sensible reason depends upon whether the curves cross during the period of their use, and whether the degree to which they cross is major. In the list above the parameterisations that cross do so well after month 50 and Segment 1 of the model, which is the cutpoint in the company model for switching to Segment 2 and the EORTC 18071[21] data. If the model does not switch to EORTC 18071 data and extrapolates using COMBI-AD data the degree of cross over for the log-logistic (R) mixture and the lognormal (U) mixture is also minimal (see Figure 17 and Figure 18 and Figure 19 and Figure 20 and Figure 21 and Figure 22).

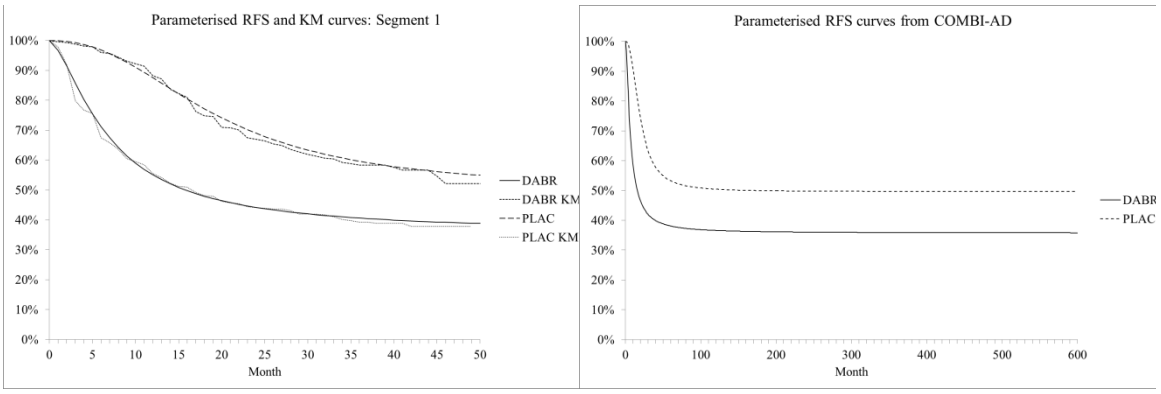


Figure 17: Company Log-Logistic (U) Mixture (Base case)

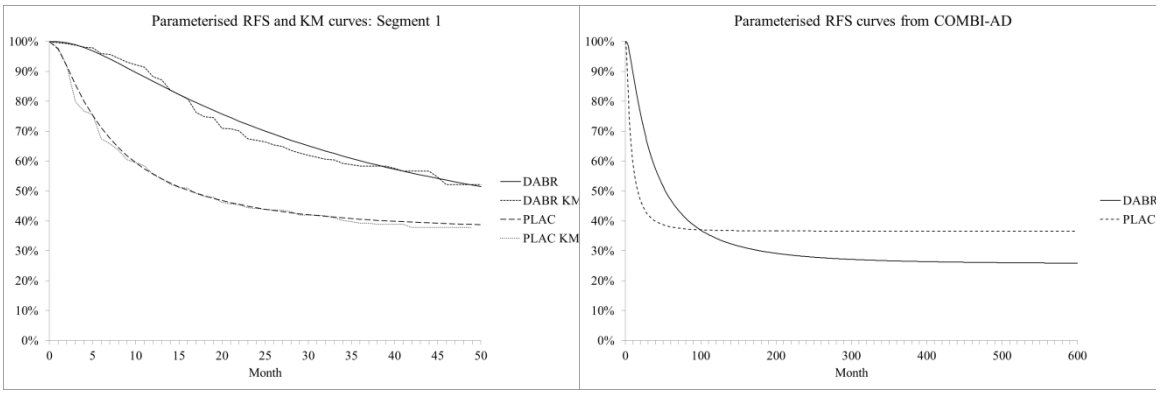


Figure 18: Company Log-Normal (R) Mixture

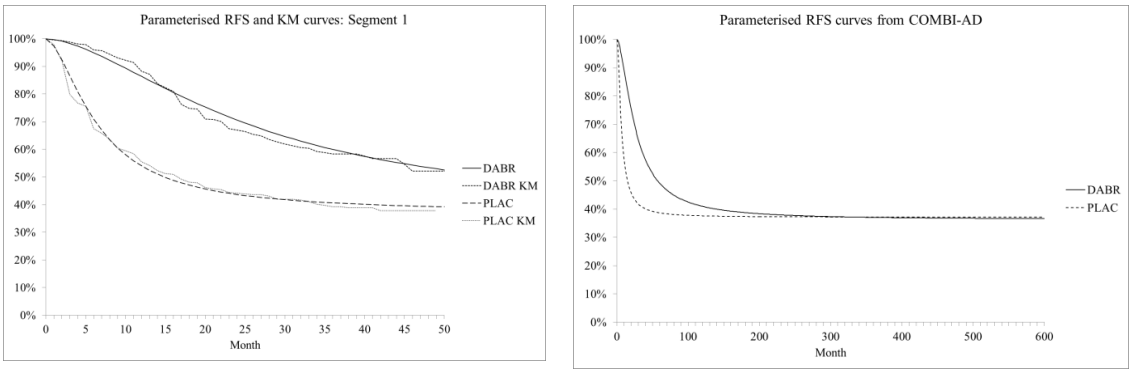


Figure 19: Company Log-Logistic (R) Mixture

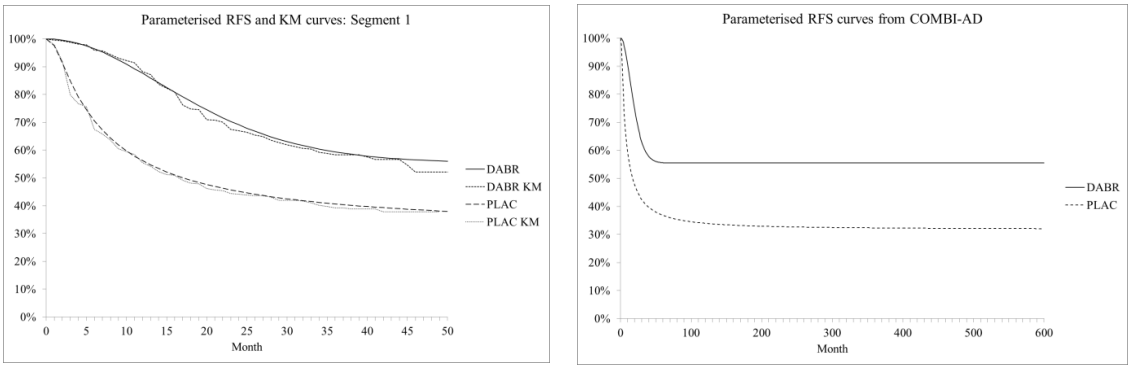


Figure 20: Company generalised gamma (U) Mixture

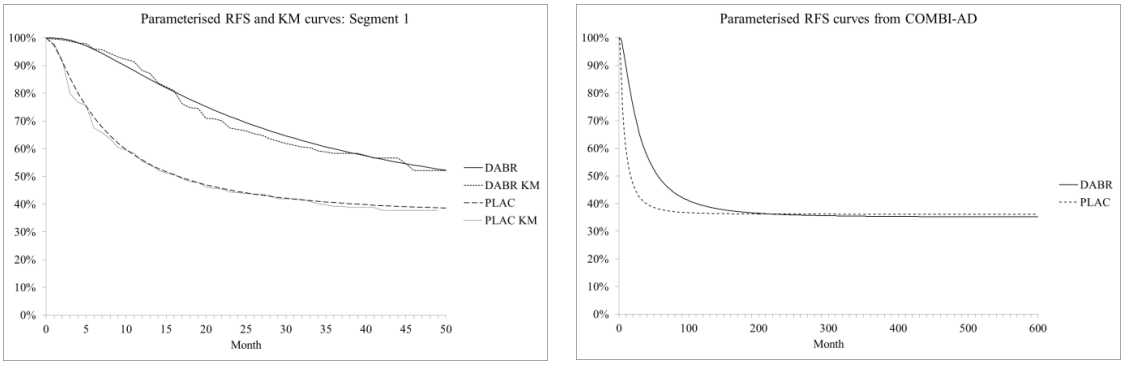


Figure 21: Company Log-Normal (U) Mixture

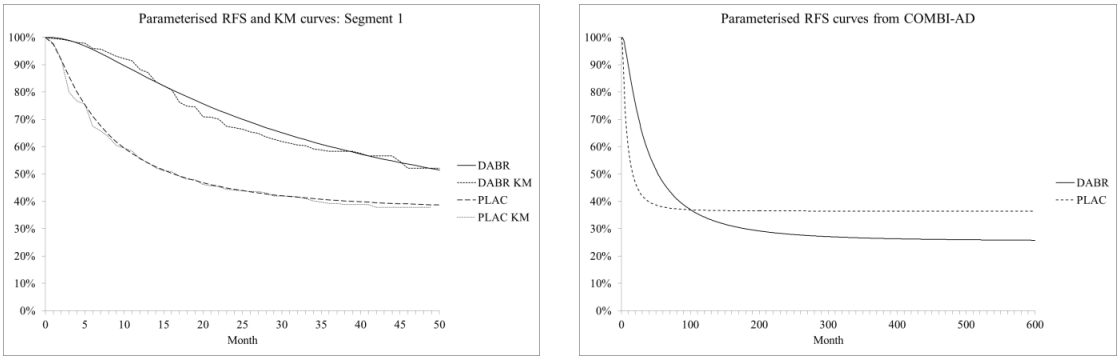


Figure 22: Company Generalised gamma (R) Mixture

In the opinion of the ERG there is little to choose between the company models presented above in terms of their visual fit to the COMBI-AD RFS KM curves. As would be expected, since all models in the above are "cure" models the hazard of a recurrence falls to zero after a period of time.

The ERG agrees with the company that it is implausible for the dabrafenib+trametinib curve to fall below that of resection alone. This rules out the log-normal (R) mixture and the generalised gamma (R) mixture models for extrapolation to 600 months, but not for fitting the curves to the point of cross-over.

It is less obvious that it is unreasonable for the curves to converge. The main differences between the above company models are:

- Those that suggest adjuvant dabrafenib+trametinib permanently cures more patients than resection alone
- Those that suggest adjuvant dabrafenib+trametinib postpones recurrences but that in the long terms recurrence rates will converge with those who did not receive adjuvant therapy.

The ERG parameterised curves are presented in Figure 23 and Figure 24:

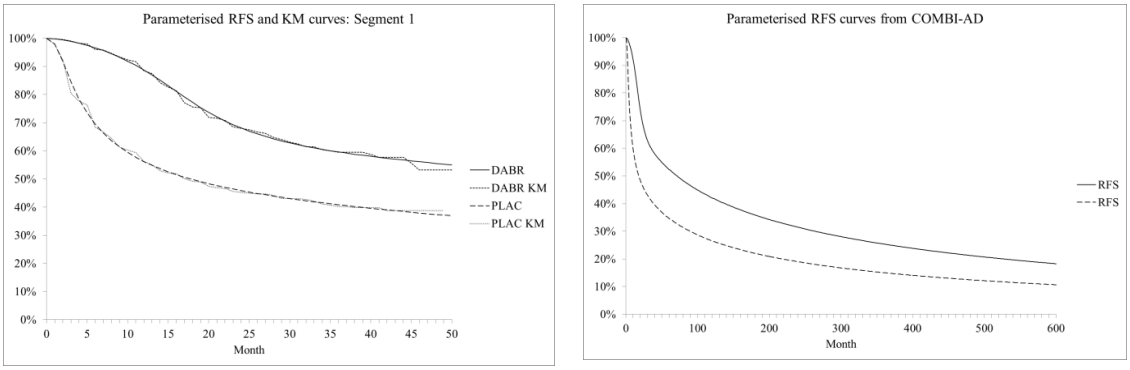
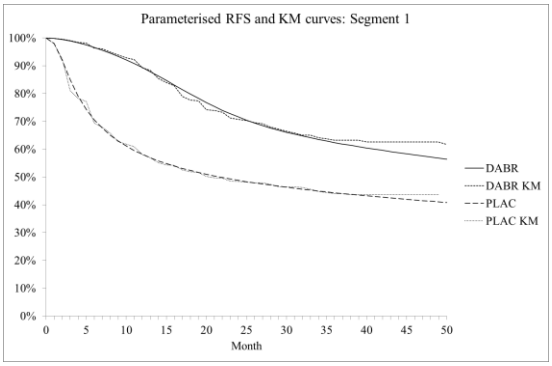


Figure 23: ERG flexible parametric fit



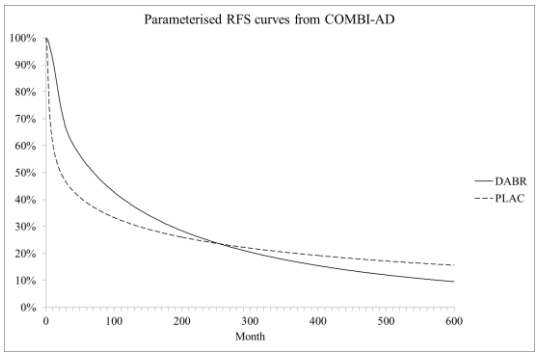


Figure 24: ERG flexible parametric competing risks fit

Bearing in mind that virtually none remain at risk at the end of the KM curves, the ERG models provide a good visual fit to the COMBI-AD data, but the competing risks extrapolation suggests that dabrafenib+trametinib tend to postpone recurrences rather than cure patients.

ERG expert opinion suggests that among patients who have not recurred after 5 years the risk of recurrence is small. ERG expert opinion also notes that it is unaware of any basic science that could explain why adjuvant dabrafenib+trametinib would have a significant "cure" effect even in the palliative setting, so anticipates that adjuvant dabrafenib+trametinib is likely to delay recurrence but have a similar "cure" rate to resection. This, in conjunction with the choice as to how long the COMBI-AD curves should be extrapolated and whether competing risks should be considered, is the central choice for the modelling. As a consequence, the ERG will present three full sets of analyses based upon:

- The company log-logistic (U) mixture model of the company base case
- The company log-logistic (R) mixture model
- The ERG competing risks model.

The other curves will also be explored.

Company base case: probability of RFS events

The company base case applies the arm specific probabilities of RFS events based upon the parameterised curves derived from COMBI-AD data for the first 50 months of the model. Thereon it applies the same probabilities of events in each arm, as derived from the parameterised curve fitted to the placebo arm of the EORTC 18071 trial.[21] This results in the following probabilities of RFS events over the course of the model (see Figure 25).

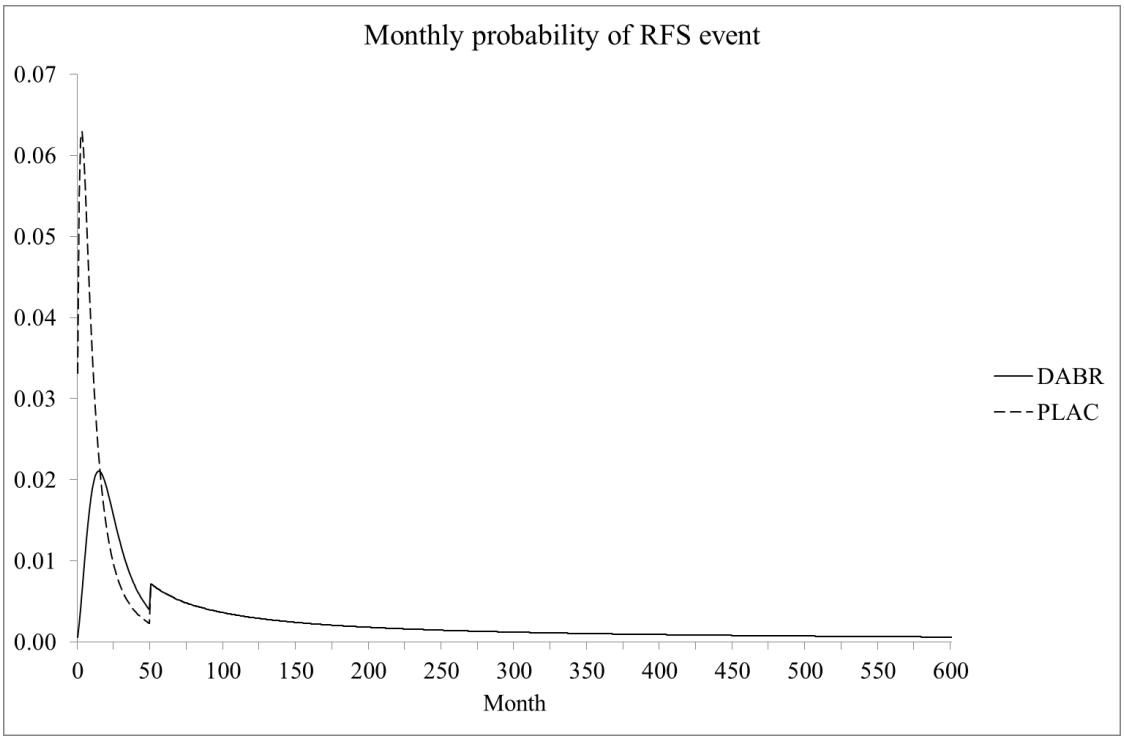


Figure 25: Monthly probabilities of RFS events

The event probabilities in the placebo arm have an initial high spike followed by a rapid tailing off to month 50. The event probabilities in the dabrafenib+trametinib arm do not have as high an initial spike. They rise more gradually, but also tail off more gradually to the extent that from month 15 to month 50 the probabilities of an RFS event in the dabrafenib+trametinib arm are above those in the placebo arm. This higher probability of an event in the dabrafenib+trametinib arm compared to the placebo arm is curtailed by the switch to common probabilities at month 50. At month 50 there is a step up in the probabilities in both arms, but rather more so in the placebo arm than the dabrafenib+trametinib arm. The ERG will explore extrapolation using the COMBI-AD curves, as well as extrapolation using the company EORTC curve from various points.

Balance between types of OS events during COMBI-AD

At clarification the company provided the COMBI-AD OS event and censoring data disaggregated by type. These can be summarised in terms of their totals. Immediately apparent is that there are somewhat more non-melanoma deaths in the placebo arm than in the dabrafenib+trametinib arm, see Table 27.

Table 27: Event totals: COMBI-AD OS Kaplan Meier curves

	Deaths		Censoring	
	Melanoma	Other	End of trial	Other
DABR	[redacted]	[redacted]	[redacted]	[redacted]
PLAC	[redacted]	[redacted]	[redacted]	[redacted]

In the above [redacted] of deaths were non-melanoma deaths in the dabrafenib+trametinib arm, while [redacted] of deaths in the placebo arm were non-melanoma deaths. If non-melanoma deaths are treated as censoring events with the event of interest being melanoma deaths the resulting KM curves tend to come together more than those of figure 7 (pg. 39) of CS Document B and to possibly broadly merge at the end of COMBI-AD. But as reviewed in greater detail in the clinical effectiveness chapter above, this imbalance is best dealt with through a competing risks analysis.

Because the cost effectiveness estimate does rely upon the modelled OS, any competing risks analysis for OS has no effect upon the model outputs. The inability of the chosen model structure to explore this is an argument against it.

Post-LR RFS calibrating hazard ratio

As shown by the company scenario analyses, the cost effectiveness estimate worsens if the post-LR RFS calibrating hazard ratio is less than the 2.53 of the company base case. The ERG understands the company method and views as intuitively appealling. But some discomfort remains due to the calibrating hazard ratio only being applied during the 1st 50 months of the model. As shown in figure 12 above this results in a precipitous decline post-LR during the 1st 50 months of the model, followed by a switch and events suddenly plateauing. This may call into question the credibility of the curves of figure 12 and that more than 90% will have had a 2nd recurrence within 50 months of their 1st recurrence. No external data supportive of this has been presented.

Quality of life: COMBI-AD

As the company notes, EQ-5D reporting rates while high initially tend to decline to month 24 which is the point at which the number of patients remaining in the trial starts to decline. During this period the mean reported quality of life values show some tendency to increase. Whether this reflects reporting bias or genuine improvements in quality of life cannot be determined. But it is notable that the mean EQ-5D evolves in a similar manner in both arms, despite reporting rates in

the placebo arm declining more precipitously than in the dabrafenib+trametinib arm. The number of patients remaining in the trial is reported against the right hand axis, with the following reporting the proportion of these patients who report their EQ-5D at the various timepoints (see Figure 26).

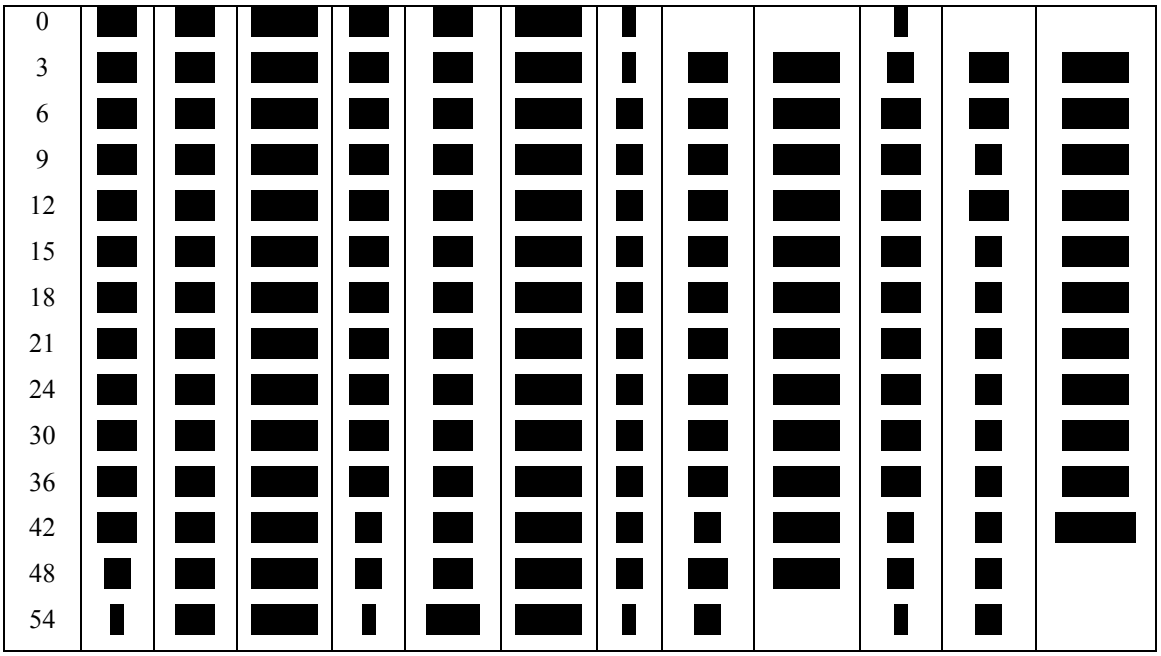
Figure 26:

It can be noted in passing that the supplementary data appendix to Weber et al. (2017)[37] shows a similar pattern in terms of the evolution of EQ-5D VAS scores among resected stage IIIB, IIIC and IV patients who were treated with either adjuvant nivolumab or adjuvant ipilimumab.

The model does not consider the quality of life values among those with a 1st recurrence that is a distant recurence. The mean quality of life values among those with a 1st recurrence that is a local recurrence are presented in Table 28.

Table 28: COMBI-AD: mean EQ-5D QoL values and reporting rates: RFS and LR patients

	RFS						Post local recurrence					
	DABR			PLAC			DABR			PLAC		
Mth	N	Rep.	Mean	N	Rep.	Mean	N	Rep.	Mean	N	Rep.	Mean



Reporting rates for those in RFS remain high for both arms throughout the COMBI-AD trial. The differential decline in reporting rates between the arms across all patients is due to reporting rates among those with a recurrence being lower coupled with more patients in the placebo arm experiencing a recurrence. The low reporting rates among those with a 1st recurrence that is a local recurrence may result in bias. As the company suggests, there may be reporting bias with only the fitter patients reporting. If so, the quality of life estimates for those with a 1st recurrence that is a local recurrence will be too high. Applying a lower quality of life value for local recurrence in the company model improves the cost effectiveness estimate for dabrafenib+trametinib compared to placebo.

Note that the trial protocol planned to analysis the QoL data using mixed effects models, and not GEEs. ERG statistical opinion suggests that this is unlikely to have much affected results.

At clarification the company provides a number additional GEE models which split the RFS health states by arm and by whether patients remain on treatment, whether patients have had a 1st recurrence of LR or DR, whether patients have had an SAE, whether patients have had an SAE split by arm and applying a continuous indicator variable for month of assessment. The SAE coefficients are not estimated to be significant and these regressions are not reported in what follows.

Splitting the RFS on treatment state by arm results in significant coefficients for both arms, with that for dabrafenib+tramatenib [redacted] being similar to that of the placebo arm [redacted]. Slightly curiously, further splitting the RFS off treatment state by arm results in coefficients for dabrafenib+tramatenib for on treatment and off treatment of [redacted] and [redacted], which are both slightly lower than the corresponding coefficients for placebo of [redacted] and [redacted]. But the confidence limits of these coefficients overlap to a degree. All coefficients in Table 29 are significant.

Table 29: Alternative quality of life regressions: central coefficients

		Base	RFS on treatment			RFS off treatment					
	Intercept	EQ-5D	Pooled	DABR	PLAC	Pooled	DABR	PLAC	DR	LR	Month
BC	0.373	0.575	-0.015	..	..	0.000	..	..	-0.077	-0.034	..
Alt1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alt2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alt3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alt4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Of note, the continuous indicator variable for month of assessment is significant in both regressions that include it and in both regressions it has a positive if small coefficient, though as noted above there may be some reporting bias through time.

The quality of life values that result from the first four regressions in the above, when applied to a pooled baseline value of [redacted], presented in Table 30. For the Alt4 regression this sets the month to zero.

Table 30: Quality of life values from alternative regressions

	RFS On treatment		RFS Off treatment				
	DABR	PLAC	Pooled	DABR	PLAC	LR	DR
BC	0.854		0.869			0.836	0.792
Alt1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]

Alt2	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Alt3	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Alt4	[redacted]		[redacted]			[redacted]	[redacted]

The values for DR are broadly in line with the values reported in the brief ERG summary of quality of life values of some of the previous NICE STAs.

Any differences between the values of the base case, as per the first regression, and those of the other three regressions appear to be relatively minor and unlikely to much affect results. ERG statistical opinion prefers the simpler model of the company base case, with this being favoured by information criteria supplied at clarification. Splitting the RFS on treatment and the RFS off treatment by arm results in the central estimates as in Alt3 results in slightly lower RFS values for dabrafenib+tramatenib compared to placebo. The ERG will apply the Alt3 values as a scenario analysis.

Dosing and number of packs dispensed during COMBI-AD

The company states in Table 2 of Document B (pg. 13) that a mean of [redacted] packs of dabrafenib and a mean of [redacted] packs of trametinib were received during COMBI-AD. This is incorrect, as the qualifying text in brackets of table 2 hints. The stated means are based upon the smallest number of 75mg packs of dabrafenib and the smallest number of 2mg packs of trametinib that could be dispensed and still be consistent with each patients' cumulative dose during COMBI-AD; i.e. the smallest possible wastage. This assumption also underlies figure 27 of Document B[b] (pg. 95).

The ERG assumption is that patients' cumulative doses are calculated based on the number of capsules consumed and not the number of packs prescribed. With this assumption, dose modifications and treatment holidays seem likely to imply that wastage and prescribing costs will be higher than implied by the company method. The COMBI-AD CSR reports the following dose modifications and interruptions (Table 31) among the 435 patients who received treatment in the dabrafenib+trametinib.

[b] The economic model performs the same calculation based upon the cumulative dose and suggests that [redacted] of the 435 patients or [redacted] received 48 packs of dabrafenib, as per Figure 27 of Document B.

Table 31: Dose modifications and interruptions

	Dabrafenib	Trametinib
Dose reductions	[redacted]	[redacted]
Dose escalations	[redacted]	[redacted]
Dose interruptions		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3+	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Any interruption	[redacted]	[redacted]
Total interruptions	[redacted]	[redacted]
Interruption duration		
≤7 days	[redacted]	[redacted]
8 to 14 days	[redacted]	[redacted]
> 14 days	[redacted]	[redacted]
Interruption reason		
Adverse event	[redacted]	[redacted]
Patient protocol violation	[redacted]	[redacted]
Other	[redacted]	[redacted]

Dose reductions and escalations may or may not increase wastage depending upon whether it is or is not always coincident with monthly follow-up visits. But they will imply a larger number of packs prescribed for a given cumulative dose than the company method, which in turn implies that a larger number of prescribing costs should be included.

Dose interruptions will cause the exhaustion of prescribed packs to no longer coincide with monthly follow-up visits. How this will be managed is unclear but it seems very likely to result in increased wastage and/or more outpatient visits for prescribing than the company method. The majority of patients had dose interruptions in their dabrafenib treatment, with the total number of dose interruptions implying that among those with at least 3 dose interruptions the mean number of interruptions was [redacted]. The corresponding mean for trametinib among those with at least 3 dose interruptions [redacted] interruptions.

At clarification, as a priority question the ERG asked the company to provide data on the numbers of packs dispensed during COMBI-AD, disaggregated into 50mg packs of dabrafenib, 75mg packs of dabrafenib, 0.5mg packs of trametinib and 2mg packs of trametinib. This data would obviate any need to infer the number of packs that are likely to be dispensed. The company response was that this data was not immediately available but would be provided in due course. The company provided some data on the 13th of June, a week before the ERG submission deadline. The data also does not appear to correspond with the COMBI-AD trial protocol; e.g. it states that 437 packs of dabrafenib were prescribed at baseline with repeat dosing thereafter being mainly at 4 weeks, but each 28 capsule pack of dabrafenib is only sufficient for 1 week given the daily dose of 2 tablets twice daily. It may be that within the data the number of dabrafenib "packs" is the number of prescriptions of 4 dabrafenib packs.

The data can be plotted against the number remaining on treatment at the start of each 4 week period. Due to there being packs/prescriptions between 4 week periods, these can be summed to give a "moving average" 4 weekly total (MA) for dabrefenib; i.e., summing week 1, 2, 3 and 4 gives the 4 weekly total for week 4, as per the black dots in what follows in Figure 27.

Figure 27: [redacted]

For dabrafenib the 4 weekly total (MA) closely follows the number remaining on treatment. To the ERG this suggests that the data relates to prescriptions and not packs, and so a mean number of 50mg prescriptions of [redacted] and a mean number of 75mg prescriptions of [redacted]. Given that the dabrafenib data appears to relate to prescriptions, with dose adjustments it may be that the number of packs per prescription sometimes falls below 4. But in the absence of other data the ERG can only sensibly apply 4 packs per prescription, which suggests a mean of [redacted] 50 mg

packs and a mean of [redacted] 75mg packs. With the dabrafenib PAS this would cost [redacted], compared to the company model costing of [redacted]: a [redacted] increase.

Due to a 28 capsule pack of trametinib being sufficient for 4 weeks, the situation is more straightforward. Prescriptions and packs will be synonymous and the data suggests a mean of [redacted] 0.5 mg packs and a mean of [redacted] 2mg packs. With the trametinib PAS this would cost [redacted], compared to the company model costing of [redacted]: a [redacted] increase.

Taken together these suggest a mean PAS inclusive drug cost of [redacted] compared to the company estimate of [redacted]: a [redacted] increase. This is a reasonably major increase and the ERG encourages the company to cross check the ERG workings, and if possibly also review the number of packs per prescription in the dabrafenib data supplied in answer to clarification question A3.

The number of prescriptions will also increase the prescribing costs that should be applied in the model. This would have relatively little effect upon costs. Of more concern is that prescribing between 4 weekly periods may suggest more intensive follow-up of patients than the company assumes. The average number of inter-4-week prescriptions compared to 4-weekly prescriptions is [redacted] for dabrafenib and [redacted] for trametinib. It seems possible that the number of outpatient visits may increase accordingly. The ERG will explore this by increasing the outpatient monitoring requirement in the dabrafenib+trametinib arm by [redacted] for those on treatment.

Treatment duration

Table 2 of Document B states that treatment duration should be for 12 months, and notes that the mean treatment duration in COMBI-AD was a little over [redacted] months. But in response to an ERG clarification question the company notes that among the [redacted] patients who completed 12 months of treatment in the dabrafenib+trametinib arm of COMBI-AD the majority, [redacted], continued treatment beyond 12 months when a month is defined as 4 weeks.

[redacted]

There may have been some crossed wires in terms of these questions. The main ERG concern is whether many patients received dabrafenib+trametinib beyond 12 months; e.g. whether any patients continued with treatment to e.g. 14 months and beyond, despite the trial protocol. Given the prescribing data this seems unlikely, but it would be helpful if the company could further clarify this before or at the 1st AC.

SAEs within the model

The company model only explicitly considers SAEs in terms of costing those that result in hospitalisations.

TA396 of dabrafenib+trametinib for unresectable stage III or stage IV disease included a wider range of adverse events though again it appears that these only affected costs in the model. The company has supplied a copy of the electronic model, which suggests SAE costs for dabrafenib+trametinib of only [redacted]. The FAD of TA396 does not suggest that either the ERG or the AC has any particular concerns about the handling of SAEs within the economic model.

The CSR of COMBI-AD notes the following concomitant medications that are presented in Table 32 for pyrexia and skin toxicities.

Table 32: Prophylactic and active treatment: Pyrexia and skin toxicities

	DABR	PLAC
Prophylactic treatment: Pyrexia Skin toxicity	[redacted]	[redacted]
Active treatment: Pyrexia Skin toxicity	[redacted]	[redacted]

There are quite large differences between the arms in terms of concomitant medications. These in themselves may not give rise to large costs, but any additional OP or GP visits for the above might be more significant.

The above also gives credence to ERG expert opinion that additional dermatology OP monitoring will be required for dabrafenib+trametinib. The ERG will assume an additional quarterly OP monitoring requirement to cover this.

The modelling of a distant recurrences

In terms of the model, patients falling into DR is a bad thing because at this point they stop accumulating QALYs. But this is compounded by the costs and QALYs that are applied when patients fall into DR. The company derives cost and QALY estimates for DR treatments from the NICE STA of pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366] and the NICE STA of trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma[c] [TA396]. It is further assumed that the balance between these treatments for DR patients is [redacted] based upon the pooled proportions of targeted therapies and immunotherapies received as first-line post-DR systemic anti-cancer therapies in COMBI-AD. The company electronic model notes that there was not a statistically significant difference between the proportions receiving post-DR treatments ([redacted]).

There is an additional problem in that during both TA366 and TA396 Committee concluded that the end of life criteria were met. To the ERG this suggests that when applying the costs and QALY estimates of TA366 and TA396 these should be monetised at a willingness to pay value of £50k per QALY. The costs and QALYs of the individual treatments and the treatments pooled [redacted] can be valued at willingness to pay values of £20k/QALY, £30k/QALY and £50k/QALY as presented in Table 33.

Table 33: Post DR treatment total costs, QALYs and monetised health benefits

	Proportion	Costs	QALYs	£20k/Q	£30k/Q	£50k/Q
TA366	[redacted]	£83,282	2.960	-£24,082	£5,518	£64,718
TA396	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled		£142,699	3.231	-£78,078	-£45,767	£18,851

[c] The total costs and QALYs for dabrafenib+trametinib correspond with the PAS inclusive estimates of the TA366 model provided by the company at clarification.

Falling into DR is estimated to further worsen the cost effectiveness of a treatment in the sense that it is less likely to be cost effective at a willingness to pay of £30k per QALY due to the pooled treatments for DR having a negative monetized health benefit at a willingness to pay of £30k per QALY. But if the treatments for DR are assessed under the end of life criteria and at a willingness to pay of £50k per QALY the monetised health benefits of pembrolizumab are high, and the monetised health benefits of the pooled treatments are positive rather than negative.

It can also be noted the while the above suggests that DR patients benefit from receiving dabrafenib+trametinib for their DR compared to receiving pembrolizumab with a net gain of [redacted] QALYs the additional [redacted] cost suggests an ICER of [redacted] per QALY. These estimates may not really be aligned or amenable to being combined.

The COMBI-AD CSR notes that "***The Investigators had the ability to obtain the unblinded treatment information*** *if necessary in the case of a medical emergency when knowing the treatment was essential to clinical management and the welfare of the patient or* ***to determine the choice of anti-cancer therapy for the recurring disease****. … The patient remained in the study for survival follow-up even if the treatment code was unblinded.* [ERG emphasis]" Table 11-7 of the CSR given the following for treatments subsequent to any recurrence (summarised in Table 34). ERG expert opinion suggests that most loco-regional recurrences would be resected with some receiving radiotherapy, so the data on pharmacological treatments may mainly relate to distant recurrences.

Table 34: [redacted]

	DABR		PLAC		Pooled	
N with recurrence	[redacted]		[redacted]		[redacted]	
Anti-cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No anti-cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any Systemic Anti-Cancer Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Small Molecule Targeted Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any BRAF Inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any MEK Inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Investigational Treatment	[redacted]					
Other Therapy	[redacted]					
Surgery	[redacted]					
Radiotherapy	[redacted]					
Total N Systemic Anti-Cancer Therapies	[redacted]					

It suggests that reasonably similar proportions of those with recurrence received systemic anti-cancer treatment in the dabrafenib+trametinib arm as in the placebo arm. The duration of post recurrence survival at the data cut is likely to be shorter in the dabrafenib+trametinib arm than in the placebo arm. This makes it difficult to draw conclusions about whether the number of systemic-anti-cancer treatments per recurrent patient differs between the arms. With the above caveat, the main differences appear to be that more received immunotherapy in the dabrafenib+trametinib arm, while more received a BRAF inhibitor in the placebo arm with the proportions roughly reversing between the arms.

ERG expert opinion questions whether there is good evidence that those receiving dabrafenib+trametinib for a distant recurrence will have a longer survival and/or a better quality of life than those receiving pembrolizumab.

ERG expert opinion also suggests that there is not good evidence of developing resistance to BRAFi and MEKi. As a consequence, a distant recurrence after having received adjuvant dabrafenib+trametinib seems more likely to be heavily mutated and active, and more likely to have developed mechanisms to bypass BRAF inhibition. As a consequence, dabrafenib+trametinib for treatment of a distant recurrence may be less effective among patients who have already received it as adjuvant treatment, reducing the total QALYs that should be attributed to it. It may also tend to reduce the proportion of these patients who would be treated with it.

Retaining the [redacted] balance of the company base case and reducing the total QALYs for patients who are assumed to receive targeted therapy at DR in the dabrafenib+tramatenib arm by 20%,

30% and 40%[d] worsens the cost effectiveness ratio from £20,039 per QALY to £23,571 per QALY, £25,848 per QALY and £28,614 per QALY respectively.

Revising the split between immunotherapy and targeted thereapy for DR patients in the dabrafenib+tramatenib arm from [redacted][e] improves the cost effectiveness ratio from £20,039 per QALY to £15,425 per QALY. This improvement is dependent upon whether these patents switch to a treatment with a higher health benefit than dabrafenib+tramatenib treatment of DR. But it should be borne in mind that these patients are being "switched" to another therapy due to dabrafenib+tramatenib treatment of DR for these patients being anticipated to have an even worse monetised health benefit than it does for patients who have not received dabrafenib+tramatenib adjuvant treatment. Consequently, the treatment they are switching to might have similar or worse monetised health benefit when compared to the monetised health benefit of dabrafenib+tramatenib treatment of DR among patients who have not received dabrafenib+tramatenib adjuvant treatment.

ERG expert opinion suggests that the split between treatments that are used by at least 10% of stage III resected UK patients not treated with adjuvant dabrafenib+trametinib who progress to a DR is likely to be around 30:30:10:10 for pembrolizumab:ipilimumab+nivolumab: dabrafenib: clinical trials.

Unfortunately, the total costs of the STA of ipilimumab+nivolumab [TA400][56] are redacted and only the company estimates of total QALYs is available: 5.09 QALYs compared to 2.90 QALYs for ipilimumab alone. The ERG revised these to remove the nested long term post progression mortality which considerably reduced the total QALYs: 2.86 QALYs compared to 1.72 QALYs for ipilimumab alone. But the FAD for TA400 notes that "*The committee did not formally consider whether the end-of-life criteria applied because the technology was considered to be a cost-effective use of NHS resources without this*". To the ERG this coupled with the total QALYs as estimated by the ERG suggests that the monetised health benefits of nivolumab in combination with ipilmumab estimated during TA400 are likely to be very much more closely aligned with those of pembrolizumab taken from TA366 than with those of dabrafenib+trametinib taken from

[d] Implemented in the *Outputs* worksheet by conditioning D12 by [redacted] respectively.

[e] Implemented in the *Cost_PostDR* worksheet by revising D8:D9 accoridingly.

TA396. Indeed, they may suggest a higher monetised health benefit for ipilimumab+nivolumab than those of pembrolizumab.

In the light of the above, for its revised base case the ERG will value the patient gains from DR treatments at £50k/QALY. It will conduct a scenario analysis that applies their total costs and total QALYs as per the company base case. The ERG will also revise the balance between the treatments for DR, its base case assuming a [redacted] split for pembrolizumab:dabrafenib+trametinib. The company preferred [redacted] split will be explored in a sensitivity analysis.

Proportion on treatment during 1st year: Minor issue

The proportion of patients remaining on dabrafenib+trametinib is derived from COMBI-AD data, the electronic model stating that "*Data on duration of exposure and RFS in COMBI-AD was employed to estimate the percentage of patients remaining on treatment at the beginning of each month among patients in RFS at the beginning of the month. This was calculated by dividing the number of patients with treatment duration greater than the month by the number of patients with RFS time greater than the month*". The COMBI-AD numbers at risk for time to treatment discontinuation (TTD) and RFS as supplied at clarification are presented below (see Table 35), together with the implied ratios and the ratios applied within the model for dabrafenib+trametinib. For reasons of space, the ratios that appear to be implied for placebo are also presented in the final column, as these can be used for scenario analyses around the quality of life values.

Table 35: Proportion remaining on treatment during year 1

			Dabrafenib+trametinib				
Period	Day	Month	TTD	RFS	Ratio	Model	PLAC
0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 1 to 28	1	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 29 to 56	29	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 57 to 84	57	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 85 to 112	85	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 113 to 140	113	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 141 to 168	141	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Day 169 to 196	169	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 197 to 224	197	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 225 to 252	225	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 253 to 280	253	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 281 to 308	281	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 309 to 336	309	11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 337 to 364	337	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

It appears that the company has applied something akin to the ratio of the numbers at risk, with which there is good agreement until the last two months of the model. Given that these ratios do not determine the drug costs of dabrafenib+trametinib in the model, but only the monitoring costs and the quality of life in the dabrafenib+trametinib arm the discrepancies during the last two months are relatively minor. The ERG will apply the values that appear to be implied by the data supplied at clarification.

SAE hospitalisation costs: Minor issue

It is not obvious why the company has chosen elective inpatient costs for SAEs. The ERG thinks that it is more sensible to apply non-elective unit costs. Calculating these on the same basis as the company elective inpatient costs implies the following costs in Table 36.

Table 36: SAE hospitalisation costs: non-elective long stay IP costs

	DABR	PLAC	Cost
Pyrexia	[redacted]	[redacted]	£2,002
Other SAEs	[redacted]	[redacted]	£3,287
Total cost	£674	£177	

The above has minimal effect upon results compared to the company base case, increasing the net cost of SAE hospitalisations from £494 to £497.

Hazard ratio applied to RFS events curve to derive post-LR events curve: Minor issue

The calculation of hazard ratio for the LR curve that minimises the difference between the modelled LR OS and the COMBI-AD post LR OS KM curves. It is consequently a function of:

- Whether the quantity that is minimised is unweighted or is weighted by the numbers at risk in the Kaplan Meier curves. In the base case it is unweighted.
- The balance between LR:DR:death that is applied to the post-LR events curve: in the base case 32:63:5 as reportedly derived from White et al.[52]

Exploring these in turn:

- Weighting the quantity that is minimised by the numbers at risk in the Kaplan Meier curves results in a hazard ratio of 2.29, which in turn marginally worsens the ICER from £20,039 per QALY to £20,695 per QALY.
- Increasing the proportion of LR events that are deaths by 5% with an LR:DR:death ratio of 27:63:10 results in a hazard ratio of 2.04, which in turn worsens the ICER from £20,039 per QALY to £21,666 per QALY.
- Increasing the proportion of LR events that are DR by 5% with an LR:DR:death ratio of 27:68:5 results in a hazard ratio of 2.42, which in turn marginally worsens the ICER from £20,039 per QALY to £20,128 per QALY.

The above suggest that for the base case RFS events curve, the model is reasonably stable in terms of the reasoanble hazard ratios that is applied to it to derive the LR events curve during the 1st 50 months of the model, when the curves are based upon the COMBI-AD data.

The above assumes that the same hazard ratio should be applied to the dabrafenib+trametinib arm as to the placebo arm. This may not be reasonable if the post-LR OS KM curves differ. It may be reasonable to anticipate that they will differ since dabrafenib+trametinib is estimated to postpone a 1st LR recurrence.

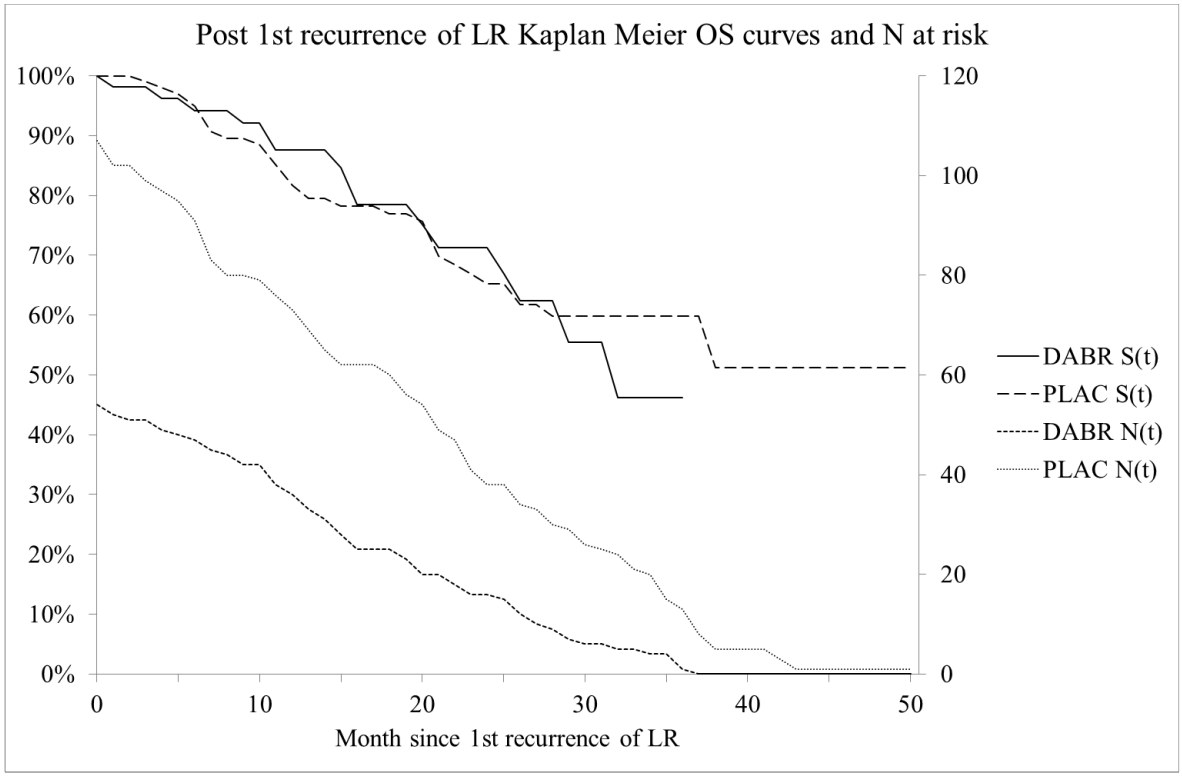


Figure 28: COMBI-AD post 1st recurrence of LR Kaplan Meier OS curves

There is relatively little difference between the post LR Kaplan Meier OS curves (Figure 28). There is some suggestion of a superior curve for dabrafenib+trametinib in the early portions of the curves. Any superiority for placebo occurs after month 30 when the numbers at risk are quite small. If there is a difference from this point it could suggest that while dabrafenib+trametinib postpones LR recurrences there could be some catching up with placebo after the recurrence occurs.

It can also be noted that the company base case differentiated the post DR OS KM curves by arm when calculating the calibration hazard ratio. In the light of this the ERG explores estimating arm specific calibration hazard ratios, the calculation of which is based upon the arm specific post LR KM OS curves. Estimating arm specific HRs results in values of 2.42 for dabrafenib+trametinib and 2.64 for placebo, which improves the ICER from £20,039 per QALY to £18,906 per QALY. If these calculations were weighted by the numbers at risk it seems likely that this would further improve the ICER due to any superiority of the placebo KM curve being towards the end of the KM curves when few are at risk.

The calibration of the model and the calculation of the hazard ratio sets the curves for LR events and DR events to be the relevant Kaplan Meier curves. But the base case then applies the resulting hazard ratio to the parameterised LR events curve of the base case. It is not obvious why calibration does not use the curves of the base case, or why the base case does not use the curves of the calibration. But applying the calibration placebo LR events Kaplan Meier curve rather than the base case parameterised curve has minimal impact upon the ICER, only worsening it to £20,041 per QALY.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG presents three full sets of analyses.

- Using the company log-logistic (U) cure model.
- Using the company log-logistic (R) cure model.
- Using the ERG competing risks model, with a common placebo risk from month 256 when the curves come together.

The model is recalibrated for each set of curves. For the period beyond 50 months the balance between events in the dabrafenib+trametinib is assumed to be as per the placebo arm. The ERG also explores extrapolating using the company EORTC placebo generalised F. curve from month 50, which by applying the same risks in each arm helps preserve the difference between dabrafenib+trametinib and placebo into the longer term.

The ERG has made two minor corrections to the company model structure. The ERG has also revised the company model along the following lines.

- Assume that those who have received dabrafenib+trametinib require the same monitoring requirement as those remaining on dabrafenib+trametinib.
- Assume an additional quarterly OP appointment to account for dermatological monitoring.
- Apply the treatment proportions that appear to be implied by the company responses at clarification.
- Revise the dabrafenib+trametinib drug costs to be based upon the company answer to clarification question A3, further qualifying prescription costs accordingly.
- Revise the proportion of DR patients who receive pembrolizumab from [redacted] to reflect expert opinion and the probably costs and effects of nivolumab+ipilimumab.

- Using the base case set of assumptions when fitting the model outputs at calibration to the post-LR COMBI-AD OS KM curve.

These changes are documented within the ERG revised electronic model.

The ERG also undertakes the following sensitivity analyses.

- SA01: Applying the EQ-5D regression that splits on treatment by arm and off treatment by arm.
- SA02: Varying the intercept term of the EQ-5D regressions by ±25% for both the base case regression and the regression that splits on treatment by arm and off treatment by arm, this resulting in approximately a ±0.1 change in the quality of life values that are applied.
- SA03: Extending the monitoring requirement for dabrafenib+trametinib by 50%.
- SA04: Varying the proportion of LR events that require resection from 10% to 0% and to 20%.
- SA05: Deriving the balance between LR, DR and death events in the post-LR modelling from the same source as for the RFS balance between events: EORTC 18071.
- SA06: Valuing the health benefits of the DR treatments at the end of life WTP of £50k/QALY.

A further set of analyses that vary the curves that are applied are also presented which apply:

- The company generalised gamma (U) cure model
- The company log-normal (U) cure model
- The ERG flexible parametric curves

The results of this modelling with the company EORTC placebo generalised F. curve being applied from month 50, month 150 and, for the log-normal (R) core model and the generalised gamma (R) cure model, the month of cross-over are also explored.

Modelling based upon the log-logistic (U) cure curves

The ERG revisions when the log-logistic (U) cure curves are applied, without extrapolation using EORTC data, result in the following RFS and OS curves in the placebo arm, and the OS curves by arm presented in Figure 29.

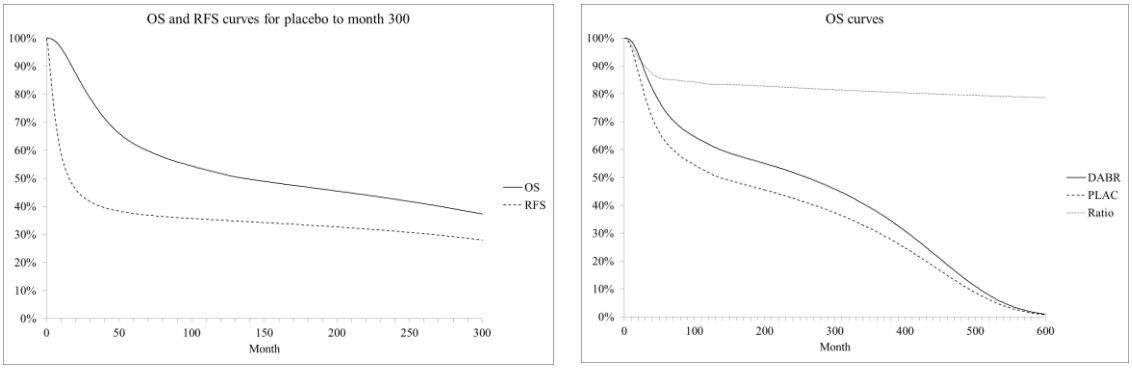


Figure 29: Revised base case and no EORTC extrapolation: Log-log (U) cure model

The above figures result in the following cost effectiveness estimates that are presented in Table 37.

Table 37: Revised base case and no EORTC extrapolation: Log-log (U) cure model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	17.876	8.586	£69,532	
Net	[redacted]	[redacted]	[redacted]	£20,701

The central estimates of the probabilistic modelling are a net cost of [redacted], a net gain of [redacted] QALYs and an ICER of £20,923 per QALY, which are aligned with the deterministic estimate (see Figure 30).

[redacted]

Figure 30: [redacted]

Extrapolating using the EORTC data from month 50 rather than the COMBI-AD data results in the following (see Figure 31 and Table 38).

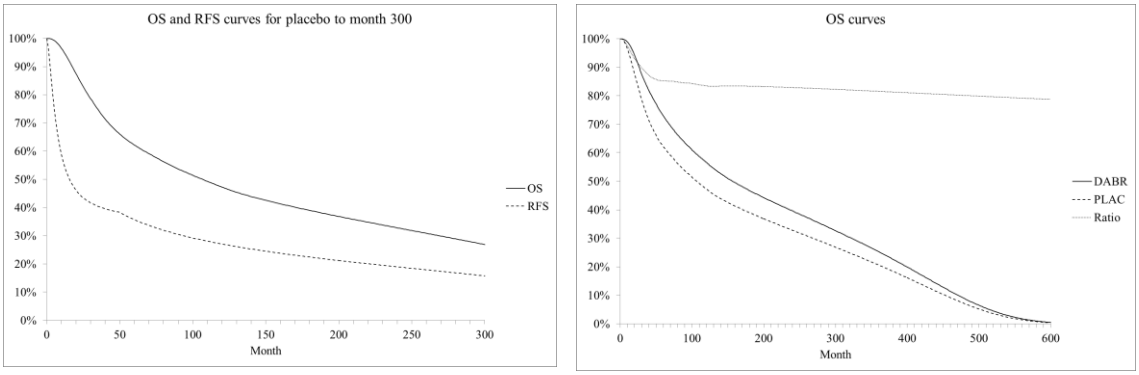


Figure 31: Revised base case with EORTC extrapolation: 50mth: Log-log (U) cure mode

Table 38: Revised base case with EORTC extrapolation: 50mth: Log-log (U) cure model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.034	7.574	£82,467	
Net	[redacted]	[redacted]	[redacted]	£26,258

The ERG sensitivity analyses result in the following (see Table 39):

Table 39: Deterministic sensitivity analyses: No EORTC extrapolation: Log-log (U) cure model

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Base case	[redacted]	[redacted]	[redacted]	£20,701
SA01: EQ-5D RFS split by arm	[redacted]	[redacted]	[redacted]	£21,734
SA02a: EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£24,134
SA02b: EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£18,134
SA02c: SA01 + EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£25,697
SA02d: SA01 + EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£18,830
SA03: DABR monitoring +50%	[redacted]	[redacted]	[redacted]	£21,929
SA04a: LR resection 0%	[redacted]	[redacted]	[redacted]	£21,329
SA04b: LR resection 20%	[redacted]	[redacted]	[redacted]	£20,073
SA05: LR events balance EORTC 18071	[redacted]	[redacted]	[redacted]	£20,764
SA06: DR costs and benefits reflect EoL[f]	[redacted]	[redacted]	[redacted]	£24,980

Since this section and the company base case are based upon the company log-logistic (U) cure model (Table 40), the ERG model revisions can be applied individually to the company base case to show their effect.

Table 40: Company base case: Log-log (U) cure model

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Company base case	[redacted]	[redacted]	[redacted]	£20,039
Model corrections	[redacted]	[redacted]	[redacted]	£19,725
Monitoring for DABR Off Tx same as On Tx	[redacted]	[redacted]	[redacted]	£20,316

[f] Rather than apply the costs of the post-DR treatments this is implemented by converting the post-DR costs into their equivalent QALY decrements at a willingness to pay of £50k/QALY, hence the increase in the net QALY gain. But having applied these QALY decrement the costs of the post-DR treatments are no longer applied, hence the increase in the net costs

Additional quarterly OP for DABR	[redacted]	[redacted]	[redacted]	£20,396
Revised treatment proportions	[redacted]	[redacted]	[redacted]	£20,117
Revised DABR drug usage	[redacted]	[redacted]	[redacted]	£23,569
Revised balance between DR treatments	[redacted]	[redacted]	[redacted]	£22,142
Calibration fits model curves to KM data	[redacted]	[redacted]	[redacted]	£20,279
All the above	[redacted]	[redacted]	[redacted]	£26,258

The main revisions are to :

- Drug use in the dabrafenib+trametinib arm
- The balance between DR treatments

Modelling based upon the log-logistic (R) cure curves

The ERG revisions when the log-logistic (R) cure curves are applied, without extrapolation using EORTC data, result in the following Figure 32.

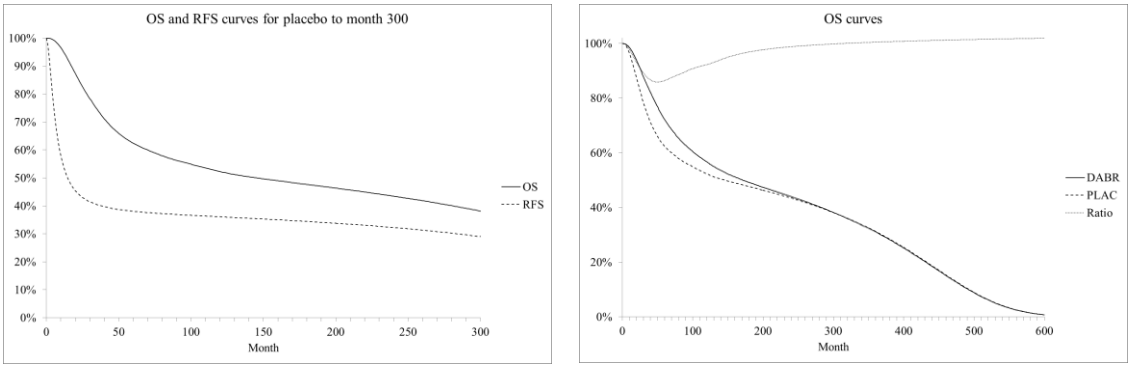


Figure 32: Revised base case and no EORTC extrapolation: Log-log (R) cure model

There is greater convergence of the OS and RFS curve in the placebo arm than in the modelling that uses the log-logistic (U) cure model, with a plateauing of the RFS curve much as in White et al. But the plateauing of the RFS curve occurs at a somewhat higher level than in White et al. The initial survival gain from dabrafenib+trametinib over placebo falls off during extrapolation and has been washed out by month 300 (see Table 41).

Table 41: Revised base case and no EORTC extrapolation: Log-log (R) cure model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	18.162	8.697	£68,280	
Net	[redacted]	[redacted]	[redacted]	£62,853

The central estimate of the probabilistic modelling are a net cost of [redacted], a net gain of [redacted] QALYs and an ICER of £63,193 per QALY, which are aligned with the deterministic estimate.

Figure 33: [redacted]

The horizontal dashed line for placebo remains at 100% up to a willingness to pay £50k/QALY and there is no uncertainty that placebo is the most cost effective option to this point, i.e. there is no probability of dabrafenib+trametinib being cost effective for willingness to pay values up to £50k/QALY.

Extrapolating using the EORTC data rather than the COMBI-AD data results in the following (see Figure 34 and Table 42).

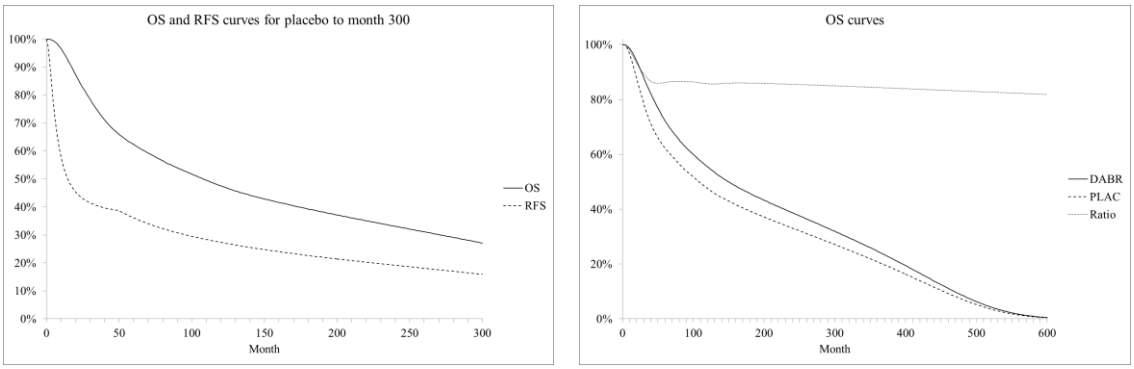


Figure 34: Revised base case with EORTC extrapolation: Log-log (R) cure model

Table 42: Revised base case with EORTC extrapolation: Log-log (R) cure model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.107	7.605	£82,162	
Net	[redacted]	[redacted]	[redacted]	£30,866

The ERG sensitivity analyses result in the following (see Table 43)

Table 43: Revised base case with EORTC extrapolation: Log-log (R) cure model

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Base case	[redacted]	[redacted]	[redacted]	£62,853
SA01: EQ-5D RFS split by arm	[redacted]	[redacted]	[redacted]	£70,752
SA02a: EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£72,018
SA02b: EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£55,790
SA02c: SA01 + EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£83,032
SA02d: SA01 + EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£61,636
SA03: DABR monitoring +50%	[redacted]	[redacted]	[redacted]	£65,675
SA04a: LR resection 0%	[redacted]	[redacted]	[redacted]	£63,847
SA04b: LR resection 20%	[redacted]	[redacted]	[redacted]	£61,859
SA05: LR events balance EORTC 18071	[redacted]	[redacted]	[redacted]	£63,716

Modelling based upon the ERG competing risks (CR) model

The ERG revisions when the ERG competing risks curves are applied, without extrapolation using EORTC data, result in the following (see Figure 35).

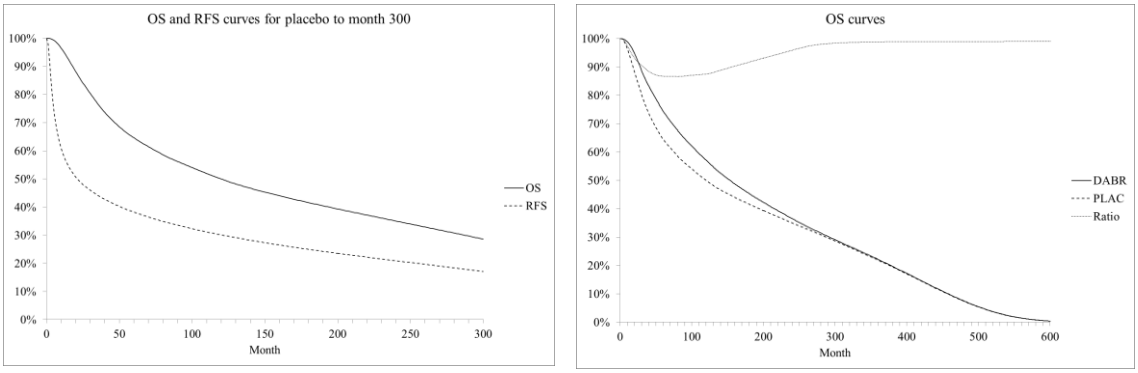


Figure 35: Revised base case and no EORTC extrapolation: ERG CR model

There is less convergence of the OS and RFS curve in the placebo arm than in the modelling that uses the log-logistic (R) cure model, and less of a plateauing of the RFS curve than in White et al. The initial survival gain from dabrafenib+trametinib over placebo falls off during extrapolation but at a slower rate than in the modelling that uses the log-logistic (R) cure model, but is still washed out by month 300 (see Table 44).

Table 44: Revised base case and no EORTC extrapolation: ERG CR model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.603	7.882	£80,290	
Net	[redacted]	[redacted]	[redacted]	£46,161

The central estimate of the probabilistic modelling are a net cost of [redacted], a net gain of [redacted] QALYs and an ICER of £46,230 per QALY, which are aligned with the deterministic estimate (see Figure 36).

[redacted]

Figure 36: [redacted]

Extrapolating using the EORTC data rather than the COMBI-AD data results in the following (Figure 37 and Table 45):

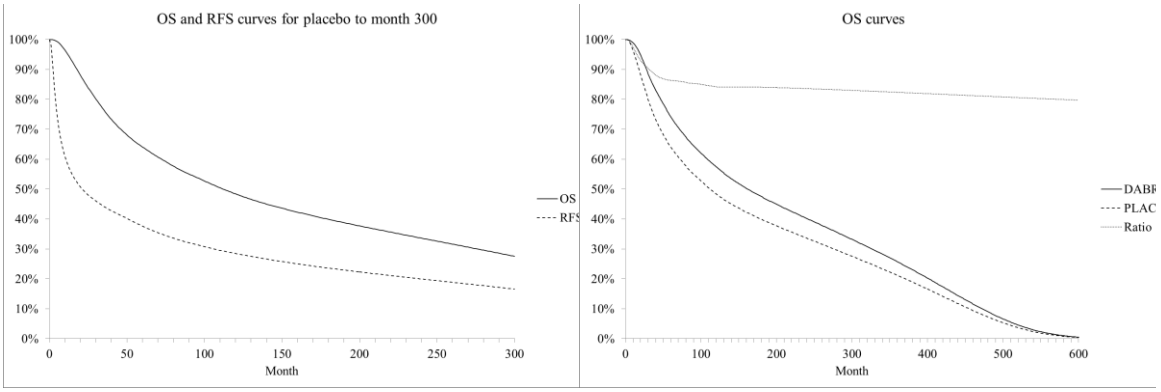


Figure 37: Revised base case with EORTC extrapolation: ERG CR model

Table 45: Revised base case with EORTC extrapolation: ERG CR model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.363	7.762	£81,154	
Net	[redacted]	[redacted]	[redacted]	£27,432

The ERG sensitivity analyses result in the following (Table 46):

Table 46: Deterministic sensitivity analyses: No EORTC extrapolation: ERG CR model

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Base case	[redacted]	[redacted]	[redacted]	£46,161
SA01: EQ-5D RFS split by arm	[redacted]	[redacted]	[redacted]	£49,492
SA02a: EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£53,061
SA02b: EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£40,873
SA02c: SA01 + EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£57,814
SA02d: SA01 + EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£43,264
SA03: DABR monitoring +50%	[redacted]	[redacted]	[redacted]	£48,347
SA04a: LR resection 0%	[redacted]	[redacted]	[redacted]	£46,954
SA04b: LR resection 20%	[redacted]	[redacted]	[redacted]	£45,369
SA05: LR events balance EORTC 18071	[redacted]	[redacted]	[redacted]	£46,530
SA06: DR costs and benefits reflect EoL[g]	[redacted]	[redacted]	[redacted]	£46,589

Modelling based upon the other curves that are a good visual fit

The other curves when used for Segment 1 and Segment 2 of the model suggest the following (see Table 47):

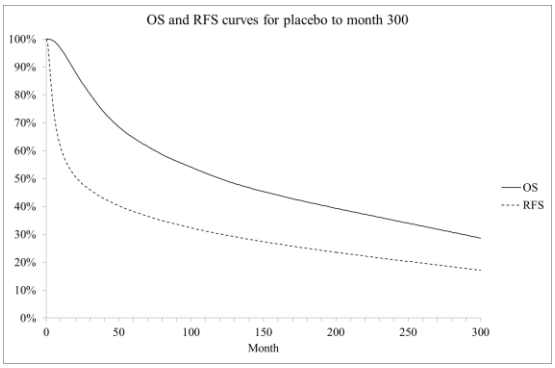
Table 47: Deterministic sensitivity analyses: alternative curves

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Company generalised gamma (U) cure	[redacted]	[redacted]	[redacted]	£11,574
Company log-normal (U) cure	[redacted]	[redacted]	[redacted]	£67,645
ERG flexible parametric	[redacted]	[redacted]	[redacted]	£20,167

Modelling based upon the ERG competing risks (CR) model

The ERG revisions when the ERG competing risks curves are applied, without extrapolation using EORTC data, result in the following (see Figure 38 and Table 48).

[g] Rather than apply the costs of the post-DR treatments this is implemented by converting the post-DR costs into their equivalent QALY decrements at a willingness to pay of £50k/QALY, hence the increase in the net QALY gain. But having applied these QALY decrement the costs of the post-DR treatments are no longer applied, hence the increase in the net costs



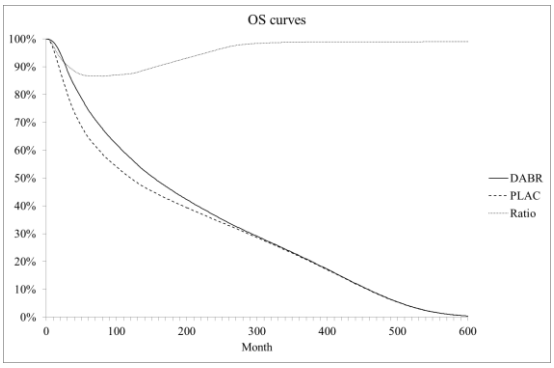


Figure 38: Revised base case and no EORTC extrapolation: ERG CR model

There is less convergence of the OS and RFS curve in the placebo arm than in the modelling that uses the log-logistic (R) cure model, and less of a plateauing of the RFS curve than in White et al. The initial survival gain from dabrafenib+trametinib over placebo falls off during extrapolation but at a slower rate than in the modelling that uses the log-logistic (R) cure model, but is still washed out by month 300.

Table 48: Revised base case and no EORTC extrapolation: ERG CR model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.603	7.882	£80,290	
Net	[redacted]	[redacted]	[redacted]	£46,161

The central estimate of the probabilistic modelling are a net cost of [redacted], a net gain of [redacted] QALYs and an ICER of £46,230 per QALY, which are aligned with the deterministic estimate (Figure 39).

[redacted]

Figure 39: [redacted]

Extrapolating using the EORTC data rather than the COMBI-AD data results in the following (Figure 40 and Table 49):

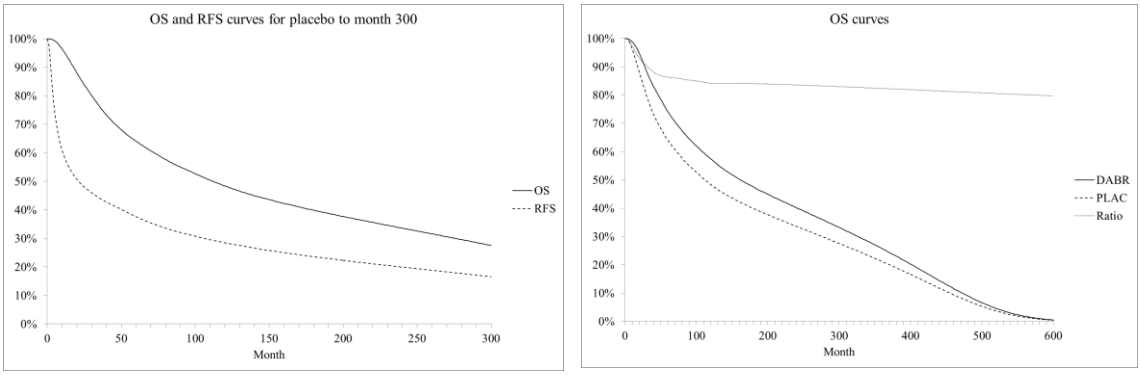


Figure 40: Revised base case with EORTC extrapolation: ERG CR model

Table 49: Revised base case with EORTC extrapolation: ERG CR model

	Undisc. LYs	QALYs	Costs	ICER
DABR	[redacted]	[redacted]	[redacted]	
PLAC	15.363	7.762	£81,154	
Net	[redacted]	[redacted]	[redacted]	£27,432

The ERG sensitivity analyses result in the following (see Table 50):

Table 50: Deterministic sensitivity analyses: No EORTC extrapolation: ERG CR model

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Base case	[redacted]	[redacted]	[redacted]	£46,161
SA01: EQ-5D RFS split by arm	[redacted]	[redacted]	[redacted]	£49,492
SA02a: EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£53,061
SA02b: EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£40,873
SA02c: SA01 + EQ-5D intercept -25%	[redacted]	[redacted]	[redacted]	£57,814
SA02d: SA01 + EQ-5D intercept +25%	[redacted]	[redacted]	[redacted]	£43,264
SA03: DABR monitoring +50%	[redacted]	[redacted]	[redacted]	£48,347
SA04a: LR resection 0%	[redacted]	[redacted]	[redacted]	£46,954
SA04b: LR resection 20%	[redacted]	[redacted]	[redacted]	£45,369
SA05: LR events balance EORTC 18071	[redacted]	[redacted]	[redacted]	£46,530
SA06: DR costs and benefits reflect EoL[h]	[redacted]	[redacted]	[redacted]	£46,589

Modelling based upon the other curves that are a good visual fit

The other curves when used for Segment 1 and Segment 2 of the model suggest the following (see Table 51):

Table 51: Deterministic sensitivity analyses: alternative curves

	DABR – PLAC net:			
	Undisc LYs	QALYs	Costs	ICER
Company generalised gamma (U) cure	[redacted]	[redacted]	[redacted]	£11,574
Company log-normal (U) cure	[redacted]	[redacted]	[redacted]	£67,645
ERG flexible parametric	[redacted]	[redacted]	[redacted]	£20,167

5.5 Conclusions of the cost effectiveness section

The company model structure and base case is unusual for three main reasons.

- It fits parameterised curves to the head-to-head trial data but does not use these for any extrapolation. Instead, extrapolation from month 50 applies common risks to both the

[h] Rather than apply the costs of the post-DR treatments this is implemented by converting the post-DR costs into their equivalent QALY decrements at a willingness to pay of £50k/QALY, hence the increase in the net QALY gain. But having applied these QALY decrement the costs of the post-DR treatments are no longer applied, hence the increase in the net costs

dabrafenib+trametinib arm and the placebo arm, based upon the placebo arm of the EORTC 18071 trial.[21] There are concerns about the generalisability of the EORTC 18071 trial population to the BRAF+ve patients of COMBI-AD. The method also essentially freezes the proportionate OS gain at the 50 month value, with survival in the placebo arm being around 80% of survival in the dabrafenib+trametinib arm from month 50 to month 600.

- When patients have a distant recurrence these patients are not modelled explicitly. Instead, total costs and total QALYs are taken from CS to NICE STAs of treatments for metastatic disease. NICE STAs of treatments for metastatic disease have typically been viewed as satisfying End of Life criteria and the total costs that are applied are large compared to the total QALYs that accrue. As a consequence, the treatments that NICE has approved as valuable due to End of Life become fairly disastrous from a cost effectiveness viewpoint when their costs and QALYs are appended to the current model. There is an argument for valuing these costs and QALYs at the End of Life willingness to pay threshold.
- Related to the above bullet, while the model does fit an OS curve to the post-DR patients this does not affect the cost effectiveness estimates and is more for validation purposes. During COMBI-AD there was a noticeably larger number of non-melanoma deaths in the placebo arm than in the dabrafenib+trametinib arm, which might argue for a competing risks analysis. But because the modelled OS does not affect the cost effectiveness estimate, it is not obvious how this could be taken into account within the economics.

The company rejects a number of parameterisations of the COMBI-AD RFS data because the dabrafenib+trametinib curve falls below the placebo curve. For a number of curves this does not occur until well into extrapolation, and is minimal to the point of being inconsequential when it does. The company has not properly justified why these curves should be rejected. In the opinion of the ERG they should be considered within the economics.

The main uncertainty is around which curves should be applied and to what extent they should be extrapolated. The company position is that the COMBI-AD log-logistic (U) cure model curves should be used to 50 months but should not be used for extrapolation, with extrapolation being based upon data from the EORTC 18071 trial instead.. The ERG notes the differences in populations between COMBI-AD and EORTC 18071. The ERG sees more merit in using

parameterised curves derived from COMBI-AD for extrapolation. This also permits the duration of benefit from dabrafenib+trametinib over placebo to be explored.

ERG expert opinion suggests that dabrafenib+trametinib may postpone recurrences but are less likely to avoid them altogether, meaning that in the longer term the proportion who are cured will converge with that of the placebo arm. This argues for the COMBI-AD log-logistic (R) cure model curves over the COMBI-AD log-logistic (U) cure model curves. It can be noted that the AIC for the (U) model may show some superiority, but the BICs are virtually identical for the two models. Convergence of cure rates further argues for the ERG COMBI-AD competing risks model curves, with an additional argument in their favour being that both a company adviser and the ERG are of the opinion that a competing risks analysis is necessary due to the COMBI-AD data definitions. Convergence of cure rates further argues that these curves should be used for extrapolation. Clearly, if the proportion who are cured by dabrafenib+trametinib tends to converge with that of placebo the cost effectiveness of dabrafenib+trametinib worsens somewhat.

While the calculation of the calibrating hazard ratio for post-LR events has intuitive appeal, it suggests that more than 90% of those with a 1st recurrence will experience a 2nd recurrence within 50 months. No external data has been provided to support this, though it can be noted that the majority of 1st recurrences are anticipated to be distant recurrences.

The proportion on treatment is applied in the quality of life calculations. Data supplied at clarification suggests that a higher proportion of dabrafenib+trametinib patients should be modelled as being on treatment, but this only marginally worsens the cost effectiveness estimate. Of more concern is data supplied at clarification which stated that for quite a large proportion of dabrafenib+trametinib patients time to treatment discontinuation was censored at day 364 and end of trial. If these patients continued to receive dabrafenib+trametinib beyond day 364 this could affect costs quite considerably. This is probably crossed wires but, either before or at the AC, it would help if the company could clarify what number of patients received any dabrafenib+trametinib after day 364 and what number of patients had a dabrafenib+trametinib prescription beyond day 364.

There is uncertainty about drug wastage during COMBI-AD. The company method is likely to underestimate this, as it applies the minimum number of packs that are consistent with individual patients' cumulative doses. Prescriptions at times other than 4-weekly, dose interruptions, dose

escalations and dose reduction are all likely to increase wastage. The ERG estimates are based upon company data supplied at clarification, though these may overestimate wastage.

Only SAE hospitalisation costs have been included. There is evidence of higher adverse events, more prophylactic medication of adverse events and more active medication of adverse events in the dabrafenib+trametinib arm. The medication costs may be minor, but any increase in OP or GR visits would be more serious. But these costs would have to rise significantly to have any real effect upon the cost effectiveness estimate. Differentiating quality of life values for RFS by arm appears to have more of an effect, which may suggest that the company base case has not entirely taken into account the quality of life effects of adverse events.

The company assumes a high proportion of stage IV patients will receive dabrafenib+trametinib for their stage IV disease. The costs of dabrafenib+trametinib treatment at stage IV are very large, so avoiding these costs improves the cost effectiveness estimate. ERG expert opinion suggests that a somewhat lower proportion of stage IV patients will receive dabrafenib+trametinib, and that some will receive nivolumab+ipilimumab. The ERG proportions worsens the cost effectiveness estimate.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG presents three sets of analyses:

- Using the company log-logistic (U) cure model
- Using the company log-logistic (R) cure model
- Using the ERG competing risks model, with a common placebo risk from month 256 when the curves come together.

The company log-logistic (U) suggests that dabrafenib+trametinib will permanently cure a larger proportion of patients. Both the company log-logistic (R) and the ERG competing risks suggest that dabrafenib+trametinib will postpone recurrences but that in the medium to long term the dabrafenib+trametinib cure rate will converge with that of placebo, which the ERG finds more persuasive.

The ERG has made two minor corrections to the company model structure. The ERG has also revised the company model along the following lines:

- Assume that those who have received dabrafenib+trametinib require the same monitoring requirement as those remaining on dabrafenib+trametinib
- Assume an additional quarterly OP appointment for dabrafenib+trametinib to account for dermatological monitoring
- Apply the treatment proportions that appear to be implied by the company responses at clarification
- Revise the dabrafenib+trametinib drug costs to be based upon the company answer to clarification question A3, further qualifying prescription costs accordingly
- Revise the proportion of DR patients who receive pembrolizumab from [redacted] to reflect expert opinion and the probable costs and effects of nivolumab+ipilimumab
- Using the base case set of assumptions when fitting the model outputs at calibration to the post-LR COMBI-AD OS KM curve.

The ERG undertakes a range of scenario analyses.

- SA01: Applying the EQ-5D regression that splits on treatment by arm and off treatment by arm

- SA02: Varying the intercept term of the EQ-5D regressions by ±25% for both the base case regression and the regression that splits on treatment by arm and off treatment by arm, this resulting in approximately a ±0.1 change in the quality of life values that are applied
- SA03: Extending the monitoring requirement for dabrafenib+trametinib by 50%
- SA04: Varying the proportion of LR events that require resection from 10% to 0% and to 20%
- SA05: Deriving the balance between LR, DR and death events in the post-LR modelling from the same source as for the RFS balance between events: EORTC 18071
- SA06: Valuing the health benefits of the DR treatments at the end of life WTP of £50k/QALY
- SA07: EORTC extrapolation from month 50 for RFS in the dabrafenib+trametinib arm, RFS in the placebo arm, Post-LR RFS in the dabrafenib+trametinib arm and Post-LR RFS in the placebo arm.

Table 52: ERG revised analyses: ICERs

	L-Log (U)	L-Log (R)	ERG CR
Base case	£20,701	£62,853	£46,161
SA01: EQ-5D RFS split by arm	£21,734	£70,752	£49,492
SA02a: EQ-5D intercept -25%	£24,134	£72,018	£53,061
SA02b: EQ-5D intercept +25%	£18,134	£55,790	£40,873
SA02c: SA01 + EQ-5D intercept -25%	£25,697	£83,032	£57,814
SA02d: SA01 + EQ-5D intercept +25%	£18,830	£61,636	£43,264
SA03: DABR monitoring +50%	£21,929	£65,675	£48,347
SA04a: LR resection 0%	£21,329	£63,847	£46,954
SA04b: LR resection 20%	£20,073	£61,859	£45,369
SA05: LR events balance EORTC 18071	£20,764	£63,716	£46,530
SA06: DR costs and benefits reflect EoL	£24,980	£61,487	£46,589
SA07: EORTC extrapolation	£26,258	£30,866	£27,432

The scenario that extrapolates from month 50 to month 600 using the EORTC placebo data rather than the arm specifc COMBI-AD data result in quite similar ICERs almost regardless of which COMBI-AD parameterisation is used for up to month 50. This is because applying common risks to each arm from 50 to month 600 effectively freezes the benefits to be as they were at month 50.

The EORTC extrapolation results in survival in the placebo arm being around 80-85% that of survival in the dabrafenib+placebo arm for month 50 to month 600.

More fully accounting for SAEs and possibly AEs that did not require hospitalisation but did require medication and possibly additional appointments wouldprobably increase costs more in the dabrafenib+trametinib arm than in the placebo arm. But given the modelled large net cost for dabrafenib+trametinib, any SAE costs would have to be quite large to have much effect on the cost effectiveness estimate. There is the suggestion, as shown in SA01, that explicitly accounting for the different SAE profiles by arm would worsen the cost effectiveness estimate.

If patients were prescribed dabrafenib or trametinib beyond day 364 of the COMBI-AD trial either the clinical data does not particularly reflect the anticipated license or costs could be somewhat higher in the dabrafenib+trametinib arm. Either would worsen the cost effectiveness estimate.

7 END OF LIFE

End of life does not apply.

8 OVERALL CONCLUSIONS

The case for adoption of dabrafenib+trametinib adjuvant therapy rests on evidence from only a single placebo controlled RCT (COMBI-AD). The primary outcome, recurrence free survival (RFS), clearly demonstrated that adjuvant treatment delayed recurrence. There was imbalance between study arms in the numbers and timing of individuals whose follow up did not extend to study cut off. Competing risk analysis suggested that this resulted in some bias in favour of adjuvant over placebo. Since RFS was the major COMBI-AD trial input into the company's economic model, such bias in the RFS estimate influences cost effectiveness estimates. The greatest uncertainty in the clinical effectiveness was whether dabrafenib+trametinib induced only a delay in recurrence or whether some patients are cured (permanent delay in recurrence they would otherwise have experienced). The observed data from COMBI-AD does not provide evidence of cure and to assume cure for some patients, in the opinion of the ERG, is not supported by the available data. The company's submission rests heavily on 50 months of observed data on RFS in COMBI-AD; for economic analysis a variety of heterogenous supplementary external sources of data were needed to facilitate patient pathways during the 50 months of observed data and beyond observation to the life time horizon. A major assumption in the use of such external data was that BRAF+ status was irrelevant for the incidence of recurrence; no evidence in support of this was presented.

The main differences of opinion between the company and the ERG in the cost effectiveness section are:

- Should the COMBI-AD parameterised curves be used for extrapolation beyond month 50, or should a common curve derived from the EORTC placebo arm be applied for RFS in the dabrafenib+trametinib arm, RFS in the placebo arm, Post-LR RFS in the dabrafenib+trametinib arm and Post-LR RFS in the placebo arm? The ERG thinks there is value in extrapolation using the COMBI-AD parameterised curves because this permit different cure rates to be explored. It also prevents the model "freezing in" the survival gain modelled at month 50 for months 50 to 600.
- Does dabrafenib+trametinib permanently cure more patients or does it mainly postpone recurrences, with cure rates converging in the longer term with those of placebo? ERG expert opinion anticipates postponement of recurrences with long term cure rates gradually converging.

- Should the model cost dabrafenib+trametinib based upon the minimum possible number of packs that could feasibly be used to satisfy patients' cumulative doses during COMBI-AD or should it be based upon the number of packs prescribed during COMBI-AD? The ERG thinks it should be based upon the number of packs, though the ERG method may overestimate wastage due to data deficiencies.
- Is it reasonable to apply the total costs and total QALYs from previous NICE assessments of stage IV disease for DR patients, when NICE assessments of stage IV disease have typically viewed it as End of Life? Should these treatments be valued at the End of Life willingness to pay? The ERG thinks that fewer patients will receive dabrafenib+trametinib for stage IV treatment than the company does, with more patients receiving pembrolizumab or nivolumab+ipilimumab. The ERG also sees merit in valuing these at the End of Life £50k/QALY threshold.

8.1 Implications for research

The follow up in COMBI-AD was too short for firm conlcusions other than that a delay in recurrence was achieved. Extended follow up from this trial is required together with monitoring for post treatment unanticipated and anticipated effects of therapy. In view of the evidence accumulating for effectiveness of several adjuvant interventions, future trials should ecompass active adjuvant treatments as comparators rather than placbo or observation.

RFS is a multicomponent composite outcome measure that appears to be widely used in adjuvant studies. More useful analyses might be directed specifically at incidence of local recurrence, distant recurrence events and also at secondary recurrence incidence following first recurrence (the latter particularly in studies where adjuvant treatment is prolonged).

The number of adjuvant studies in melanoma is increasing as new targeted therapies and immune therapies are introduced. It may now be appropriate for the adjuvants to be compared using network meta-analytic methodology.

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10 Appendix

10.1 Appendix A RFS proportional hazards

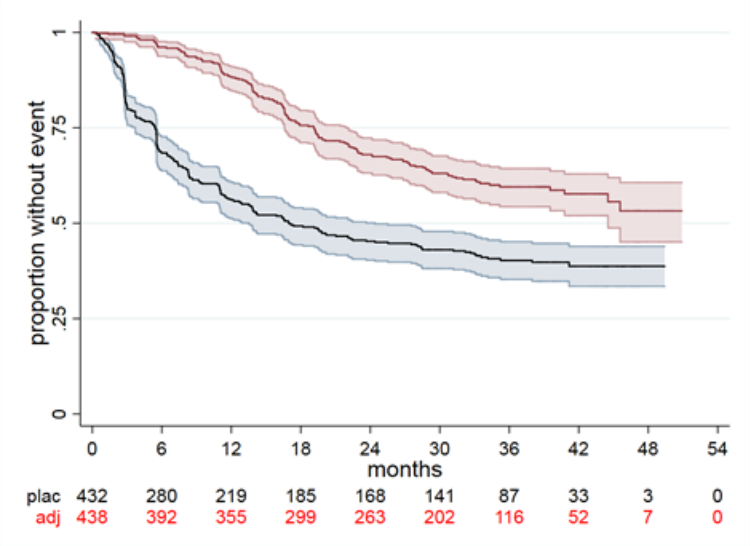

Figure 41: KM analysis of RFS (CS Figure 13) using data supplied in clarification (A4)

Visual inspection of the KM plot suggests that the proportional hazards assumption is unlikely to hold. The results of the test for proportional hazards are shown below; visual inspection indicates the lines gradually approach each other and do not remain parallel and so not support the proportional hazards assumption.

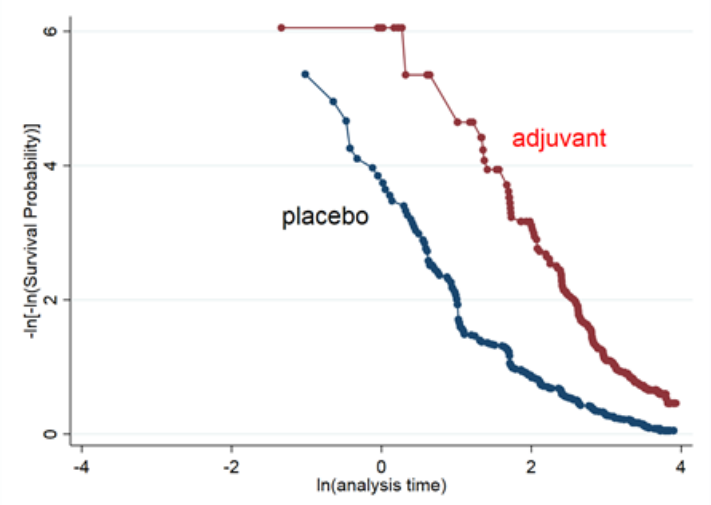

Figure 42: Graphical test of proportional hazards assumption

When followed by a chi squared test the following results was obtained.

	rho	chi2	df	Prob>chi2
ad1pbo0	0.39984	60.15	1	0
global test		60.15	1	0

An alternative graphical test is shown in Figure 43; for proportional hazards to hold we would expect the scaled Schoenfeld residuals to parallel the HR line, which visual inspection shows is not the case.

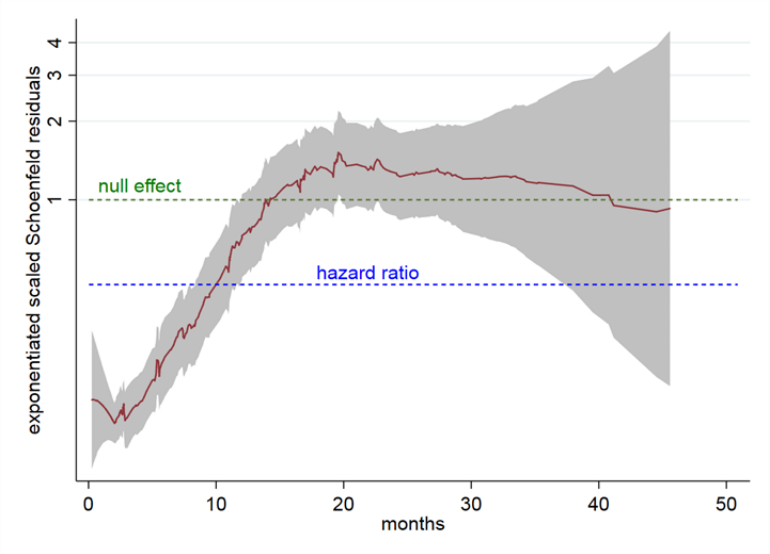

Figure 43: Graphical test of proportional hazards assumption

10.2 Appendix B Information criteria scores for ERG parametric models of RFS

With treatment as indicator

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
gamma	870	-1075.15	-1020.83	4	2049.664	2068.738
exponential	870	-1112.73	-1083.83	2	2171.666	2181.203
weibull	870	-1102.98	-1075.93	3	2157.859	2172.165
gompertz	870	-1084.54	-1057.94	3	2121.873	2136.179
lognormal	870	-1080.41	-1036.47	3	2078.932	2093.238
loglogistic	870	-1090.63	-1050.23	3	2106.466	2120.772
flex df3	870	.	-1048.67	5	2107.342	2131.185

Adjuvant arm; treatment not an indicator

Model	Obs	ll(null)	ll(model)	df	AIC	BIC

gamma	438	.	-404.57	3	815.1393	827.3859
exponential	438	-415.365	-415.365	1	832.7308	836.813
weibull	438	-410.607	-410.607	2	825.2134	833.3779
gompertz	438	.	-415.138	2	834.2763	842.4407
lognormal	438	.	-404.597	2	813.1929	821.3574
loglogistic	438	.	-405.987	2	815.9746	824.139
flex df 3	438	.	-393.564	4	795.1278	811.4567

Placebo arm; treatment not an indicator

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
gamma	432	.	-604.351	3	1214.703	1226.908
exponential	432	-668.468	-668.468	1	1338.935	1343.004
weibull	432	-646.726	-646.726	2	1297.453	1305.59
gompertz	432	.	-617.136	2	1238.272	1246.409
lognormal	432	.	-621.945	2	1247.889	1256.026
loglogistic	432	.	-630.968	2	1265.936	1274.073
flex df 3	432	.	-600.696	4	1209.391	1225.665

10.3 Appendix C Comparison of model hazards

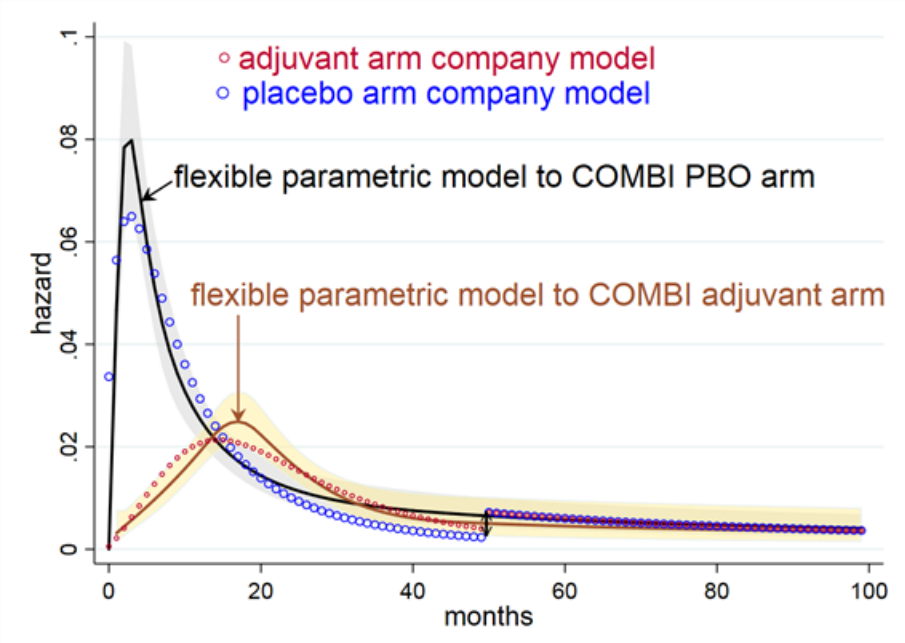

Figure 44: Company composite RFS model compared to ERG flexible parametric model

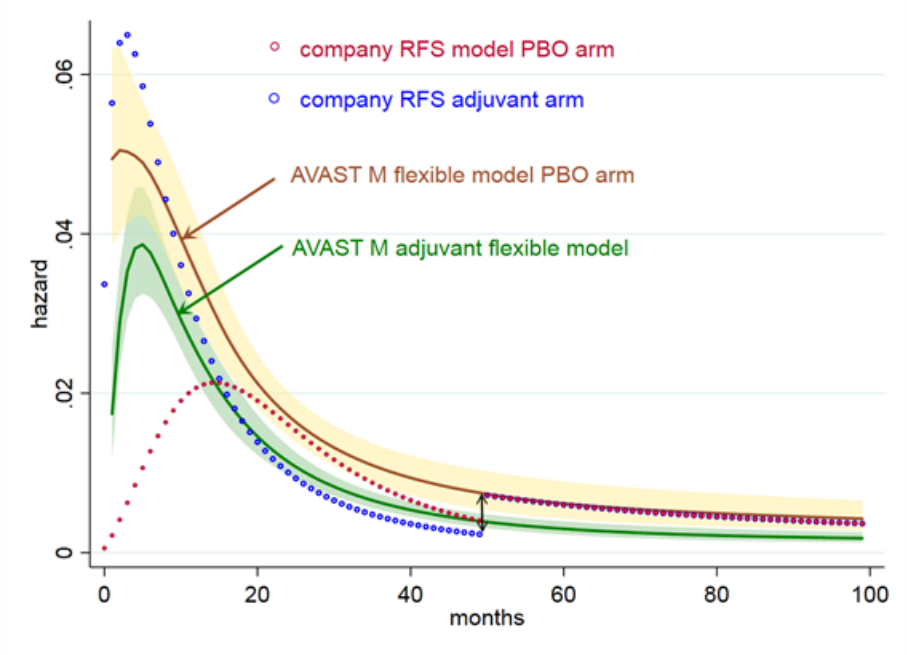

Figure 45: Company composite RFS model compared flexible parametric models for each arm of AVAST-M

For guidance on how to format Tables and Figures, please see SOP WE Preparation and submission of Final Reports to NICE and NETSCC V4.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma [ID1226]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 4 July 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.

Summary of factual inaccuracies in the ERG report from Warwick Evidence

Thank you for the opportunity to review the ERG report for factual inaccuracies. Further to this, please find below a summary of our *key* findings with further details of all our findings provided in the subsequent pages of this pro-forma.

Clinical effectiveness issues

- The ERG incorrectly describe and interpret the primary end-point (relapse-free survival) of the COMBI-AD trial and consequently suggest that dabrafenib plus trametinib may *postpone* recurrences. This is contradictory to the evidence from the COMBI-AD trial which shows that adjuvant treatment with dabrafenib plus trametinib resulted in a statistically significant and clinically meaningful reduction in the risk of relapse (hazard ratio [HR] 0.47; 95% confidence interval [CI]: 0.39–0.58; $p=1.53x10^{-14}$).[1]
- The competing risk analysis employed by the ERG is based on inaccurate assumptions and therefore the use of the associated efficacy estimates in the economic model and ensuing cost-effectiveness results are highly uncertain.
- The ERG indicate that Novartis has underestimated the need for cardiac monitoring in patients treated with adjuvant dabrafenib plus trametinib. This is incorrect since the monitoring schedule included in our submission is consistent with current consensus guidelines for the follow up of high-risk cutaneous melanoma in the UK (2013)[2] as well as the Summary of Product Characteristics (SmPC) for the interventions.[3, 4]

Cost-effectiveness issues

- The ERG's estimates of cost-effectiveness are underpinned by a competing risk analysis that is inappropriate due to inaccurate assumptions and a lack of access to emerging more mature data.
- The ERG's selection of extrapolations are based on an unfounded premise that the curves will ultimately converge. The most recent available evidence is inconsistent with this notion as emerging 40-month follow up data[5] suggest that the curves are beginning to diverge.
- The ERG's summary of the company's approach is incorrect and incomplete.

Typographical/confidentiality highlighting issues

- We have noted several cases of typographical errors and errors in the marking of confidential data.

We kindly request that the ERG consider our comments in this response document and make the necessary amendments to their report.

Kind regards,

[redacted]

HEOR Manager, Novartis Pharmaceuticals UK Ltd

Please note that all information highlighted in yellow and underlined should be treated as "academic in confidence" and highlighted in turquoise and underlined should be treated as "academic in confidence" in this document should be considered as confidential in nature

Clinical Issues

Issue 1 Incorrect description and interpretation of the primary end-point of the COMBI-AD study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 11, 12, 13, 39, 43, 55, 56, 72, 135. The ERG describe the primary end-point of the COMBI-AD trial as recurrence-free survival, when the primary end-point was *relapse*-free survival.[1]	We request that the definition of the primary end-point be corrected from recurrence-free survival to relapse-free survival throughout the report.	Although these terms are interchangeable, and appear related in the literature,[6] to avoid confusion we request that the definition of the primary end-point be corrected throughout the report to reflect the true protocol definition of this clinical trial outcome.	No change made. The ERG agree that these terms are interchangeable in the literature, therefore "confusion" pre dates the ERG report. Furthermore the submission itself uses the terms "recurrence" and "relapse" interchangeably in specifying the events of interest in their outcomes (e.g compare Tables 12 and 14).
Pages 13, 20, 24 When interpreting the results of the primary outcome of the COMBI-AD trial, the ERG do not accurately discuss the results in context of the trial outcomes: *"The company's Kaplan Meier (KM) analysis of the primary outcome measure (RFS) clearly demonstrated that combination adjuvant therapy with dabrafenib and trametinib considerably delayed recurrence; for RFS a*	Please update as indicated below: *"The company's Kaplan Meier (KM) analysis of the primary outcome measure (RFS) clearly demonstrated that combination adjuvant therapy with dabrafenib and trametinib ~~considerably delayed~~ significantly reduced the risk of relapse; for RFS a hazard ratio (HR) of 0.47 (95% CI: 0.39–0.58; P<0.001) was estimated"*	In the COMBI-AD trial, relapse-free survival (RFS) was significantly longer with dabrafenib plus trametinib compared with placebo, representing a 53% lower risk of recurrence (HR for recurrence or death: 0.47; 95% CI: 0.39–0.58; $p=1.53x10^{-14}$ by stratified log-rank test).[1] This result provides both a statistically significant and clinically meaningful robust evidence base for the efficacy of dabrafenib plus	No change made. The estimation of the hazard ratio quoted assumes that proportional hazards hold. As documented in the ERG appendix A the available evidence does not support this assumption, rendering the quoted HR difficult to interpret. interpret (see: B Alexander, J Schoenfeld, LTrippa *Hazards of Hazard Ratios — Deviations from Model Assumptions in Immunotherapy. N*

hazard ratio (HR) of 0.47 (95% CI: 0.39–0.58) was estimated" (page 13)		trametinib in this indication. The ERG's description of *'delayed'* is therefore not an accurate reflection of the significance of the results or the sustained duration of effect given the data from COMBI-AD show that even after resection, 44% of patients who undergo routine surveillance will relapse within 1 year compared to 12% of patients receiving adjuvant treatment with dabrafenib plus trametinib.[1] It should also be noted that the improvement in RFS with dabrafenib plus trametinib is sustained throughout the 3-year follow up.[5]	*Engl J Med 378;12 nejm.org March 22, 2018;* *Hernan MA. The Hazards of Hazard Ratios. Epidemiology. 2010 21(1): 13–15.)* The ERG note that in the company's expert opinion document (REF 57) slide 10 states: "*The relapse free survival plot shows that treatment is delaying relapse between Year 1 and Year 2"*
"The study demonstrated a clear and substantial delay in RFS resulting from combination therapy" (page 20) *"There is clear evidence that adjuvant treatment delays recurrence"* (page 24)	*"The study demonstrated a clear and statistically significant reduction in the risk of relapse ~~substantial delay in RFS~~ resulting from combination therapy"* *"There is clear evidence that adjuvant treatment ~~delays~~ significantly reduces the risk of recurrence"*		No change made – please see above response (pages 13, 20, 24)
Pages 13, 14 The definition of RFS is incorrect and misleading. *"RFS was a composite outcome encompassing death (from melanoma or other cause) recurrence (local and/or distant), a new primary melanoma (SPM), and censoring with ongoing follow up or with premature follow up ended (PEFU)"*	Please update to: *"RFS was a composite outcome encompassing death (from melanoma or other cause) recurrence (local and/or distant), a new primary melanoma (SPM). ~~and censoring~~ Patients with ongoing follow up or with premature "follow up ended" were censored (PEFU)"*	PEFU was not defined as a component of the RFS outcome. The inaccurate reporting of the definition of trial endpoints and censoring should be amended to reflect the correct definitions.	Changed

Issue 2 The ERG's justifications for performing competing risk analysis of time-to-event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 18, 46, 129 The ERG states *"Convergence of cure rates further argues for the ERG COMBI-AD competing risks model curves, with an additional argument in their favour being that both a company adviser and the ERG are of the opinion that a competing risks analysis is necessary due to the COMBI-AD data definitions. Convergence of cure rates further argues that these curves should be used for extrapolation"*	We propose the following underlined amendments to the text, wherever reference is made to the company advisor in the report: *"~~Convergence of cure rates further argues for the ERG COMBI-AD competing risks model curves, with an additional argument in their favour being that both a company adviser and t~~The ERG are of the opinion that a competing risks analysis is necessary due to the COMBI-AD data definitions. ~~Convergence of cure rates further argues that these curves should be used for extrapolation.~~"*	The ERG has taken the comments received from a company advisor out of context. The advisor did not advise that PEFU be considered as a competing event for RFS, but rather suggested considering RFS events (LR, DR and death) separately as opposed to using RFS directly and applying a constant proportion of events. However, following further discussion, and considering the low number of death events in RFS, it was felt that modelling RFS events individually would increase uncertainty and complicate the development of the cost-effectiveness model; as such, the model was based on the aggregate RFS events with the probability of each type event. Consequently, the statement that the company advisor was of the opinion that a competing risk analysis was necessary is inaccurate and misleading since this does not accurately reflect the opinion of the expert.	Changed on page 18 and 129. The context of the company advisors comment made available to the ERG (company's expert opinion document (Ref 57 Power Point Slide 76) under the heading **"***How is the time to distant recurrence calculated in the model?"* was the statement "*What I would have expected to have happened would be some competing risk type of analysis and actually model those recurrence events separately and treat them as sensitive…*" The ERG checked the power point Ref 57 for any comments on the advisor statement but found none. The ERG believes the CR analysis is consistent with the expression "*some competing risk type of analysis*" and the aim was to analyse "*recurrence events separately*"

		Furthermore, convergence of cure rates, if that were to be the case, does not necessarily provide a rationale for use of a competing risk framework since convergence of cure rates can be observed for some distributions fit to failure time data when competing risk analysis is not employed. Given that, there is no evidence of convergence from the more mature data set of COMBI-AD with approximately 40 months of follow up (data cut 30 Apr 2018);[5] the ERG's rationale for a competing risk analysis is therefore unfounded and inconsistent with the available evidence. Whilst we appreciate that the ERG did not have access to this data since it became available after our company submission to NICE and we note that according to procedure new information should not be submitted at this stage, we would like to highlight that this more mature data contradicts the ERG's assertions that the observed data from COMBI-AD converges. Consequently, we would be happy to provide this new data if given permission to do so.	The ERG did not make ANY such statement; the ERG has searched the ERG report for this statement but could not find it. The ERG has not been privy to this later data, nor was the ERG notified of its existence in the company submission or in clarification responses.

Issue 3 The ERG's competing risk analysis is inappropriate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG's competing risk analysis is inappropriate, since PEFU and SPM were considered as competing risks for RFS events: **Page 14** *"the ERG conducted a CR analysis of RFS in which PEFU and SPM were considered as a CR"* **Pages 53–60** *"Patients experiencing "Follow up ended" ([redacted] people respectively in adjuvant and placebo arms) were treated as experiencing CRs following Graham et al. 2013. SPM (affecting 6 and 7 patients in adjuvant and placebo arms respectively) was also considered a CR"*	If the ERG would like to conduct a competing risk analysis, we propose that they do so in which PEFU and SPM are ***not*** considered as competing risks.	The ERG's competing risk analysis of RFS is fundamentally flawed in that PEFU and SPM are considered as competing events rather than censoring events. Since PEFU and SPM preclude *observation* of the event of interest but do not preclude *occurrence* of the event of interest, it is more appropriate to consider these events as censoring events and not as competing risks. Considering PEFU and SPM as competing risks leads to an underestimation of the risk of recurrence since patients who experience these events may subsequently experience loco-regional recurrence (LR), distant recurrence (DR), or death, but because patients were not followed for recurrence after first RFS event, any such events would not be recorded. The ERG reference the methodology by Graham *et al.* (2013)[7] in their approach to their analysis, however Novartis has some concerns about the relevance of this approach in the	No change made. ERG believe these concerns are essentially matters of opinion. Rather than factual errors In Kaplan Meier analysis one hopes the extent of premature drop out (premature loss to follow up) is minimal and if present is balanced between arms. There is some imbalance in the Combi trial and the ERG do not see this addressed in the submission. The ERG CR analysis offers an alternative method to KM censoring in order to address such imbalance; this resulted in a relatively minor reduction in the estimated restricted mean survival difference between study arms. The company are correct that ERG has considered PEFU as a competing event for recurrence and that after PEFU recurrence events were not recorded in the trial.

		context to the COMBI-AD trial. Graham *et al.* (2013) investigated whether the association between sexual risk behaviour and HIV-1 acquisition in female sex workers in Kenya changed after accounting for loss to follow up with competing risks regression. In this study anecdotal reports suggested that common reasons for loss to follow up included relocating and stopping sex work for a new job or steady partner. Consequently, loss to follow up could be associated with a lower HIV-1 risk in this case and therefore it may be considered reasonable to assume loss to follow up as a competing risk. However, in the context of the COMBI-AD trial, there is no reason to believe that patients with PEFU are at a lower risk of recurrence than those who remain in the trial, and as such, the basis for the competing risk analysis is misplaced. Since the RFS estimates are a key driver of the economic model, it stands to reason that such bias in the ERG's analysis and estimates of RFS has a major influence on the cost-effectiveness analyses and subsequently casts uncertainty on	The company is also correct in asserting that this procedure leads to a (slightly) lower risk of recurrence estimate; however the point of the analysis was to explore if this was equitable between study arms; and it was found it was not quite to be so, presumably because of the imbalance in numbers and timing of PEFU shown in ERG Figure 1. Because no recurrences were recorded after PEFU there is no way of knowing whether these patients are at the same, greater or smaller risk than other participants. The CE model is **not** sensitive to whether CR or KM analysis is used but to parameterizations used to extrapolate beyond the CR or KM data e.g. If the placebo arm of EORCT

		the ERG's cost-effectiveness estimates.	18071) is employed for extrapolation then use of CR or KM analysis has very minor impact on the cost-effectiveness estimate.
Page 20 *"The company and the ERG therefore both conducted a CR analysis"*	Please update as follows: *"Following a request from the ERG, the company and the ERG therefore both conducted a CR analysis"*	The statement is misleading since Novartis only conducted this analysis upon request from the ERG. It was not conducted as part of our original submission as it was not considered appropriate.	Changed.
Page 20 ***"**The ERG analysis suggested that the company's KM analysis may overestimate the benefit of dabrafenib/trametinib adjuvant therapy by approximately 11% and 21% (for RFS and OS, respectively)"* **Page 48** *".....results of the ERG CR analysis (section 4.6), suggest that a KM analysis may overestimate the gain from adjuvant over placebo in restricted mean survival to 41 months by approximately 21%"*	Please consider removing this text: *~~"The ERG analysis suggested that the company's KM analysis may overestimate the benefit of dabrafenib/trametinib adjuvant therapy by approximately 11% and 21% (for RFS and OS, respectively)."~~* *~~".....results of the ERG CR analysis (section 4.6), suggest that a KM analysis may overestimate the gain from adjuvant over placebo in restricted mean survival to 41 months by approximately 21%."~~*	This statement is misleading and potentially infers a bias in Novartis's estimates of efficacy in favour of dabrafenib plus trametinib. Kaplan-Meier survival analyses and competing risk analyses are different methods of analysing time-to-event failure data. Our original Kaplan-Meier analysis estimates the prognosis and treatment effects with regards to recurrence or death, whereas the competing risks analysis conducted by the ERG provides estimates of the prognosis and treatment effects for patients up to the point where they experience PEFU. Since RFS events that might occur after a PEFU are effectively ignored, it is inappropriate to compare the	Changed. Restricted mean survival estimates were compared. These can be estimated from KM and CR analysis.

		results of one approach directly with the other and it is not surprising that the estimates differ between the two analyses, with the estimates from the competing risk analysis lower than the original Kaplan Meier analysis. Finally, in order to validate the results of the primary RFS analysis, sensitivity analyses were conducted per the COMBI-AD study protocol. The results of the sensitivity were consistent with the primary analyses, confirming the robustness of the primary analysis results (HR ranging between [redacted] and the upper bound of the 95% CIs being far below 1 for all sensitivity analyses [please refer to Table 11-4 in the CSR[8]]).	The HRs reported assume that proportional hazards hold. As documented in the ERG appendix A the available evidence does not support this assumption, rendering the quoted HRs difficult to interpret (see above for references)

Issue 4 Assertions that dabrafenib plus trametinib may postpone recurrences

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 ERG expert opinion suggests that *"dabrafenib+trametinib may postpone recurrences but are less likely to avoid them altogether; meaning that in the longer term the proportion who are cured will converge with that of the placebo arm. This argues for the COMBI-AD*	The text should acknowledge that dabrafenib plus trametinib potentially may prevent recurrences and be corrected to: *"Dabrafenib+trametinib reduces recurrences as shown in the COMBI-AD trial."*	Although Novartis respects the opinion of the ERG expert, which is based on the data available at the time, we strongly disagree with the notion that dabrafenib plus trametinib *delays* recurrence. This notion is inconsistent with the results of the primary analysis of the COMBI-AD trial which show	No change made. The ERG have quoted expert opinion; this is not a factual error. Although, as mentioned in the ERG report, it is possible that DAB+TRAM prevents some relapses/recurrences, the

log-logistic (R) cure model curves over the COMBI-AD log-logistic (U) cure model curves. It can be noted that the AIC for the (U) model may show some superiority, but the BICs are virtually identical for the two models" **Page 95** ***"**ERG expert opinion also notes that it is unaware of any basic science that could explain why adjuvant dabrafenib+trametinib would have a significant "cure" effect even in the palliative setting, so anticipates that adjuvant dabrafenib+trametinib is likely to delay recurrence but have a similar "cure" rate to resection"* **Page 129** *"ERG expert opinion suggests that dabrafenib+trametinib may postpone recurrences but are less likely to avoid them altogether, meaning that in the longer term the proportion who are cured will converge with that of the placebo arm"* **Page 135** *"ERG expert opinion anticipates postponement of recurrences with long term cure rates gradually converging"*		that dabrafenib plus trametinib *significantly lowers* the rate of recurrence compared with placebo (HR 0.47; 95% CI: 0.39–0.58; p=1.53x10^{-14} by stratified log-rank test).[1] Since the risk of relapse diminishes with time,[2] and the literature confirms a minor increase in the proportion of patients experiencing a recurrence after 3 years,[9-15] it is expected there will be a low rate of additional RFS events in both the treatment and placebo arms of the COMBI-AD trial after 3 years of follow up. This is consistent with the ERG expert opinion, which suggests *"that among patients who have not recurred after 5 years the risk of recurrence is small",* and as such it is also reasonable to consider that dabrafenib plus trametinib may *prevent* recurrences. New analyses conducted by Novartis in response to questions received from the Committee for Medicinal Products for Human Use (post NICE submission) provide an additional 10 months of data from the COMBI-AD trial (approximately 40 months follow	ERG do not accept that beyond the COMBI observed period there is good evidence that "cures" in the adjuvant

		up; data cut 30 Apr 2018) in relation to the primary analysis (30-Jun-2017 cut-off). These new analyses show that dabrafenib and trametinib continues to demonstrate a consistent and robust clinical RFS benefit over placebo [redacted] Whilst we appreciate that the ERG did not have access to these data and understand that procedurally new information should not be submitted at this stage, this more mature data contradicts the ERG's assertions that the observed data from COMBI-AD postpones recurrences with long-term cure rates gradually converging (page 135: "*observed data from COMBI-*	arm will be more frequent than in the placebo arm. With regard to HRs please see above. ERG have not been privy to this more mature data. See above regarding lack of support for proportional hazards in estimating HRs The ERG agree that more mature data is desirable; however ERG do not and did

		AD does not provide evidence of cure and to assume cure for some patients, in the opinion of the ERG, is not supported by the available data") As such, we kindly ask the ERG and the committee to consider this emerging evidence given that it is material and contradictory to the ERG's previous assertions. We would be very happy to supply this new data if given permission to do so.	not have access to this new data, and in fact were not made aware of its existence until receipt of this factual error document. It is difficult to understand how such unavailable data becomes relevant in a factual error check. Its inclusion for this purpose clearly indicates that these are matters of interpretation rather than of factual error.

Issue 5 Incorrect descriptions of secondary outcomes in the COMBI-AD trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47 The ERG have omitted freedom from relapse (FFR) from their description of secondary outcomes: *"CS Table 8 specified the following secondary outcomes: OS, distant metastasis free survival (DMFS, defined in section 2.3.1), and safety"*	For completeness, please update as follows: *"CS Table 8 specified the following secondary outcomes: OS, distant metastasis free survival (DMFS), freedom from relapse (FFR), (defined in section 2.3.1) and safety"*	All of the secondary outcomes of the COMBI-AD trial should be recorded.	Changed.

Issue 6 Incorrect reporting of adverse event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 The mean duration of diarrhoea should be marked as confidential.	Please update the text to: *"it was confirmed that there were no reported discontinuations of treatment due to diarrhoea which was mainly transient with* [redacted]	This information is considered AIC.	Changed, now highlighted.
Page 53 The number of patients experiencing serious adverse events (SAEs) should be marked as confidential.	*"In clarification question C2 it was stated that* [redacted] *patients experiencing SAE's in the placebo arm had a causality that was reported as related to the study treatment"*	This information is considered AIC.	Changed, now highlighted.

Issue 7 Incorrect description of treatment duration/exposure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 *"A 12-month treatment duration was anticipated"*	Please update the text to reflect the treatment rules according to the COMBI-AD study protocol and draft SmPC: *"~~A 12-month~~ The treatment duration was stipulated as a period of 12 months"*	The COMBI-AD protocol **stipulated** a treatment duration of 12 months ("Subjects in both arms will receive treatment for 12 months or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent").[16]	Changed
The ERG highlights some potential confusion and concern on whether patients received dabrafenib plus trametinib beyond 12 months:	We kindly request that the ERG update their report to acknowledge that only 1 patient received treatment for more than 365 days and 2 patients received 365 days of	It is incorrect to state that patients were censored at day 364 and at the end of the trial.	No ERG error. No revision required.

Page 19 *"Of more concern is data supplied at clarification which states that for quite a large proportion of dabrafenib+trametinib patients time to treatment discontinuation was censored at day 364 and end of trial. If these patients continued to receive dabrafenib+trametinib beyond day 364 this could affect costs quite considerably. It would help if the company could clarify what number of patients received any dabrafenib+trametinib after day 364 and what number of patients had a dabrafenib+trametinib prescription beyond day 364"* *"But in response to an ERG clarification question the company notes that among the [redacted] patients who completed 12 months of treatment in the dabrafenib+trametinib arm of COMBI-AD the majority, [redacted], continued treatment beyond 12 months when a month is defined as 4 weeks"* **Page 23** *"If patients were prescribed dabrafenib or trametinib beyond day 364 of the COMBI-AD trial either the clinical data does not particularly reflect the anticipated*	treatment, and therefore remove the below text: ~~*Of more concern is data supplied at clarification which states that for quite a large proportion of dabrafenib+trametinib patients time to treatment discontinuation was censored at day 364 and end of trial. If these patients continued to receive dabrafenib+trametinib beyond day 364 this could affect costs quite considerably. It would help if the company could clarify what number of patients received any dabrafenib+trametinib after day 364 and what number of patients had a dabrafenib+trametinib prescription beyond day 364"*~~ ~~*"But in response to an ERG clarification question the company notes that among the [redacted] patients who completed 12 months of treatment in the dabrafenib+trametinib arm of COMBI-AD the majority, [redacted], continued treatment beyond 12 months when a month is defined as 4 weeks."*~~ ~~*"If patients were prescribed dabrafenib or trametinib beyond day 364 of the COMBI-AD trial either the clinical data does not particularly reflect the anticipated license or*	No patients were censored and [redacted] (treatment duration calculated as the maximum of the end treatment date for dabrafenib plus trametinib and the treatment start time + 1). [redacted]	But the further clarification is welcome and can be raised at the AC. In response to ERG clarification question A7 the company replied "In the COMBI-AD trial, the number of patients in the dabrafenib plus trametinib arm that completed 12 months of treatment, completed more than 12 months of treatment, and continued treatment after an LR, DR or SPM was [redacted] The company reply to the ERG clarification question A7 used the term censored in its response [redacted]

license or costs could be somewhat higher in the dabrafenib+trametinib arm". **Page 105** [redacted] *"There may have been some crossed wires in terms of these questions. The main ERG concern is whether many patients received dabrafenib+trametinib beyond 12 months; e.g. whether any patients continued with treatment to e.g. 14 months and beyond, despite the trial protocol. Given the prescribing data this seems unlikely, but it would be helpful if the company could further clarify this before or at the 1st AC."*	~~*costs could be somewhat higher in the dabrafenib+trametinib arm".*~~ [redacted] ~~*"There may have been some crossed wires in terms of these questions. The main ERG concern is whether many patients received dabrafenib+trametinib beyond 12 months; e.g. whether any patients continued with treatment to e.g. 14 months and beyond, despite the trial protocol. Given the prescribing data this seems unlikely, but it would be helpful if the company could further clarify this before or at the 1st AC."*~~		[redacted] error is consequently that of the company.
Page 102	Please correct as follows:	Please update to accurately reflect the dose reductions and escalations from the COMBI-AD trial.	The clarification is welcome and the proposed changes are accepted.

Data on dose reductions and escalations incorrectly reported in table 31: *Dose reductions* [redacted] [redacted] *Dose escalations* [redacted] [redacted]	*Dose reductions* [redacted] [redacted] *Dose escalations* [redacted] [redacted]		The discrepancy has crept in due to the CSR only reporting percentages with no decimal points, meaning that the ERG has to infer the patient numbers from these and the baseline n=435.

Issue 8 Comment on the formulation of dabrafenib plus trametinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14: *"The ERG also feel that the absence of non-oral formulations of dabrafenib/trametinib could limit its overall marketability"*	Please consider removing this statement.	The product's marketability is irrelevant to the decision problem.	Changed

Issue 9 Placebo composition

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53 *"On that basis the ERG had serious reservation regarding the safety, chemical composition and*	Please consider removing this sentence: ~~*"On that basis the ERG had serious reservation regarding the safety, chemical composition and*~~	The placebo in COMBI-AD was inert: as per study protocol, matching placebo capsules for dabrafenib (50 mg and 75 mg) and	Changed

pharmacodynamics of the placebo substance, as one would traditionally expect it to be inert"	~~*pharmacodynamics of the placebo substance, as one would traditionally expect it to be inert"*~~	placebo tablets for trametinib (0.5 mg and 2 mg) were provided to the study sites and these capsules/tablets contained exactly the same inactive ingredients and film coatings as the dabrafenib plus trametinib active study treatment.[16] It is therefore unlikely that the adverse events (AEs) experienced by patients in the placebo arm were unique to the placebo substance and it is probable that the events in the placebo arm were due to underlying disease and/or other co-morbidities. The reporting of AEs in the placebo arm of oncology studies is commonplace and not unique to COMBI-AD. Indeed that the rates of AEs and SAEs in the placebo arm of the COMBI-AD trial are similar to the rates of AEs and SAEs observed in the placebo arms of other randomised controlled trials for the adjuvant treatment of resected stage III melanoma (EORTC-18071 trial[10] and BRIM8[17]). As such, the occurrence of AEs and SAEs in patients receiving placebo is not unique to COMBI-AD.	

Issue 10 Incorrect description of FDA label

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 *"The FDA label[13] suggests that Dabrafenib causes a risk of cardiomyopathy, defined as a reduction in the Left Ventricular Ejection Fraction (LVEF) by ≥10%...."*	Please replace this text with the following: "*The FDA Prescribing Information for dabrafenib lists cardiomyopathy as a known side effect under section "Warnings & Precautions"*	This statement is factually incorrect. The current FDA label for dabrafenib in melanoma reads:[18] TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1, 2.1) TAFINLAR is indicated, in combination with trametinib, for the: • treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2, 2.1) • adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. (1.3, 2.1) • treatment of patients with metastatic non-small cell	Changed

		lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. (1.4, 2.1) The FDA label does not mention risk of cardiomyopathy. This is listed in the Prescribing Information, under "Warnings & precautions" alongside other known side effects, and the wording is: *"Cardiomyopathy: Assess LVEF before treatment with TAFINLAR and trametinib, after one month of treatment, then every 2 to 3 months thereafter."*	

Issue 11 Purpose of BRAF testing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 *"Those with recurrences are likely to require additional BRAF testing to determine whether or not the current treatment is successful or if alternative adjuvant treatment strategies may be required"*	Please remove text as follows: ~~*"Those with recurrences are likely to require additional BRAF testing to determine whether or not the current treatment is successful or if alternative adjuvant treatment strategies may be required."*~~	BRAF testing does not indicate whether a treatment is successful or not, as it is not a marker for efficacy. The BRAF test is conducted to determine the cancer's mutational status, and is only done once (usually at the time of diagnosis). This is in line with recommendations in both NICE clinical guidelines for the management of melanoma (NG14) and consensus guidelines for the follow up of high-risk	Deleted

		cutaneous melanoma in the UK (2013).[2, 19] In addition, it should be noted that the BRAF V600 mutation has shown early and continued involvement throughout the course of disease progression in melanoma, and is often found to be present in the primary lesion and corresponding metastatic lesions.[20] This provides evidence that a patient's BRAF status is unlikely to change throughout the course of their disease.	

Cost-effectiveness issues

Issue 12 Incorrect description of company approach to modelling and extrapolating trial data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 *"the company rejects a number of parameterisations of the COMBI-AD RFS data because the dabrafenib+trametinib curve falls*	Please consider updating the text to: *"the company rejects a number of parameterisations of the COMBI-AD RFS data because the*	These statements are incorrect and misleading. A number of factors were considered for our selection of the parameterised curves including the statistical fit, visual fit and clinical plausibility (refer to pages 70–74 of company submission). In addition, Table N.3.1 in Appendix N provides a comprehensive rationale for the inclusion and exclusion of parametric distributions for RFS in the model. In addition, our company response to clarification question C1 also provided justifications for why particular curves were included or excluded.	Page 18: No factual error. No revision required. The company response to clarification cites when deciding whether the curves are sensible or not, the reasons for rejection "high long tem hazard" or "curves

below the placebo curve. For a number of curves this does not occur until well into extrapolation, and is minimal to the point of being inconsequential when it does. The company has not properly justified why these curves should be rejected. In the opinion of the ERG they should be considered within the economics" This statement is incorrect since Novartis provided rationale in both the company submission (pages 70–73) and in response to the clarification questions (e.g. C1). **Page 90**	*dabrafenib+trametinib curve falls below the placebo curve. For a number of curves this does not occur until well into extrapolation, and is minimal to the point of being inconsequential when it does. ~~The company has not properly justified why these curves should be rejected.~~ In the opinion of the ERG they should be considered within the economics"*	For plausibility, curves were not considered in the economic model if the dabrafenib plus trametinib and placebo curves crossed or converged, or the curves were associated with a high long-term hazard for recurrence. These criteria were considered reasonable since 34 months of follow up in the dabrafenib plus trametinib arm at the primary analysis showed that there was no catch-up in the risk of recurrence and therefore no reason to believe that the risk of recurrence would suddenly increase. Moreover, previous studies in the adjuvant setting have shown that patients with stage III disease have a very high risk of recurrence in the first 3 years with the risk (e.g. hazard) of recurrence reducing significantly with time (approximately 80% of all recurrences occur within 3 years).[2] In addition, as described previously, more mature data from the COMBI-AD trial (post NICE submission; data-cut 30 Apr 2018) show that the RFS [redacted] These data further support the choice of curves selected in our company submission and are inconsistent with the ERG's working premise that the curves will converge.	cross of meet". Only one of these reasons is chosen for each pair of curves that are rejected. For instance, for Llog (R) Cure the reason given for rejection is or "curves cross of meet". The company for the for Llog (R) Cure also does not consider the degree of cross over and takes an overly absolutist approach in the opinion of the ERG. Page 90: No factual error. No revision required. Similar to the above table N3.1 in its rejection of pairs of curves only ever cites a single reason for the rejection of a pair of curves: • Poor visual fit to the observed data • Clinical plausibility - crossing of curves The company appears to confuse rejection of pair of curves with selection of curves from the remaining alternatives.

"The company rejects a number of parameterised curves on the basis of their visual fit to the Kaplan Meier curves"	*"The company rejects a number of parameterised curves on the basis of their visual fit to the Kaplan Meier curves, statistical fit and clinical plausibility"*		
Pages 19, 98 *"While the calculation of the calibrating hazard ratio for post-LR events has intuitive appeal, it suggests that more than 90% of those with a 1st recurrence will experience a 2nd recurrence within 50 months. No external data has been provided to support this, though it can be noted that the majority of 1st recurrences are anticipated to be*	Please update to: *"While the calculation of the calibrating hazard ratio for post-LR events has intuitive appeal, it suggests that more than 90% of those with a 1st recurrence will experience a 2nd recurrence within 50 months. ~~No~~ External data from a study conducted by Salama et al. (2017) analysing the timing and patterns of recurrence in early stage melanoma was provided to*	It is incorrect to state that no external sources were provided to support the calibration hazard ratio since we describe in our company submission (page 84–85) how a study by Salama *et al.* (2017)[21] provides a similar hazard ratio for a second recurrence versus a first. We also describe in our submission how clinical experts deemed this estimate to be reasonable.	The proposed revision is accepted. Pages 19, 129

distant recurrences"	*support this. It can be noted that the majority of 1st recurrences are anticipated to be distant recurrences."*		
Page 45 *"Although the composite RFS outcome may be appropriate as an overall estimate of clinical effectiveness, it is less well suited to the company's model design for economic analysis (CS Figure 12); indeed untangling the various strands of the composite outcome poses problems that appear to contribute to the considerable complexity of the economic model"*	Please update to: "Although the composite RFS outcome may be appropriate as an overall estimate of clinical effectiveness, it is less well suited to the company's model design for economic analysis (CS Figure 12); ~~indeed untangling the various strands of the composite outcome poses problems that appear to contribute to the considerable complexity of the economic model"~~	This statement is not accurate, since it is necessary to account for the different types of RFS events irrespective of whether a competing risk analysis is undertaken or not.	Changed

Page 58 *"In extrapolation to a life time horizon, the company's chosen model for the observed period produces a clinically implausible almost complete cessation of events after the maximum observation time. According to the company's 50 year prediction (pg. 83) using external data, the adjuvant and placebo arms reach between 16% (placebo) and 25% (adjuvant) without failure of RFS. The flexible parametric modes reach 11% and 18%, respectively, at 50 years"*	Please consider re-wording this text since it infers that the company's estimate of 16% is implausible but 11% is plausible.	This description is incorrect since the EORTC-18071 placebo data are used to extrapolate post the observed period in the COMBI-AD trial. Since RFS events in the placebo arm of the EORTC-18071 trial are applied to both arms of the COMBI-AD trial, RFS events do continue after the observed period in the COMBI-AD trial. Death from other causes is also included. In addition, the statement around the model predictions is subjective and, in the absence of long-term data, it is unclear what is considered plausible for the lifetime.	Changed. ERG comment: This is the nub of the problem. Many models are likely equally plausible or implausible for life time extrapolation; many will influence the estimated ICER.

Page 73 *"Given the model structure chosen by the company a problem arises. COMBI-AD only recorded 1st recurrences so cannot provide a post-LR RFS curve"*	Please update to: *~~Given the model structure chosen by the company a problem arises.~~ COMBI-AD only recorded 1st recurrences, so cannot provide a post-LR RFS curve"*	The statement is incorrect since this is a limitation of trial data as opposed to the model structure.	No factual error. No revision required. The model structure requires the modelling of post-LR recurrences. A problem arises due to this since COMBI-AD did not record this. If the model structure did not require the modelling of post-LR recurrences the problem would not arise. Which is the better model structure does not affect this.
Pages 73, 74 The company's selected curve for the COMBI-AD trial period is incorrectly described as: *"Log-likelihood-U-Cure"*	Please update to: *"Log-~~likelihood-~~logistic (U) Cure"*	Update to reflect the true parametric distribution.	Amended.

Issue 13 The use of external data for the estimation of long term outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG were concerned that a trial in a different population to the COMBI-AD trial was used to estimate RFS in the long-term: **Pages 38, 61, 62, 64, 65** The ERG state the AVAST-M trial *"would be more likely to be generalizable to the UK...The most noticeable difference between trial populations, other than BRAF status was the inclusion of 16% and 11% stage IIB and IIA patients in AVAST-M"* **Page 62** *"The ERG notes several potentially relevant differences between the COMBI-AD and EO-18071 trials"* *"...the proportion of BRAF+ in EO 18071 is unknown and probably <50%"*	We propose that the ERG update their report to acknowledge the limitations of their assumptions about the AVAST-M trial: • By considering a trial with a mixed BRAF population, the ERG is also implicitly assuming 'equivalence' for BRAF status • The outcome disease free interval (DFI) was not the primary endpoint of the AVAST-M trial, whereas RFS was the primary endpoint in the COMBI-AD and EORTC-18071 studies. It is unclear if the differences in the definitions of recurrence and the primary endpoints may impact the comparisons • AVAST-M was an open-label trial where COMBI-AD and EORTC-18071 were both robust double-blinded RCTs • The inclusion of patients with stage II disease (27%) and a better prognosis (reflected by higher DFI in the placebo arm of the AVAST-M compared to RFS in EORTC18071) may potentially bias the efficacy outcomes against dabrafenib plus trametinib versus placebo. Please update this statement to	It is necessary for the ERG to present a fair and balanced summary of the different trials, given that it is more likely that the stage of disease is likely to be more prognostic than the other factors cited such as UK patients and sample size. In addition, it is incorrect to state that the proportion of BRAF positive patients in the EORTC-18071 trial is *probably <50%* when this information is unknown.	Changed on page 62, 63 The company's expert opinion document (ref 57) states that the prevalence of BRAF+ melanoma in the UK is 40%; if there is a significant difference to this in the EORCT18071 trial then the 18071 placebo arm becomes less relevant to the UK population and to the decision problem.

	"...the proportion of BRAF+ in EO 18071 is unknown ~~and probably <50%~~"		
Page 62 *"...The ERG notes the CS remarks (pg. 21) that due to its significant toxicity ipilimumab has an uncertain risk-benefit ratio; this suggests that withdrawals and incomplete follow up patterns may likely differ between COMBO-AD and EO 18071 and exert a curve-changing influence on RFS analysis"*	Please remove this text *"~~.....The ERG notes the CS remarks (pg. 21) that due to its significant toxicity ipilimumab has an uncertain risk-benefit ratio; this suggests that withdrawals and incomplete follow up patterns may likely differ between COMBO-AD and EO 18071 and exert a curve-changing influence on RFS analysis~~"*	The inference that the toxicity of ipilimumab and any associated withdrawals or incomplete follow up in EORTC-18071 trial may exert a curve-changing influence on the RFS analysis is factually incorrect, since our RFS analysis uses the placebo arm of this trial. Consequently, the risk-benefit profile of ipilimumab has no relevance to the placebo arm of this trial and its use in our RFS analysis.	Changed.
Page 63 The ERG state they *"find this particular application unusual in that usually large population surveys or registries are the source for external data rather than another small scale RCT"*	We propose the ERG acknowledge in this text that there are no large population surveys or registries that provide information on RFS in patients with stage III melanoma.	For completeness and transparency, this should be updated.	Changed.

Issue 14 Modelling of overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48 The ERG indicates that the higher rate of non-melanoma deaths in the placebo arm may be due to poorer health at baseline or differences between post recurrence treatments: *"There was also imbalance between arms in the numbers of patients who died from non-melanoma or unknown causes (16 placebo, 6 adjuvant). The higher rate in the placebo arm may be suggestive of poorer health at baseline amongst placebo patients compared to adjuvant patients or differences in post-recurrence treatments between arms"*	Please update this sentence as proposed: *"The higher rate in the placebo arm may be suggestive of ~~poorer health at baseline amongst placebo patients compared to adjuvant patients or~~ differences in the type of post-recurrence treatments received between arms"*	At baseline, both the placebo and dabrafenib plus trametinib arms were well balanced for known prognostic factors in melanoma (i.e. disease stage, number of positive lymph nodes, type of lymph node involvement, primary tumour ulceration and in transit metastases). The higher rate of deaths in the placebo arm is therefore unlikely due to poorer health at baseline. Notably, similar proportions of patients in both arms received post-recurrence therapy.	No change made. ERG believes its statement is reasonable, the ERG was not referring to melanoma-specific status but inferring the potential influence of other health conditions (comorbidities).
Page 48 The ERG incorrectly suggest that the company did not use overall survival (OS) from the trial in the model because OS is likely to be influenced by post recurrence therapy: "*The OS experienced by patients in each arm of the trial is likely influenced by post-recurrence*	Please update this sentence as proposed: *The OS experienced by patients in each arm of the trial is likely influenced by post-recurrence treatments received (and whether patients experience subsequent recurrence(s) after a first recurrence). Should such treatments differ between arms this may introduce bias in the comparison of adjuvant versus placebo. ~~It may be that this is a reason why the results for OS~~*	The model structure facilitates the modelling of OS through the use of intermediate events (LR and DR), and as explained in our company submission (pages 65–66), a simplifying approach was taken since the outcomes associated with DR are the downstream effect related to the efficacy of metastatic treatments, and are not the subject of this appraisal.	Changed.

treatments received (and whether patients experience subsequent recurrence(s) after a first recurrence). Should such treatments differ between arms this may introduce bias in the comparison of adjuvant versus placebo. It may be that this is a reason why the results for OS from COMBI-AD have not been made use of in the company's economic model"	~~*from COMBI-AD have not been made use of in the company's economic model.*~~		
Page 88 The ERG incorrectly assumes a constant proportion of death events in the model: *"Further, although greater than 90% of deaths before 10 years were attributable to melanoma or its treatment, most deaths after 15 years were unrelated to melanoma. ~~This may call into question the reasonableness of assuming a constant proportion of events being deaths, and indeed of modelling recurrences and melanoma deaths among those who have not had a 1st recurrence after 10-15 years~~"*	Please update as follows: *"Further, although greater than 90% of deaths before 10 years were attributable to melanoma or its treatment, most deaths after 15 years were unrelated to melanoma. ~~This may call into question the reasonableness of assuming a constant proportion of events being deaths, and indeed of modelling recurrences and melanoma deaths among those who have not had a 1st recurrence after 10-15 years~~*	This statement is incorrect and misleading since the model does not make this assumption. In the model, the proportion of deaths in the RFS curve is constant, however general population mortality is applied.	No factual error. No revision required. The model does assume a constant balance between events for a given health state in Segment 2, and overlays general population mortality on this.

Page 97 *".....10% of deaths were non-melanoma deaths in the dabrafenib+trametinib arm, while 17% of deaths in the placebo arm were non-melanoma deaths. If non-melanoma deaths are treated as censoring events with the event of interest being melanoma deaths the resulting KM curves tend to come together more than those of figure 7 (pg. 39) of CS Document B and to possibly broadly merge at the end of COMBI-AD."*	Please consider removing this text as follows *~~".....10% of deaths were non-melanoma deaths in the dabrafenib+trametinib arm, while 17% of deaths in the placebo arm were non-melanoma deaths. If non-melanoma deaths are treated as censoring events with the event of interest being melanoma deaths the resulting KM curves tend to come together more than those of figure 7 (pg. 39) of CS Document B and to possibly broadly merge at the end of COMBI-AD."~~*	This statement is misleading since it is not appropriate to treat non-melanoma related deaths as censoring events. Moreover, as highlighted by the ERG themselves, this imbalance is best considered through a competing risks analysis.	No factual error. No revision required.
Pages 120, 122 *"..... convergence of the OS and RFS curve in the placebo arm than in the modelling that uses the log-logistic (U) cure model, with a plateauing of the RFS curve much as in White et al. But the plateauing of the RFS curve occurs at a somewhat higher level than in White et al"*	*"..... convergence of the OS and RFS curve in the placebo arm than in the modelling that uses the log-logistic (U) cure model, with a plateauing of the RFS curve much as in White et al. ~~But~~ Although the plateauing of the RFS curve occurs at a somewhat higher level than in White et al, it should be noted that the COMBI-AD trial and White et al study were conducted in different patient populations"*	This is misleading since the White *et al.* (2002) study was conducted in a different patient population to the COMBI-AD trial. Changes in treatment landscape for patients with recurrence may explain the difference in results from the model versus the study by White *et al.* (2002).[22] Most notably, the White *et al.* (2002) study was conducted prior to the era of targeted and immunotherapies, where given the limited treatment options available, it would be expected that all patients with relapse would die in time and that RFS and OS would converge.	No factual error. No revision required. The company uses data from White et al as key model inputs, due to a lack of alternatives. The ERG accepts that the treatment of patients has moved on, but in a similar vein uses the data from White et al as the most reasonable that is available due to a lack of anything exactly specific to the patient group and current therapies being available.

		However, given the introduction of targeted and immunotherapies in recent years, it would be expected that the RFS and OS curves would not converge (as is observed in our company model output) and as verified by the most up to date COMBI-AD data so far. Consequently, the differences in the patient population should be acknowledged in the ERG's descriptions and justifications.	The ERG does not argue that the vertical positions of the curves should be identical, or even that they should necessarily converge at the same rate. But it does feel that the pattern between RFS and OS observed in White et al is still informative and does provide some sense check of the modelled relationship between RFS and OS. The ERG is slightly confused by the company arguments around the introduction of targeted and immunotherapies. For placebo resected stage III patients would these not be given after progression? If so would the RFS and OS curve for these patients not still tend to come together as before?

Issue 15 Modelling of distant recurrence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107 *"It can also be noted the while the above suggests that DR patients benefit from receiving*	Please remove this text: ~~*"It can also be noted the while the above suggests that DR patients benefit from receiving dabrafenib+trametinib for their DR*~~	This statement is misleading and irrelevant, since the comparators in these metastatic appraisals were different (TA396: dabrafenib	No factual error. No revision required.

dabrafenib+trametinib for their DR compared to receiving pembrolizumab with a net gain of 0.48 QALYs the additional £106k cost suggests an ICER of £219k per QALY. These estimates may not really be aligned or amenable to being combined"	~~*compared to receiving pembrolizumab with a net gain of 0.48 QALYs the additional £106k cost suggests an ICER of £219k per QALY. These estimates may not really be aligned or amenable to being combined"*~~	monotherapy, and TA366: ipilimumab).	The comparators are different but the comparators are not considered. Only the costs and QALYs of the single arms are considered. It can be argued that the pembrolizumab modelling is not specific to the BRAF positive. But if this invalidates the comparison of the ERG, it invalidates the company inclusion of the total costs and QALYs.

Issue 16 Incorrect description of resources and costs in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 The ERG incorrectly state *"Monitoring costs are differentiated between the arms during the 1st year, with monthly OP visits and six-monthly ECHO and MUGA cardiac monitoring for those receiving dabrafenib+trametinib"*	Please update to *"Monitoring costs are differentiated between the arms during the 1st year, with monthly OP visits and ~~six~~ three-monthly ECHO or MUGA cardiac monitoring for those receiving dabrafenib+trametinib"*	The costs of imaging surveillance with echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) are implemented every 3 months in our model, according to consensus guidelines for the follow up of high-risk cutaneous melanoma in the UK (2013).[2]	No factual error. There are 4 cardiac monitoring tests in the 1st year. Neither the ERG wording nor the proposed company wording is wrong, but neither are particularly clear on this. The ERG accepts that the wording could be clearer and has revised it.

Page 27 *"Although the CS does take into account the cost implications of 3-monthly Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA) scanning during the 12-month treatment phase, the ERG found that the cost implications of this had not been taken into consideration following completion of treatment with Dabrafenib and Trametinib in the original CS"* **Page 40** *"the ERG considered that the company may have underestimated resources required for follow up for echocardiography"*	*"~~Although the CS does take into account the cost implications of 3-monthly Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA) scanning during the 12-month treatment phase, the ERG found that the cost implications of this had not been taken into consideration following completion of treatment with Dabrafenib and Trametinib in the original CS.~~ The CS takes into account the cost implications of 3-monthly ECHO or MUGA scanning during the 12-month treatment phase as per SPC"* Please consider removing this statement: *~~"the ERG considered that the company may have underestimated resources required for follow up for echocardiography"~~*	Cost implications of ECHO and MUGA scanning following completion of treatment had been taken into consideration by Novartis. This resource use was not underestimated, as it follows the guidance in the SmPCs.[3, 4] Additional scanning post-treatment is not mandated in the SmPCs for dabrafenib or trametinib, and therefore this is not an underestimation: *"If dabrafenib is being used in combination with trametinib and absolute decrease of >10% in left ventricular ejection fraction (LVEF) compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN), please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib"* "*Trametinib should be used with caution in patients with impaired left ventricular function. Patients with left ventricular dysfunction, New York Heart Association Class II, III, or IV heart failure, acute coronary syndrome within the past 6 months, clinically significant*	No change made. The guidelines are designed for melanoma and may not necessarily be applicable to the specific *dabrafenib + trametinib* adjuvant scenario or other new adjuvant interventions

		uncontrolled arrhythmias, and uncontrolled hypertension were excluded from clinical trials; ***safety of use in this population is therefore unknown. LVEF should be evaluated in all patients prior to initiation of treatment with trametinib, one month after initiation of therapy, and then at approximately 3-monthly intervals while on treatment*** *(see section 4.2 regarding dose modification)."*	

Issue 17 Incorrect description of calculation of drug costs in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 The ERG state there is uncertainty around drug wastage in the trial and suggest that drug costs have been underestimated: "*The company method is likely to underestimate this, as it applies the minimum number of packs that are consistent with individual patients' cumulative doses Prescriptions at times other than 4-weekly, dose interruptions, dose escalations and dose reduction are all likely to increase wastage. The ERG estimates are based upon company data supplied at*	The ERG's assessment of drug wastage is incorrect: "*The company method ~~is likely to underestimate this, as it~~ applies the ~~minimum~~ maximum number of packs that are consistent with individual patients' cumulative doses Prescriptions at times other than 4-weekly, dose interruptions, dose escalations and dose reduction are all likely to increase wastage. The ERG estimates are based upon company data supplied at clarification that indicate that clinical trial stock is dispensed to give 32 days of treatment to cover the 28+/-4 day protocol visit schedule window. Consequently this may overestimate wastage"*	The method used to calculate drug costs is conservative since it considers the *maximum* number of packs required to deliver the cumulative dose, and as assumes that open packs of medication are costed in full (i.e. assuming wastage) and any packs that are not open would be returned. As explained in our response to the ERG's clarification questions, both dabrafenib and trametinib were dispensed in quantities to enable 32 days of treatment to cover the +/-4-day window for each patient visit in the clinical trial setting. For	There is a factual error but not as described by the company. It would have been better worded as: "…*as it applies the minimum number of packs of 75mg dabrafenib tablets that are consistent with individual patients' cumulative doses".* The ERG is concerned about the allusions to return of drugs in the context of the NHS which raises further uncertainty about wastage under the trial, and how it will relate to the probable wastage

clarification, though these may overestimate wastage"		example, if a patient was unable to attend a scheduled trial visit on Day 28, they would have enough drug to last them the extra 4 days, as per protocol, a cycle is defined as 28 days (+/-4 days). The ERG's estimates are based on the amount of drug dispensed and do not consider the amount of drug returned. As such, we agree with the ERG that their estimates are likely to over-estimate drug costs and wastage since in clinical practice patients would routinely be dispensed a 28-day supply.	in practice in the NHS when full packs will be prescribed.
Page 101 *"...This is incorrect, as the qualifying text in brackets of table 2 hints. The stated means are based upon the smallest number of 75mg packs of dabrafenib and the smallest number of 2mg packs of trametinib that could be dispensed and still be consistent with each patients' cumulative dose during COMBI-AD; i.e. the smallest possible wastage"*	Please update to: *"…~~This is incorrect, as the qualifying text in brackets of table 2 hints.~~ The stated means are based upon the ~~smallest~~ maximum number of 75mg packs of dabrafenib and the smallest number of 2mg packs of trametinib that could be dispensed and still be consistent with each patients' cumulative dose during COMBI-AD; i.e. ~~the smallest possible~~ includes wastage"*	The ERG's interpretation of how the cumulative dose and number of packs are used to calculate drug costs is incorrect. In order to estimate the total number of packs of dabrafenib and trametinib per patient, the cumulative dose for each patient was divided by the total number of mg in a pack (based on 28 x 75 mg for dabrafenib and 30 x 2 mg for trametinib) *rounding up* to the nearest whole number.	No factual error. No revision required. The ERG understands the rounding up. But this is still likely to fail to account for dose changes, interruptions etc. wastage effects. For instance, as per the ERG report given a lack of clarity and data definitions in the company response the ERG has assumed that columns C and D of the company response to A3 relate to prescriptions and not packs as stated. At Wk0 all are prescribed 75mg presumably for a period of 4 weeks, but at Wk1 a number

			of patients are also prescribed 50mg. What has happened to their 75mg prescriptions?

Issue 18 Incorporation of QoL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 *"Benefit valuation: Unknown. The company only states that COMBI-AD EQ-5D-3L is consistent with the NICE reference case, but does not state whether it is valued using the usual UK social tariff"*	UK social Tariffs were used. Please update the report to reflect this clarification.	Further clarification has been provided.	No factual error. No revision required. The company can state this at the AC if required.
There are inconsistencies between the ERG's description of the quality of life values for RFS: **Page 19** *"Differentiating quality of life values for RFS by arm appears to have some effect, which may suggest that the company base case has not entirely taken into account the quality of life effects of adverse events"* **Page 101** *"Any differences between the values of the base case, as per the first regression, and those of*	Please consider updating as follows: *"Differentiating quality of life values for RFS by arm appears to have some <u>minor</u> effect, which may suggest that the company base case has not entirely taken into account the quality of life effects of adverse events, <u>however, ERG statistical opinion prefers the simpler model of the company base case</u>."*	For consistency and transparency, this should be updated.	No factual error. No revision required.

the other three regressions appear to be relatively minor and unlikely to much affect results.			

Issue 19 Explanation of exploratory and sensitivity analyses undertaken by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 21, 114, 118, 120, 132 ERG description of the company model is unclear and misleading: *...''the company log-logistic (U) cure model"* **Page 96** *... ''the company log-logistic (U) mixture model of the company base case"*	Please amend these sentences as follows: *... ''the company log-logistic (U) ~~cure~~ mixture model during the observed COMBI-AD trial period and the generalised-F model for EORTC 18071 placebo post trial"* *...''the company log-logistic (U) mixture model during the COMBI-AD trial and the generalised-F model for EORTC 18071 placebo post trial for the company base case"*	For transparency, it should be made clear in the ERG report that our company base case model was the log-logistic (U) mixture model during the observed period of the COMBI-AD trial with the generalised-F model for EORTC-18071 data for the lifetime time horizon.	No factual error. No revision required.
Page 21 *"Both the company log-logistic (R) and the ERG competing risks suggest that dabrafenib+trametinib will postpone recurrences but that in the medium to long term the dabrafenib+trametinib cure rate will converge with that of placebo, which the ERG finds more persuasive"*	Please reword this statement since the ERG curve selection was based on an *assumption* that the curves will converge as opposed to any empirical evidence that they will converge.	The statement is misleading since there is no evidence to suggest that the curves will converge and it is inconsistent with the findings observed in the most recent data from the COMBI-AD trial (data-cut 30 Apr 2018) which show that the RFS [redacted] Given the multiple curves available in the model, it seems	No factual error, no revision required

		that the ERG has selected a curve which converges.	

Typographical/confidentiality highlighting issues

Issue 20 Prevalence of the BRAF mutation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 There is a typographical error for the frequency of BRAF mutations: *"Approximately 40-650% of cutaneous melanomas harbour mutations in BRAF."*	Please update this sentence to: *"Approximately 40-650% of cutaneous melanomas harbour mutations in BRAF."*	This is a typographical error that should be corrected.	Changed

Issue 21 Incorrect spelling of the technology being assessed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 16, 100, 101, 109 Typographical errors in the spelling of the intervention	Please update tramatinib/tramatenib/tremetinib to trametinib.	Incorrect spelling of trametinib that should be corrected.	Changed

Issue 22 Incorrect description of technology being assessed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 23, 134 The ERG incorrectly describes the adjuvant treatment arm as "dabrafenib+placebo" *"The EORTC extrapolation results in survival in the placebo arm being*	Please update this sentence to: *"The EORTC extrapolation results in survival in the placebo arm being around 80-85% that of survival in the dabrafenib+placebo trametinib arm for month 50 to month 600"*	This is a typographical error that should be corrected.	Changed

around 80-85% that of survival in the dabrafenib+placebo arm for month 50 to month 600"			

Issue 23 Incorrect reference to unblinding

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35 *"Participants, investigators and site personnel (Novartis) were blinded to treatment allocations. However, the investigator/treating physician could un-blind treatment assignment in case of emergency. The trial protocol states that details of un-blinding were provided in the CS. Details of un-blinding were not described in the CS"*	*"Participants, investigators and site personnel (Novartis) were blinded to treatment allocations. However, the investigator/treating physician could un-blind treatment assignment in case of emergency. ~~The trial protocol states that details of un-blinding were provided in the CS. Details of un-blinding were not described in the CS."~~*	The COMBI-AD trial protocol does not refer to the company submission, therefore the original statement is factually incorrect.	Typographical error. Revised. *The trial protocol states that details of un-blinding will be recorded in the eCRF.*

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1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's definition of the decision problem matches the population, intervention, and the comparator described in the final NICE scope. The decision sought to estimate the clinical effectiveness and cost-effectiveness of oral adjuvant combination therapy with dabrafenib plus trametinib in the treatment of adult patients who had had complete resection for stage III melanoma carrying a BRAF V600 mutation. The comparator was routine surveillance. The major clinical effectiveness outcomes were recurrence-free survival (RFS), overall survival (OS) and safety. Other outcomes included distant metastasis-free survival and health related quality of life (HRQoL).

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company were derived from a single international randomised placebo-controlled trial (COMBI-AD) undertaken at 169 sites in 26 countries. The study was initiated in early 2013 and study cut-off for the submission was the end of June 2017, at which time the median follow was 2.8 years. Randomisation of patients (438 and 432 to adjuvant and placebo arms, respectively) was stratified according to their *BRAF* mutation status (V600E or V600K) and disease stage (IIIA, IIIB, or IIIC). The study was described as double blind. The treatment duration was stipulated as a period of 12 months. The primary outcome was RFS established by study investigators at visits scheduled every 3 months to month 24 and every 6 months thereafter. OS was designated a pre-specified secondary outcome.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Based on the company submission (CS) CONSORT diagram there appeared to be an imbalance between study arms in numbers and timing of patients for whom follow up terminated before study cut off. This imbalance could potentially influence outcome measures, especially those involving time to event analysis such as RFS and OS.

The company's Kaplan Meier (KM) analysis of the primary outcome measure (RFS) clearly demonstrated that combination adjuvant therapy with dabrafenib and trametinib considerably delayed recurrence; for RFS a hazard ratio (HR) of 0.47 (95% CI: 0.39–0.58) was estimated. RFS was a composite outcome encompassing death (from melanoma or other cause) recurrence

(local and/or distant), a new primary melanoma (SPM), and censoring with ongoing follow up or with premature follow up ended (PEFU). There was some imbalance in the numbers and timing of the latter censorings. These multiple components of RFS occur at different times. In response to the opinion expressed by an expert consulted by the company that some competing risk (CR) type of analysis should have been undertaken, the ERG conducted a CR analysis of RFS in which PEFU and SPM were considered as a CR. The results indicated that the difference between arms in restricted mean RFS to 41 months estimated by KM analysis of 9.44 months (95% CI: 7.36 – 11.52) represented a modest overestimate of approximately 11% relative to that estimated using the CR analysis (8.35 months: 95% CI: 6.61 – 10.08). Similarly, for the specified secondary outcome of OS, the company's KM analysis yielded a difference between arms in restricted mean survival to 42 months of 2.31 months (95% CI: 0.96 – 3.66) an approximate 21% overestimate relative to CR analysis (1.83 months, 95% CI: 0.27 – 5.05). It should be noted that the company did not employ the COMBI-AD OS analysis in its economic analysis. There was no difference between arms in quality of life measures (EQ-5D-3L) undertaken in the COMBI-AD study. The ERG expressed concerns regarding safety outcomes recorded in COMBI-AD and other studies of dabrafenib and trametinib. The ERG was concerned that a trial in a different population (patients with BRAF status undetermined) was used in the economic model in order to extrapolate the short term observed RFS outcome in COMBI-AD; this use has assumed an "equivalence" between a trial with mixed BRAF population and a trial with an exclusively BRAF+ population; there appears to be some inconsistency of approach between clinical and cost effectiveness considerations. Given such an assumption it would appear logical to have conducted a network meta-analysis comparing clinical effectiveness reported from various alternative adjuvant treatments. No indirect treatment comparisons were undertaken in the CS.

The ERG is in agreement with the company over the costs of hospitalisation for the treatment of common, non-severe side effects such as pyrexia, but feel that costs for more potentially life-threatening adverse events, such as haemorrhage and uncommon, and potentially serious non-life-threatening effects such as uveitis are difficult to predict in a non-trial setting. Certain side effects such as impaired glycemic control, may impact on primary care services, as opposed to hospital costs, while others such as diarrhoea which affect the absorption of the drug may reduce compliance, which in itself is difficult to predict with certainty.

Furthermore, whilst the company has acknowledged the costs of mandatory baseline and serial monitoring of cardiac function for patients on treatment, the ERG feel that these costs may have

underestimated the true monitoring requirements, as the onset or recovery of left ventricular function from cardiomyopathy may post-date the treatment period. It was also felt that routine dermatology input from the onset of treatment would be essential to monitor for recurrence or progression of underlying melanoma or onset of novel skin malignancies. Last of all, with a number of adverse events taking place in the placebo arm, for which there remains doubt as to the aetiology, whether from the placebo substance itself or progression of underlying patient comorbidities, the ERG had concerns regarding the chemical composition of the placebo. The ERG therefore feels that in an indefinite proportion of cases, it may have been difficult to decipher whether adverse events in the treatment arm were also due to progression of the underlying disease or due to dabrafenib or trametinib itself.

1.4 Summary of cost effectiveness submitted evidence by the company

The company builds a de novo cohort markov model with a 1 month cycle, a 50 year horizon and the following health states:

- All patients start in RFS, events for which are either loco-regional recurrence (LR), distant recurrence (DR) or death. Treatments costs, monitoring costs, quality of life values and the like are applied to patients in the RFS health state for each cycle of the model.
- Those who have an LR move into the LR health state, with their RFS (post-LR RFS) then being modelled, the events for which are also either another loco-regional recurrence (LR), a distant recurrence (DR) or death. Treatments costs, monitoring costs, quality of life values and the like are applied to patients experiencing an LR recurrence event for each cycle of the model.
- Those who have a DR, whether this is an RFS event or a LR-RFS event, are not really modelled. These patients simply have a total cost and a total QALY applied to them, derived from TA366 and TA396. The DR health state is an absorbing health state, much like death.

The model structure is consequently unusual because the cost effectiveness estimate is not reliant upon any modelled OS, despite it being anticipated that OS will differ between the arms.

The model is segmented into two periods. Up to 50 months which corresponded with the longest follow-up during COMBI-AD, and 50 to 600 months.

- For RFS up to 50 months the company applies arm specific log-logistic (U) cure parameterised curves based upon COMBI-AD data
- For RFS from 50 months the company applies common probabilities of events derived from a company parameterisation of the placebo arm of the EORTC 18071 trial of adjuvant ipilimumab versus placebo
- For post-LR RFS up to 50 months the company applies the same curves as for RFS up to 50 months, but qualified by a 2.53 hazard ratio
- For post-LR RFS from 50 months the company applies the same common probabilities of events as applied for RFS from 50 months, but with a greater proportion of these events being deaths.

General population mortality risks are also applied.

COMBI-AD EQ-5D-3L data is analysed to give quality of life values of 0.854 for patients receiving dabrafenib+trametinib, 0.869 for all other patients in RFS amd 0.836 for LR. The regression also yields an estimate of 0.792 for DR, but this is not applied in the model. Quality of life values subsequent to baseline are age weighted by UK norms.

The mean drug use is based upon the minimum number of whole packs of dabrafenib and the minimum number of whole packs of trametinib that could have been prescribed that are consistent with each COMBI-AD patient's cumulative dose. This results in estimated means of [redacted] packs of dabrafenib and [redacted] packs of trametinib. Prescribing costs of £13.90 are also included.

Monitoring costs are differentiated between the arms during the 1st year, with monthly OP visits and six-monthly ECHO and MUGA cardiac monitoring for those receiving dabrafenib+trametinib compared to quarterly visits and no additional cardiac monitoring for those who have ceased dabrafenib+trametinib and those in the placebo arm.

Incident LR patients are mainly assumed to be resected, with some additional visit costs. Incident DR patients are estimated to accrue a further 3.23 QALYs at a total cost of £143k, based upon the model outputs given in the CSs to TA366: pembrolizumab for unresectable or stage IV melanoma

- Related to the above bullet, while the model does fit an OS curve to the post-DR patients this does not affect the cost effectiveness estimates and is more for validation purposes. During COMBI-AD there was a noticeably larger number of non-melanoma deaths in the placebo arm than in the dabrafenib+trametinib arm, which might argue for a competing risks analysis. But because the modelled OS does not affect the cost effectiveness estimate, it is not obvious how this could be taken into account within the economics.

The company rejects a number of parameterisations of the COMBI-AD RFS data because the dabrafenib+trametinib curve falls below the placebo curve. For a number of curves this does not occur until well into extrapolation, and is minimal to the point of being inconsequential when it does. The company has not properly justified why these curves should be rejected. In the opinion of the ERG they should be considered within the economics.

The main uncertainty is around which curves should be applied and to what extent they should be extrapolated. The company position is that the COMBI-AD log-logistic (U) cure model curves should be used to 50 months but should not be used for extrapolation, with extrapolation being based upon data from the EORTC 18071 trial instead. The ERG notes the differences in populations between COMBI-AD and EORTC 18071. The ERG sees more merit in using parameterised curves derived from COMBI-AD for extrapolation. This also permits the duration of benefit from dabrafenib+trametinib over placebo to be explored.

ERG expert opinion suggests that dabrafenib+trametinib may postpone recurrences but are less likely to avoid them altogether, meaning that in the longer term the proportion who are cured will converge with that of the placebo arm. This argues for the COMBI-AD log-logistic (R) cure model curves over the COMBI-AD log-logistic (U) cure model curves. It can be noted that the AIC for the (U) model may show some superiority, but the BICs are virtually identical for the two models. Convergence of cure rates would further argue for the ERG COMBI-AD competing risks model curves, with an additional argument in their favour being that both a company adviser and the ERG are of the opinion that a competing risks analysis is desirable due to the COMBI-AD data definitions. Any convergence of cure rates further argues that these curves should be used for extrapolation. Clearly, if the proportion who are cured by dabrafenib+trametinib tends to converge with that of placebo the cost effectiveness of dabrafenib+trametinib worsens somewhat.

While the calculation of the calibrating hazard ratio for post-LR events has intuitive appeal, it suggests that more than 90% of those with a 1st recurrence will experience a 2nd recurrence within 50 months. External data from a study conducted by Salama et al. (2017) analysing the timing and patterns of recurrence in early stage melanoma was provided to support this. It can be noted that the majority of 1st recurrences are anticipated to be distant recurrences.

The proportion on treatment is applied in the quality of life calculations. Data supplied at clarification suggests that a higher proportion of dabrafenib+trametinib patients should be modelled as being on treatment, but this only marginally worsens the cost effectiveness estimate. Of more concern is data supplied at clarification which states that for quite a large proportion of dabrafenib+trametinib patients time to treatment discontinuation was censored at day 364 and end of trial. If these patients continued to receive dabrafenib+trametinib beyond day 364 this could affect costs quite considerably. It would help if the company could clarify what number of patients received any dabrafenib+trametinib after day 364 and what number of patients had a dabrafenib+trametinib prescription beyond day 364.

There is uncertainty about drug wastage during COMBI-AD. The company method is likely to underestimate this, as it applies the minimum number of packs of 75mg dabrafenib tablets that are consistent with individual patients' cumulative doses. Prescriptions at times other than 4-weekly, dose interruptions, dose escalations and dose reduction are all likely to increase wastage. The ERG estimates are based upon company data supplied at clarification, though these may overestimate wastage.

Only SAE hospitalisation costs have been included. There is evidence of higher adverse events, more prophylactic medication of adverse events and more active medication of adverse events in the dabrafenib+trametinib arm. The medication costs may be minor, but any increase in OP or GP visits would be more serious. But these costs would have to rise significantly to have a major effect upon the cost effectiveness estimate. Differentiating quality of life values for RFS by arm appears to have some effect, which may suggest that the company base case has not entirely taken into account the quality of life effects of adverse events.

The company assumes a high proportion of stage IV patients will receive dabrafenib+trametinib for their stage IV disease. The costs of dabrafenib+trametinib treatment at stage IV are very large, so avoiding these costs improves the cost effectiveness estimate. ERG expert opinion suggests that a somewhat lower proportion of stage IV patients will receive dabrafenib+trametinib, and

that some will receive nivolumab+ipilimumab. The ERG proportions worsens the cost effectiveness estimate.

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

1.6.1 Strengths

The ERG considers the overall quality of the company's systematic review to be reasonable. Following systematic review, the clinical effectiveness evidence submitted were derived from a single well-conducted international randomised placebo-controlled trial (COMBI-AD) undertaken at 169 sites in 26 countries. The ERG considers that the baseline demographic characteristics of patients recruited in the COMBI-AD trial were comparable to those of the relevant patients in the UK. The company present the results from this trial investigating the effectiveness of daily oral adjuvant therapy combining dabrafenib and trametinib in the treatment of patients after complete surgical resection. No other comparable adjuvant studies in this population have been identified. The COMBI-AD trial is directly relevant to the decision problem. The study demonstrated a clear and substantial delay in RFS resulting from combination therapy. There was also an apparent effect benefitting OS, although data were rather immature for both outcomes (median follow up 2.8 years) especially for OS.

From a cost-effectiveness perspective, the CS is well-written and clear. Very few points required clarification, which was limited to requesting additional data and analyses. The company electronic model is a model of good documentation. This aspect cannot be praised enough. Given the complexity of the model, it has been an enormous help to the ERG. The company was also notably helpful clarifying some aspects of the model prior to formal clarification.

1.6.2 Weaknesses and areas of uncertainty

There was some numerical and timing imbalance between study arms in patients ending follow up before study cut off that may influence effectiveness estimates. Following a request from the ERG, the company and the ERG therefore both conducted a CR analysis. Relative to the company's KM analysis the ERG CR analysis yielded lower estimates of the difference between arms in the estimation of restricted mean survival by about 11% for RFS and 21% for OS. Because follow up was insufficient however one of the major uncertainties is whether the therapy merely delays disease recurrence, so that recurrence in the intervention arm eventually 'catches up' with that in the control arm, or whether

The ERGs revised analyses and ICERs are as follows:

	L-Log (U)	L-Log (R)	ERG CR
Base case	£20,701	£62,853	£46,161
SA01: EQ-5D RFS split by arm	£21,734	£70,752	£49,492
SA02a: EQ-5D intercept -25%	£24,134	£72,018	£53,061
SA02b: EQ-5D intercept +25%	£18,134	£55,790	£40,873
SA02c: SA01 + EQ-5D intercept -25%	£25,697	£83,032	£57,814
SA02d: SA01 + EQ-5D intercept +25%	£18,830	£61,636	£43,264
SA03: DABR monitoring +50%	£21,929	£65,675	£48,347
SA04a: LR resection 0%	£21,329	£63,847	£46,954
SA04b: LR resection 20%	£20,073	£61,859	£45,369
SA05: LR events balance EORTC 18071	£20,764	£63,716	£46,530
SA06: DR costs and benefits reflect EoL	£24,980	£61,487	£46,589
SA07: EORTC extrapolation	£26,258	£30,866	£27,432

The scenario that extrapolates from month 50 to month 600 using the EORTC placebo data rather than the arm specifc COMBI-AD data result in quite similar ICERs almost regardless of which COMBI-AD parameterisation is used for up to month 50. This is because applying common risks to each arm from 50 to month 600 effectively freezes the benefits to be as they were at month 50. The EORTC extrapolation results in survival in the placebo arm being around 80-85% that of survival in the dabrafenib+ trametinib arm for month 50 to month 600.

More fully accounting for SAEs and possibly AEs that did not require hospitalisation but did require medication and possibly additional appointments would probably increase costs more in the dabrafenib+trametinib arm than in the placebo arm. But given the modelled large net cost for dabrafenib+trametinib, any SAE costs would have to be quite large to have much effect on the cost effectiveness estimate. There is the suggestion, as shown in SA01, that explicitly accounting for the different SAE profiles by arm would worsen the cost effectiveness estimate.

If patients were prescribed dabrafenib or trametinib beyond day 364 of the COMBI-AD trial either the clinical data does not particularly reflect the anticipated license or costs could be somewhat higher in the dabrafenib+trametinib arm. Either would worsen the cost effectiveness estimate.

disease with prior evidence of lymph node involvement and further sub classification of stage IIID is unlikely to affect OS of Stage III patients as a group and would have been included in the study as potential participants. Nevertheless, it is likely that over time, availability of adjuvant treatment options will be stratified further according to sub-categories of Stage III disease and for AJCC Stage IIC (a group for whom prognosis is deemed worse than Stage IIIB), as the UK continues to adopt the new AJCC 8th Editionn staging guidelines.

Approximately 40-65% of cutaneous melanomas harbour mutations in BRAF. Molecular alterations in this pivotal oncogene result in the constitutive activation of key components of the mitogen-activated kinase (MAPK) pathway, which results in uncontrolled tumour growth, proliferation and survival. These mutations occur most commonly in exon 15 at codon 600 (BRAFV600), of which 75% are characterised by the substitution of the amino acid valine by glutamic acid at residue 600 (BRAFV600E). A less frequent mutation BRAFV600K involves the substitution of valine by lysine in 10-30% of BRAFV600 melanomas.[6] Patients with BRAFV600E and BRAFV600K positive completely resected Stage III melanoma were the subjects included in the COMBI-AD trial of adjuvant therapy. The mutation was detected by genetic testing of the primary melanoma or lymph node tissue using a central reference laboratory.[2]

We note that the regulatory approval was granted by the US Food and Drug Administration for the first time on April 30 2018 to Dabrafenib and Tremetinib in combination, based on the findings of the COMBI-AD trial for the treatment of BRAFV600E or BRAFV600K melanoma with evidence of lymph node involvement following complete resection.[7] Previously approval was acquired for BRAF-mutant metastatic melanoma only, based on the findings of the BREAK-3 trial.[6, 8] This approval was granted after the company's current submission to NICE. In Europe, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for Dabrafenib (applied by GlaxoSmithKline) on 27 June 2013[9] and Trametinib (by Novartis Europharm Ltd.) on 23 February 2017[10] for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. These positive recommendations were subsequently approved by the European Medicines Agency, which granted a marketing authorisation valid throughout the European Union for Dabrafenib on 26 August 2013[11] and Trametinib on 30 June 2014.[12]

2.2 Critique of company's overview of current service provision

On pages 21-24, the company provides an overview of the current UK guidelines for the treatment pathway of resected AJCC stage III melanoma and proposes the positioning of Dabrafenib and Trametinib in the adjuvant setting. They appraise a series of clinical guidelines for the management of stage III melanoma and describe the NICE guidelines which recommend clinical follow-up with imaging for stage III disease following complete resection with completion lymphadenectomy, at three-monthly intervals for the first three years following resection and then at six-monthly intervals for the subsequent two years. Adjuvant radiotherapy may be considered for Stage IIIB or IIIC melanoma if the risk of local recurrence is estimated to outweigh the risk of significant adverse events. Surveillance imaging is advised during follow-up and computerised tomography (CT) scans are advised to aid staging in the initial stages.[4]

The ERG was in agreement with the company that there are currently no recommended medical or systemic treatments for AJCC Stage III melanoma, regardless of the genetic subtype, in the adjuvant setting, following surgical excision. Similarly, the ERG's clinical advisor confirmed that there is no adjuvant treatment options for stage IIC patients who are at high risk of disease recurrence. Patients are offered three monthly surveillance consultations usually shared between Plastic surgery and Medical oncology with six-monthly CT scans for chest, abdomen and pelvis. A brain MRI may or may not also be required. Hence, the ERG considers that this conservative method of clinical surveillance alone, was thus deemed a fair comparator against Dabrafenib and Trametinib therapy in the context of this appraisal, as depicted in Figure 4 on page 23 of the CS.

In the view of the ERG the company's overview of the current service provision was adequate. The ERG note that the company recommend treatment for 12 months. The mean duration of exposure to Dabrafenib and Trametinib in the trial was less than this with means of 8.2 and 8.3 months respectively (CS table 19 on pg. 50). The ERG suggest that in practice, the average treatment duration may be < 12 months since the presence of serious adverse effects and other factors will compromise treatment compliance.

The ERG also considered that a number of additional measures will be required to follow up patients treated with Dabrafenib and Trametinib for routine monitoring of adverse effects.
The FDA prescribing information for Dabrafenib[13] lists cardiomyopathy as a known side effect under section "Warnings & Precautions". It is defined as a reduction in the Left Ventricular Ejection Fraction (LVEF) by ≥10%, hence all patients who take the medication are likely to need baseline and possibly subsequent serial echo-cardiography.

a confidential CSR summary which have been submitted to the ERG. The COMBI-AD trial was relevant to the company's decision problem in terms of population, intervention, comparator and outcomes (see section 3 for comparison to the NICE decision problem).

Conduct of the trial

The trial was designed to investigate dabrafenib in combination with trametinib in the adjuvant treatment of melanoma after surgical resection. Oral intake of 150 mg of dabrafenib (twice a day) plus 2 mg of tramerinib (once a day) or of placebo was assigned randomly in a 1:1 ratio for a double blind controlled period of 12 months. Participants, investigators and site personnel (Novartis) were blinded to treatment allocations. However, the investigator/treating physician could un-blind treatment assignment in case of emergency. The trial protocol states that details of un-blinding will be recorded in the eCRF. Details of un-blinding were not described in the CS. Treatments given daily for 12 months, the first dose (150 mg of Dabrafenib and 2.0 mg of Trametinib or placebo) was administered in the morning at the same time every day. The second dose of treatment (150 mg of Dabrafenib or placebo) was to be administered 12 hours after the first dose. Treatments were taken orally with approximately 200 mL of water under fasting conditions either 1 hour before or 2 hours after a meal. Participants were enrolled between January 2013 and December 2014 and the clinical cut-off was 30th June 2017. The conduct of the trial was clearly presented though details of un-blinding were not clear.

Selection of participants

The CS reported the key inclusion criteria in Table 8 page 28 and Appendix L; in summary these were patients aged ≥ 18 years, and had undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma, which carried BRAF V600E or V600K mutations. Patients had not undergone previous systemic anticancer treatment or radiotherapy for melanoma, had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). Patients with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were also eligible. The ERG noted that CS Table 8 (pg. 28) did not mention the requirement for BRAF mutations. A number of exclusion criteria were listed under 'Exceptions' in the CS Appendix L page 141. The trial records[2] stated additional exclusion

Events not as deaths: c] Loco & distant recurrence	7	7
Events not as deaths: d] New primary melanoma	6	7
Total censorings	272	184
Censoring due to no recurrence or death & follow up ongoing	[redacted]	[redacted]
Censorings due to no recurrence or death & follow up ended	[redacted]	[redacted]

Two types of censored patients were detailed in CS Table 12: Censored "follow up ongoing" was defined in Table 12 footnote as "*Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from the study by the data cut-off for the primary analysis (30th June 2017)*". Censored "follow up ended" was defined as "*Patients censored with follow-up ended are the remaining censored patients*". The ERG interpret these latter patients to be those who did not experience recurrence or death (any cause) and whose follow up terminated before the study cut off (30th June 2017). According to the CONSORT diagram, possible reasons (other than death) for not being in follow up at the study cut off included: loss to follow up, withdrawal from the study, and investigator discretion.

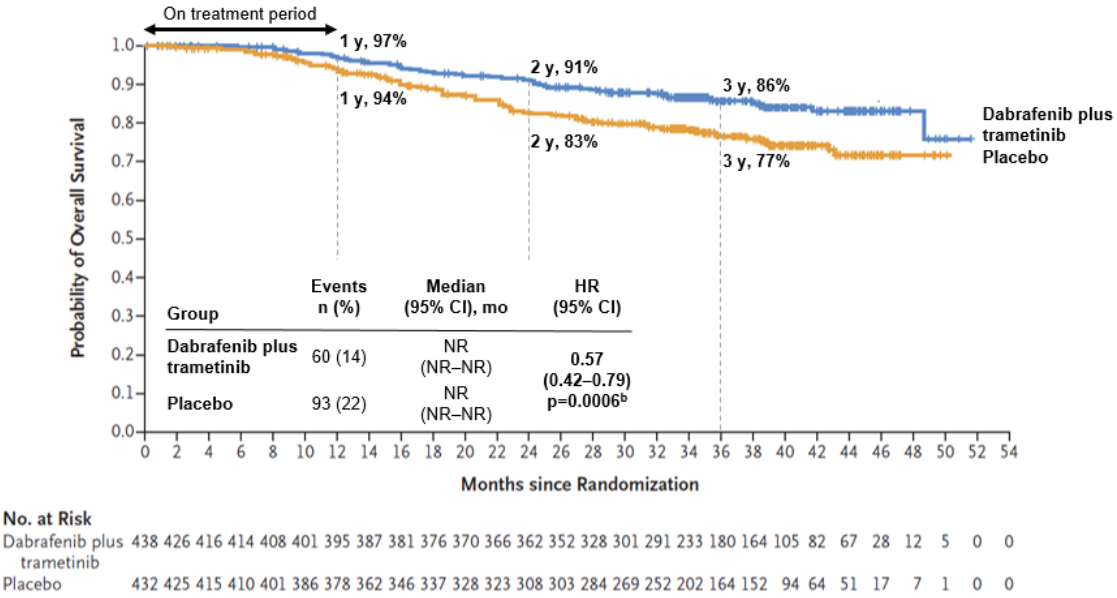
In the CS cost effectiveness section (3.3.1 pg. 71) a further KM analysis of "RFS" is presented (CS Figure 13); this was used in the economic analysis on the basis of clinical advice that new primary melanoma (SPM), in the absence of observed recurrence, should not be considered a recurrence event and should instead be censored. This reduced the total events to 160 and 241 in adjuvant and placebo arms respectively and increased the censorings to 278 (adjuvant) and 191 (placebo). The analysis does not correspond to any reported in the clinical effectiveness section and appears to have been introduced specifically for economic modelling. In clarification (question A12) the company supplied the following statistics for the Figure 13 analysis: HR 0.47 (95% CI, 0.38–0.57) P<0.001, these numbers are almost indistinguishable from the RFS analysis of Figure 6. In this additional RFS analysis patients could follow one of several pathways as summarised in Table 7. Although the composite RFS outcome may be appropriate as an overall estimate of clinical effectiveness, it is less well suited to the company's model design for economic analysis (CS Figure 12).

For pathway C (death from any cause counted as a recurrence) the underlying assumption appears to be that death was actually preceded by a recurrence but that this was not detected (possibly due to gaps between monitoring times), hence such deaths may be legitimately recorded as RFS-like events. If the death is directly related to melanoma this seems reasonable. However, if the death is not from melanoma assuming that it was preceded by recurrence does not seem sensible. Only 3 and 1 patients in the adjuvant and placebo arms respectively followed pathway C.

Specified secondary outcomes; Overall survival (OS)

CS Table 8 specified the following secondary outcomes: OS, distant metastasis free survival (DMFS), freedom from relapse (FFR), (defined in section 2.3.1) and safety. These are described and critiqued in the following section.

The OS results from COMBI-AD were not employed in the company's economic analysis.



OS was defined as the time from randomisation to death from any cause in the ITT population. The results were presented in the form of a KM analysis (CS Figure 7, shown above), a HR estimate (0.57; 95% CI: 0.42–0.79), and a stratified logrank P value (0.0006) for the comparison of adjuvant versus placebo treatment. Median survival was not reached in either arm. There were 60 and 93 events, respectively, in adjuvant and placebo arms. Table 8 summarises the breakdown of events and censorings.

Table 8: Events and Censorings in the OS KM analysis shown in CS Figure 7

	Adjuvant (N 438)	Placebo (N 432)
Events	60	93
Total censorings	378	339
Censorings due no death by the end of follow up	331	277
Censorings for PEFU before death occurred	47	62

There is numerical imbalance between arms in the censorings due to PEFU. Because PEFU will preclude observation of a death event before end of study the ERG requested information during clarification (question A5) that would allow CR analysis to be done; results of the ERG CR analysis (section 4.6), suggest that a KM analysis may overestimate the gain from adjuvant over placebo in restricted mean survival to 41 months by approximately 21%. There was also imbalance between arms in the numbers of patients who died from non-melanoma or unknown causes (16 placebo, 6 adjuvant). The higher rate in the placebo arm may be suggestive of poorer health at baseline amongst placebo patients compared to adjuvant patients or differences in post-recurrence treatments between arms. The OS experienced by patients in each arm of the trial is likely influenced by post-recurrence treatments received (and whether patients experience subsequent recurrence(s) after a first recurrence). Should such treatments differ between arms this may introduce bias in the comparison of adjuvant versus placebo.

Specified secondary outcomes: Distant metastasis free survival (DMFS)

DMFS was defined as "the interval from randomisation to the date of first distant metastasis or date of death, whichever occurred first" (CS pg. 39). The results were presented in the form of a KM analysis (CS Figure 8, shown below), a HR estimate (0.51; 95% CI: 0.40–0.65), and a stratified logrank P value (<0.001) for the comparison of adjuvant versus placebo treatment. Median survival was not reached in either arm. The breakdown of events and censorings are summarised in Table 9.

risk of fatal haemorrhage with Dabrafenib and that the risk of haemorrhage increases when it is combined with Trametinib.[28] Additionally, the ERG felt that Dabrafenib and Trametinib may impair glycemic control of diabetic patients in a primary care setting, which may have additional cost implications for their hypoglycaemic medication, which would optimally be managed by the General Practitioner / Community diabetic clinics and not in the hospital setting. 27% (4/15) of patients with a history of diabetes in COMBI-d receiving Dabrafenib with Trametinib and 13% (2/16) of patients with a history of diabetes receiving single-agent Dabrafenib required an upregulation of hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia based on laboratory values occurred in 5% (11/208) and 0.5% (1/208) of patients receiving Dabrafenib with Trametinib respectively, compared with 4.3% (9/209) for Grade 3 hyperglycemia and no patients with Grade 4 hyperglycemia for patients receiving single-agent Dabrafenib.[14]

An additional side effect flagged up by the FDA label was uveitis, which is stated to have occurred in 1% (6/586) of patients receiving Dabrafenib across multiple clinical trials and in 2% (9/559) of patients receiving Dabrafenib with Trametinib across randomized melanoma trials.[7] The ERG was of the view that additional costs are likely to be required for routine opthalmological monitoring which were not clarified in the initial CS report. However, in clarification question B12 it was stated that ophthalmological monitoring would not be carried out routinely and referral for ophthalmic assessments would only be undertaken if patients were to become symptomatic. The cost-implications of this are difficult to predict and uncertain in nature. Other side effects mentioned in the FDA label which did not appear to affect any patients in the COMBI-AD trial included Glucose-6-phosphate-dehydrogenase deficiency and embryo-foetal toxicity.[7]

Whilst the ERG was in agreement with the company that many of the less severe side effects such as pyrexia can be alleviated by self-treatment measures, the ERG was concerned that side effects which may potentially be responsible for malabsorption of the drugs, such as diarrhoea, stated on Table 24 on page 56 of the CS, to have taken place with grade 1 severity in 115 of the patients on the treatment arm, may preclude further compliance and efficacy of the treatment. Reassuringly in clarification question C6 it was confirmed that there were no reported discontinuations of treatment due to diarrhoea which was mainly transient with a [redacted]. However it is difficult to predict whether this will hold as true in the clinical setting as it did in the trial setting. This is an important consideration for any of the adverse effects reported. It was also confirmed that no dose modifications due to diarrhoea were due to malabsorption. However, the

ERG considers that for the future it might be advisable to consider alternative formulations of the treatment for those who cannot take oral formulations. Novartis have however confirmed that no alternative formulations are currently available.

Furthermore, in acknowledgment of the fact that 12% of patients died due to melanoma and that a new primary melanoma was reported in 11 patients from the Dabrafenib plus Trametinib group the ERG felt it would be important to classify whether or not these incidences of melanoma were BRAF V600 positive. It was confirmed that a BRAF V600E/K mutation was detected in all relapse samples except in 1 secondary primary melanoma. The company also stated that since the majority of deaths occurred >30 days following the last dose of the study treatment, it remains possible that the disease may progress following cessation of treatment following the one year treatment protocol. This raises doubts as to whether 12 months is likely to remain an adequate treatment duration in the clinical setting, a timeframe which may expand in the future as more clinical evidence arises. This may require additional costs for BRAF testing and may modify the treatment plan for the patients affected.

As an aside, the ERG initially requested further clarification as to why patients in the placebo arm suffered from side effects, especially serious side effects. It was not known whether these effects were due to the placebo substance, progression of the underlying stage III melanoma or whether or not any alternative explanations could be offered. In response, the company confirmed that any adverse event including serious adverse events were defined as "any untoward medical occurrence in a subject or clinical investigation subject, temporarily associated with the use of a medicinal produce, whether or not considered related to the medicinal product". In clarification question C2 it was stated that [redacted] patients experiencing SAE's in the placebo arm had a causality that was reported as related to the study treatment and that the remaining patients in the placebo arm were assumed to have most likely experienced an SAE due to underlying disease comorbidities, a proposition which was backed by our clinical expert. On that basis the ERG expressed concerns over the safety, chemical composition and pharmacodynamics of the placebo substance, as one would traditionally expect it to be inert. Further clarification as to why the remaining patients on the placebo arm, who supposedly suffered SAEs owing to underlying disease and comorbidities may have helped identified which adverse effects in the treatment arm were directly related to Dabrafenib and Trametinib products and which due to underlying disease.

which of these is selected will have a small effect on the economic model output when not used for extrapolation. For extrapolation to a life time horizon (50 years) the company employed external data, sourced from an adjuvant RCT comparing ipilimumab versus intravenous placebo.

The company's choice of model for Figure 13 was made on basis of the three criteria: a] AIC BIC score, b] visual fit, c] clinical plausibility. The models explored by the company all incorporated treatment as an indicator. The ERG doubt that this is obligatory especially when the observed KM plots differ substantially in shape; the ERG found no evidence to support an assumption of proportional hazards Appendix A (pg. 143) The selected model exhibited a good visual fit to the KM plot (Figure 15) and relative to most other models a low AIC BIC scores (3708.5 and 3737.0), and it was considered clinically plausible. The ERG explored standard parametric models and flexible parametric models with and without treatment as an indicator. With treatment as indicator these generated low IC scores but relatively poor visual fits compared to the company selected model. With models fitted separately to each arm (treatment not an indicator) flexible parametric models generated visual fits as good as those of those of company selected model; AIC BIC values were low (Appendix B pg. 145), but cannot be compared with those from models using treatment as an indicator. Table 13 and Figure 4 summarise similarities and differences between the company selected model and flexible models.

Table 13: Comparison of the company's RFS models and flexible parametric models

Criterion	Company selected model	Flexible parametric model
Visual fit	good	equivalent or better
IC	AIC 3708.5, BIC 3737.0	PBO AIC 795.1, BIC 811.5 ADJ AIC 1209.4, BIC 1225.7
Clinical plausibility during observation time	yes	yes
Clinical plausibility in extrapolation	no	yes

advantage of AVAST-M over EO 18071 is that the trial was conducted in UK patients, while EO 18071 was an international study (99 centers in 19 countries in 3 continents) likely to have recruited few UK patients (COMBI-AD enrolled only [redacted] UK placebo arm patients). In the ERG's opinion, because AVAST was undertaken in an exclusively UK patient population extrapolation using AVAST-M would be more likely to be generalizable to the UK. Furthermore, AVAST-M is a larger (1347 participants) and longer study (to 8 years); the control arm received "observation" and would likely reflect the current UK alternative to a licenced treatment with adjuvant. Unlike COMBI, AVAST-M was an open label trial. The most noticeable difference between trial populations, other than BRAF status was the inclusion of 16% and 11% stage IIB and IIA patients in AVAST-M (Table 14).

Table 14: Percentages of stage III patients in three adjuvant trials

	AVAST-M		EO 18071[21]		COMBI-AD	
	observation		placebo		placebo	
IIB	109	16%	0		0	
IIC	72	11%	0		0	
IIIA	95	14%	98	20.6%	71	16%
IIIB	253	38%	182	38.2%	187	43%
IIIC	143	21%	196	41.2%	166	38%
III unknown					8	2%

ii) The ERG notes several potentially relevant differences between the COMBI-AD and EO-18071 trials. Of first importance is the fact that the studies were undertaken in different populations; all participants in COMBI-AD were BRAF+ whereas the proportion of BRAF+ in EO 18071 is unknown. This seems relevant in view of the CS statement that BRAF V600 mutations drive disease progression (e.g., CS Table 2). However in describing the use of EO 18071, CS states that "the exact prognostic role of BRAF V600 mutations in melanoma remains uncertain" (pg. 75), and "in the absence of evidence to suggest that there would be a difference in outcomes for patients in the adjuvant setting, it is assumed that outcomes in the EORTC 18071 trial would be similar irrespective of BRAF status". To the ERG it seems odd to justify an assumption on the basis of no evidence. Similarly to the ERG it would appear odd to have conducted an adjuvant trial in BRAF+ patients (i.e. COMBI-AD) under an assumption that BRAF status has no direct relevance for recurrence outcomes. Furthermore, if this assumption is accepted then the ERG would expect other adjuvant trials with unknown BRAF status to be explored for extrapolation.

iii) The company used clinical expert advice in deciding the most suitable parametric model of the EO 18071 trial PBO arm to use for extrapolation. According to Jackson et al. 2016[33] the elicitation of expert opinion on beliefs about survival extrapolation is rare in the use of external data (no example was found in the Jackson study). Details of how expert opinion(s) were elicited by the company were not provided.[25] Although the use of external data is sometimes used in extrapolation of survival analyses[33] the ERG find this particular application unusual in that usually large population surveys or registries are the source for external data rather than another small scale RCT; however it is possible there is a lack of such studies. Jackson et al. discuss the potential and the challenges of such procedures.[33]

A further alternative to the RFS extrapolation undertaken by the company is to employ the CR analysis of RFS described above rather than the company's KM analysis shown in CS Figure 13. Figure 7 summarises two similar extrapolations of this type undertaken by the ERG. Both employ the company's generalised F model of the placebo arm of the EO 18071 trial; in one, the extrapolation follows from week 41 of the CR non-parametric plot and in the other, from week 41 of flexible parametric fits to the CR analysis.

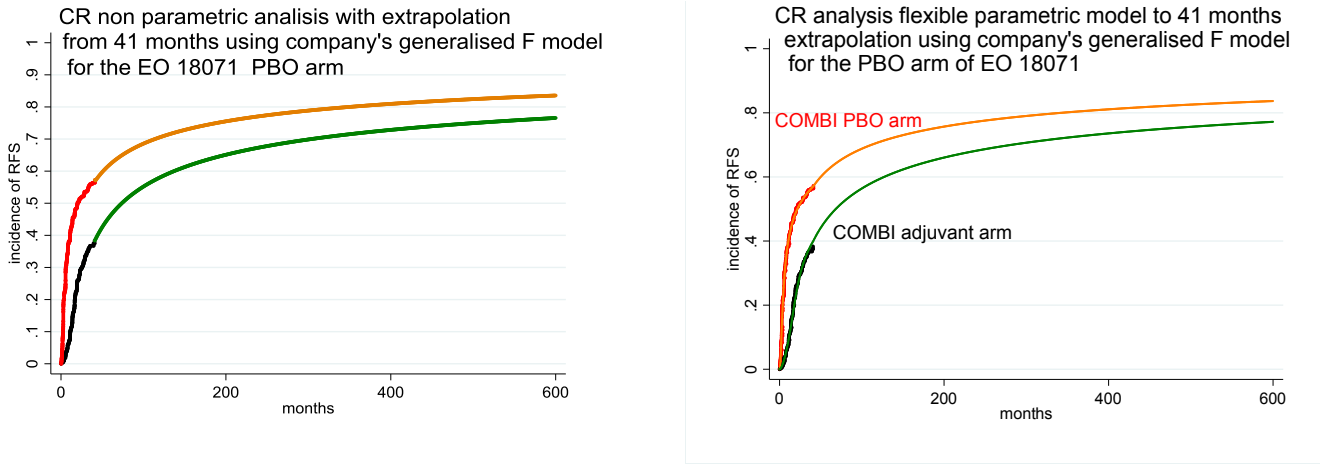


Figure 7: CR analysis of RFS; extrapolations to 50 years

It should be noted that the extrapolations indicated in Figure 7 deliver considerably less advantage of adjuvant over placebo than the company's extrapolation depicted in CS Figure 22 B.

Typically the curve that is applied during Segment 1 of the model differs from the curve that is applied in Segment 2 of the model, as does the splitting of events into LR, DR and Deaths. Note that the model permits the cut-point between Segment 1 and Segment 2 to be at any point. It is not limited to being at 50 months.

For RFS:

- Segment 1:
  - Arm specific RFS curves derived from COMBI-AD Kaplan Meier data: Log-logistic-U-Cure
  - Arm specific splitting of events into LR, DR and Death from COMBI-AD data of 34:64:1.9 for dabrafenib+trametinib and 44:55:0.4 for placebo.
- Segment 2:
  - Common to both arms an RFS curve derived from the placebo arm of EORTC 18071[21] reconstructed Kaplan Meier data: Generalised-F curve
  - Common to both arms splitting of events into LR, DR and Death from the placebo arm of EORTC 18071[21] of 35:62:3.

Given the model structure chosen by the company a problem arises. COMBI-AD only recorded 1st recurrences so cannot provide a post-LR RFS curve.

- For Segment 1 the company assumes that the shape of the LR-RFS curve will be the same as that of the placebo RFS curve, but with a hazard ratio applied to best fit the post-LR modelled survival over 50 months with the COMBI-AD post-LR OS Kaplan Meier data. The hazard ratio of 2.53 is derived in the model by:
  - setting all patients to start in the LR-RFS health state,
  - assuming that LR-RFS curve follows the COMBI-AD placebo RFS Kaplan Meier curve, qualified by the hazard ratio,
  - assuming that the LR-RFS events split between LR, DR and deaths is 32:63:5 based upon the White et al[52] study of 2,505 patients with melanoma with resected regional lymph node metastasis,
  - assuming that the DR-OS curve follows the COMBI-AD placebo DR-OS Kaplan Meier curve, and
  - varying the hazard ratio to minimise the sum of squares difference between the modelled LR-OS and the COMBI-AD placebo LR-OS Kaplan Meier curve.

For the post-LR RFS curve this results in:

- Segment 1:
  - Common to both arms the same curve as the placebo RFS Segment 1 curve derived from COMBI-AD Kaplan Meier data with the probability of events increased by a 2.53 hazard ratio: Log-logistic-U-Cure
  - Common to both arms splitting of events into LR, DR and Death based upon the White et al.[52] study of 32:63:5.
- Segment 2:
  - Common to both arms the same curve as the RFS Segment 2 curve derived from placebo arm of EORTC 18071[21] reconstructed Kaplan Meier data: Generalised-F curve
  - Common to both arms splitting of events into LR, DR and Death based upon the White et al. study[52] of 32:63:5.

1.6.3 Population

The model uses a number of data sources (Table ***17***) for the different elements of the model. Only the parameterised RFS curves that are applied for the 1st 50 months of the model can be unambiguously described as applying to BRAF V600+ve patients who when at stage III had their disease resected.

Table 17: Population data sources within the model

	Segment 1: 1st 50 months	Segment 2: After the 1st 50 months
RFS	COMBI-AD arm specific RFS parameterised curves. COMBI-AD arm specific balance between LR, DR and deaths events.	EORTC 18071[21] placebo arm parameterised curve. EORTC 18071[21] placebo arm balance between LR, DR and deaths events, common to both arms.
LR	COMBI-AD placebo arm RFS parameterised curve. US registry data split between LR, DR and deaths events, common to both arms.	EORTC 18071[21] placebo arm parameterised curve. US registry data split between LR, DR and deaths events, common to both arms.
DR	Total costs and QALYs for DR are applied to DR incident patients. These are drawn from TA366: Pembrolizumab for advanced melanoma not previously treated with ipilimumab, and	

recurrence in the company model improves the cost effectiveness estimate for dabrafenib+trametinib compared to placebo.

Note that the trial protocol planned to analysis the QoL data using mixed effects models, and not GEEs. ERG statistical opinion suggests that this is unlikely to have much affected results.

At clarification the company provides a number additional GEE models which split the RFS health states by arm and by whether patients remain on treatment, whether patients have had a 1st recurrence of LR or DR, whether patients have had an SAE, whether patients have had an SAE split by arm and applying a continuous indicator variable for month of assessment. The SAE coefficients are not estimated to be significant and these regressions are not reported in what follows.

Splitting the RFS on treatment state by arm results in significant coefficients for both arms, with that for dabrafenib+ trametinib [redacted] being similar to that of the placebo arm [redacted]. Slightly curiously, further splitting the RFS off treatment state by arm results in coefficients for dabrafenib+ trametinib for on treatment and off treatment of [redacted] and [redacted], which are both slightly lower than the corresponding coefficients for placebo of [redacted] and [redacted]. But the confidence limits of these coefficients overlap to a degree. All coefficients in Table 29 are significant.

Table 29: Alternative quality of life regressions: central coefficients

		Base	RFS on treatment			RFS off treatment					
	Intercept	EQ-5D	Pooled	DABR	PLAC	Pooled	DABR	PLAC	DR	LR	Month
BC	0.373	0.575	-0.015	..	..	0.000	..	..	-0.077	-0.034	..
Alt1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alt2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alt3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alt4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Of note, the continuous indicator variable for month of assessment is significant in both regressions that include it and in both regressions it has a positive if small coefficient, though as noted above there may be some reporting bias through time.

The quality of life values that result from the first four regressions in the above, when applied to a pooled baseline value of [redacted], presented in Table 30. For the Alt4 regression this sets the month to zero.

Table 30: Quality of life values from alternative regressions

	RFS On treatment		RFS Off treatment				
	DABR	PLAC	Pooled	DABR	PLAC	LR	DR
BC	[redacted]	-	[redacted]	-	-	[redacted]	[redacted]
Alt1	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Alt2	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]
Alt3	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Alt4	[redacted]	-	[redacted]	-	-	[redacted]	[redacted]

The values for DR are broadly in line with the values reported in the brief ERG summary of quality of life values of some of the previous NICE STAs.

Any differences between the values of the base case, as per the first regression, and those of the other three regressions appear to be relatively minor and unlikely to much affect results. ERG statistical opinion prefers the simpler model of the company base case, with this being favoured by information criteria supplied at clarification. Splitting the RFS on treatment and the RFS off treatment by arm results in the central estimates as in Alt3 results in slightly lower RFS values for dabrafenib+ trametinib compared to placebo. The ERG will apply the Alt3 values as a scenario analysis.

Dosing and number of packs dispensed during COMBI-AD

The company states in Table 2 of Document B (pg. 13) that a mean of [redacted] packs of dabrafenib and a mean of [redacted] packs of trametinib were received during COMBI-AD. This is incorrect, as the qualifying text in brackets of table 2 hints. The stated means are based upon the smallest number of 75mg packs of dabrafenib and the smallest number of 2mg packs of trametinib that could be

dispensed and still be consistent with each patients' cumulative dose during COMBI-AD; i.e. the smallest possible wastage. This assumption also underlies figure 27 of Document B[1] (pg. 95).

The ERG assumption is that patients' cumulative doses are calculated based on the number of capsules consumed and not the number of packs prescribed. With this assumption, dose modifications and treatment holidays seem likely to imply that wastage and prescribing costs will be higher than implied by the company method. The COMBI-AD CSR reports the following dose modifications and interruptions (Table 31) among the 435 patients who received treatment in the dabrafenib+trametinib.

Table 31: Dose modifications and interruptions

	Dabrafenib	Trametinib
Dose reductions	[redacted]	[redacted]
Dose escalations	[redacted]	[redacted]
Dose interruptions		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3+	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Any interruption	[redacted]	[redacted]
Total interruptions	[redacted]	[redacted]
Interruption duration		
≤7 days	[redacted]	[redacted]
8 to 14 days	[redacted]	[redacted]
> 14 days	[redacted]	[redacted]
Interruption reason		
Adverse event	[redacted]	[redacted]
Patient protocol violation	[redacted]	[redacted]
Other	[redacted]	[redacted]

[1] The economic model performs the same calculation based upon the cumulative dose and suggests that [redacted] of the 435 patients or [redacted] received 48 packs of dabrafenib, as per Figure 27 of Document B.

ERG expert opinion also suggests that there is not good evidence of developing resistance to BRAFi and MEKi. As a consequence, a distant recurrence after having received adjuvant dabrafenib+trametinib seems more likely to be heavily mutated and active, and more likely to have developed mechanisms to bypass BRAF inhibition. As a consequence, dabrafenib+trametinib for treatment of a distant recurrence may be less effective among patients who have already received it as adjuvant treatment, reducing the total QALYs that should be attributed to it. It may also tend to reduce the proportion of these patients who would be treated with it.

Retaining the [redacted] balance of the company base case and reducing the total QALYs for patients who are assumed to receive targeted therapy at DR in the dabrafenib+ trametinib arm by 20%, 30% and 40%[2] worsens the cost effectiveness ratio from £20,039 per QALY to £23,571 per QALY, £25,848 per QALY and £28,614 per QALY respectively.

Revising the split between immunotherapy and targeted thereapy for DR patients in the dabrafenib+ trametinib arm from [redacted][3] improves the cost effectiveness ratio from £20,039 per QALY to £15,425 per QALY. This improvement is dependent upon whether these patents switch to a treatment with a higher health benefit than dabrafenib+ trametinib treatment of DR. But it should be borne in mind that these patients are being "switched" to another therapy due to dabrafenib+tramatenib treatment of DR for these patients being anticipated to have an even worse monetised health benefit than it does for patients who have not received dabrafenib+ trametinib adjuvant treatment. Consequently, the treatment they are switching to might have similar or worse monetised health benefit when compared to the monetised health benefit of dabrafenib+ trametinib treatment of DR among patients who have not received dabrafenib+ trametinib adjuvant treatment.

ERG expert opinion suggests that the split between treatments that are used by at least 10% of stage III resected UK patients not treated with adjuvant dabrafenib+trametinib who progress to a DR is likely to be around 30:30:10:10 for pembrolizumab:ipilimumab+nivolumab: dabrafenib: clinical trials.

[2] Implemented in the *Outputs* worksheet by conditioning D12 by [redacted] respectively.
[3] Implemented in the *Cost_PostDR* worksheet by revising D8:D9 accoridingly.

- Related to the above bullet, while the model does fit an OS curve to the post-DR patients this does not affect the cost effectiveness estimates and is more for validation purposes. During COMBI-AD there was a noticeably larger number of non-melanoma deaths in the placebo arm than in the dabrafenib+trametinib arm, which might argue for a competing risks analysis. But because the modelled OS does not affect the cost effectiveness estimate, it is not obvious how this could be taken into account within the economics.

The company rejects a number of parameterisations of the COMBI-AD RFS data because the dabrafenib+trametinib curve falls below the placebo curve. For a number of curves this does not occur until well into extrapolation, and is minimal to the point of being inconsequential when it does. The company has not properly justified why these curves should be rejected. In the opinion of the ERG they should be considered within the economics.

The main uncertainty is around which curves should be applied and to what extent they should be extrapolated. The company position is that the COMBI-AD log-logistic (U) cure model curves should be used to 50 months but should not be used for extrapolation, with extrapolation being based upon data from the EORTC 18071 trial instead. The ERG notes the differences in populations between COMBI-AD and EORTC 18071. The ERG sees more merit in using parameterised curves derived from COMBI-AD for extrapolation. This also permits the duration of benefit from dabrafenib+trametinib over placebo to be explored.

ERG expert opinion suggests that dabrafenib+trametinib may postpone recurrences but are less likely to avoid them altogether, meaning that in the longer term the proportion who are cured will converge with that of the placebo arm. This argues for the COMBI-AD log-logistic (R) cure model curves over the COMBI-AD log-logistic (U) cure model curves. It can be noted that the AIC for the (U) model may show some superiority, but the BICs are virtually identical for the two models. Convergence of cure rates would further argue for the ERG COMBI-AD competing risks model curves, with an additional argument in their favour being that both a company adviser and the ERG are of the opinion that a competing risks analysis is desirable due to the COMBI-AD data definitions. Any convergence of cure rates further argues that these curves should be used for extrapolation. Clearly, if the proportion who are cured by dabrafenib+trametinib tends to converge with that of placebo the cost effectiveness of dabrafenib+trametinib worsens somewhat.

The EORTC extrapolation results in survival in the placebo arm being around 80-85% that of survival in the dabrafenib+ trametinib arm for month 50 to month 600.

More fully accounting for SAEs and possibly AEs that did not require hospitalisation but did require medication and possibly additional appointments wouldprobably increase costs more in the dabrafenib+trametinib arm than in the placebo arm. But given the modelled large net cost for dabrafenib+trametinib, any SAE costs would have to be quite large to have much effect on the cost effectiveness estimate. There is the suggestion, as shown in SA01, that explicitly accounting for the different SAE profiles by arm would worsen the cost effectiveness estimate.

If patients were prescribed dabrafenib or trametinib beyond day 364 of the COMBI-AD trial either the clinical data does not particularly reflect the anticipated license or costs could be somewhat higher in the dabrafenib+trametinib arm. Either would worsen the cost effectiveness estimate.

END OF LIFE

End of life does not apply.

Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma

ADDENDUM to the ERG report

ERG's additional cost-effectiveness analyses

Produced by Warwick HTA Group

Date completed 12 July 2018

The pre-meeting briefing document includes a presentation of the ERG flexible fit RFS curves. In the light of this the ERG includes an additional set of analyses which apply these curves.

Table 01: Updated set of ERG analyses

	L-Log (U)	L-Log (R)	ERG Flex	ERG CR
Base case	£20,701	£62,853	£20,167	£46,161
SA01: EQ-5D RFS split by arm	£21,734	£70,752	£20,814	£49,492
SA02a: EQ-5D intercept -25%	£24,134	£72,018	£23,447	£53,061
SA02b: EQ-5D intercept +25%	£18,134	£55,790	£17,703	£40,873
SA02c: SA01 + EQ-5D intercept -25%	£25,697	£83,032	£24,461	£57,814
SA02d: SA01 + EQ-5D intercept +25%	£18,830	£61,636	£18,114	£43,264
SA03: DABR monitoring +50%	£21,929	£65,675	£20,404	£48,347
SA04a: LR resection 0%	£21,329	£63,847	£20,770	£46,954
SA04b: LR resection 20%	£20,073	£61,859	£19,564	£45,369
SA05: LR events balance EORTC 18071	£20,764	£63,716	£20,181	£46,530
SA06: DR costs and benefits reflect EoL	£24,980	£61,487	£24,274	£46,589
SA07: EORTC extrapolation	£26,258	£30,866	£23,513	£27,432

The ERG flexible fit RFS curves do not converge and as a consequence result in a similar cost effectiveness estimate to the company log-logistic (U) cure model curves. The ERG flexible fit RFS curves also continue to decline during the period of extrapolation rather than plateauing as per the company log-logistic (U) cure model curves. This could account for the superior cost-effectiveness estimates within some of the sensitivity analyses when employing the ERG flexible fit RFS curves compared to those of employing the company log-logistic (U) cure model curves.