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.

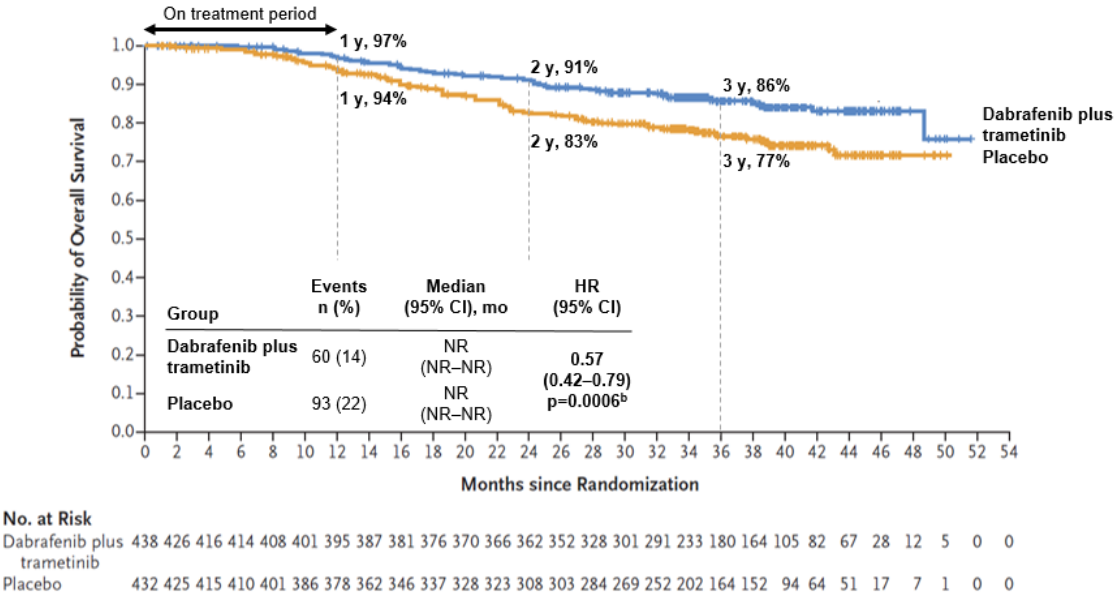
In the CS cost effectiveness section (3.3.1 pg. 71) a further KM analysis of "RFS" is presented (CS Figure 13); this was used in the economic analysis on the basis of clinical advice that new primary melanoma (SPM), in the absence of observed recurrence, should not be considered a recurrence event and 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.

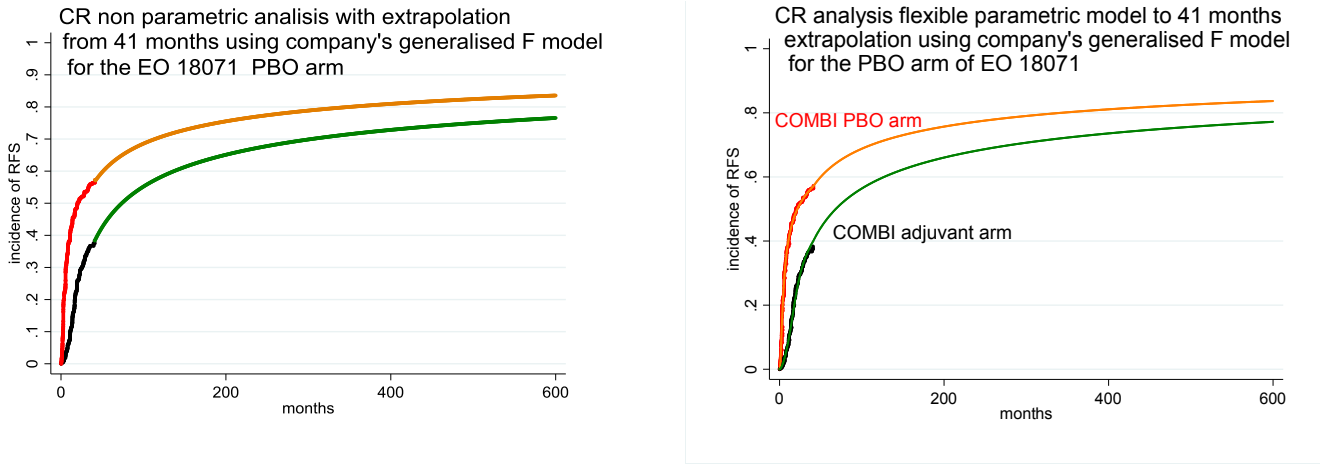


Figure 7: CR analysis of RFS; extrapolations to 50 years

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.