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

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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ERG: Warwick Evidence

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19 July 2018

Key issues - cost effectiveness 1

- The key driver for additional QALYs with adjuvant therapy is staying in the recurrence free state and avoiding disseminated disease and death
- The key cost offsets for the adjuvant treatment are the costs of being in the disseminated disease state with further drug and administration costs

Given the main driver of the model is staying recurrence free what are the committee's view of the following:

- Is it appropriate to use data from the placebo arm of a study of adjuvant immunotherapy 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?

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Key issues - cost effectiveness 2

- 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) model, suggesting that treatment postpones recurrence
  - ERG's flexible parametric fit and competing risks models also suggest that treatment postpones recurrence
  - should competing risks methodology 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?
- Is it realistic that around half of people with metastatic disease in the model received further dabrafenib plus trametinib?
- What are the committee's conclusions on possible underestimation of costs associated with adverse events and monitoring?
- Is the technology innovative?

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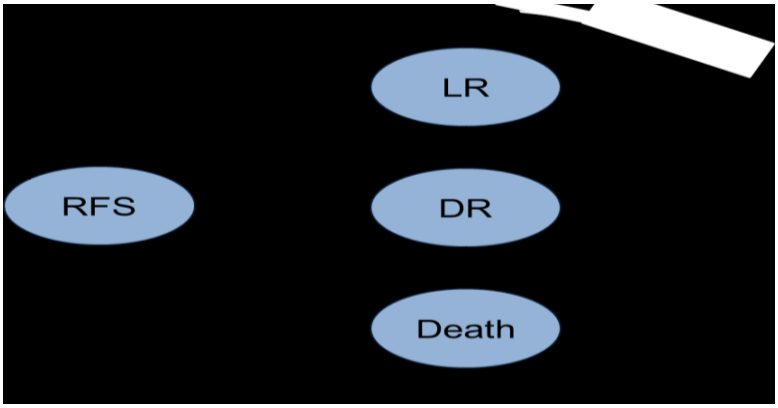
Company's 4 state-transition model



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.

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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 1 year of 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, after this, curves fitted to the model and the splitting of events into LR, DR and deaths differ in the 2 segments

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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 during trial follow up
- 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 after the observed trial period: estimated from placebo arm of EORTC 18071
- 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

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Company's modelling for 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 : 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 reflection of the RFS observed in the trial

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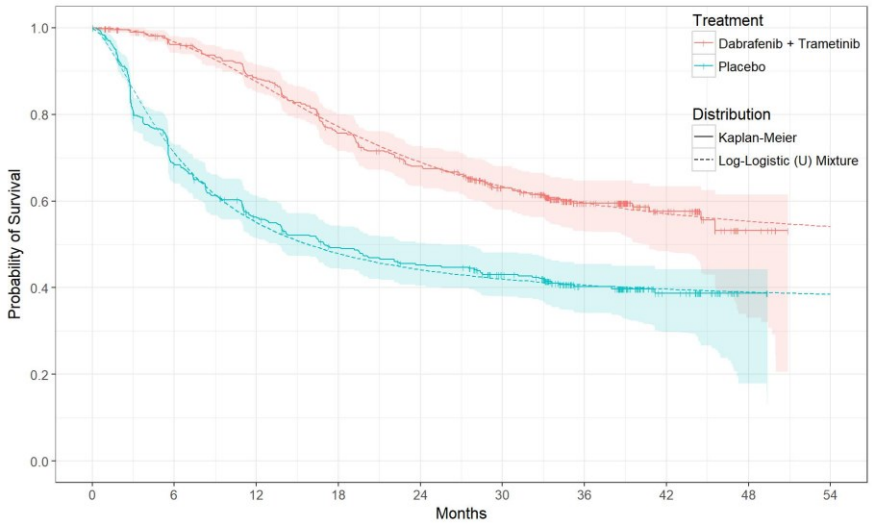
Modelling of RFS during observed period of COMBI-AD: log-logistic unrestricted mixture-cure model fitted for the first 50 months of trial



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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
- 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

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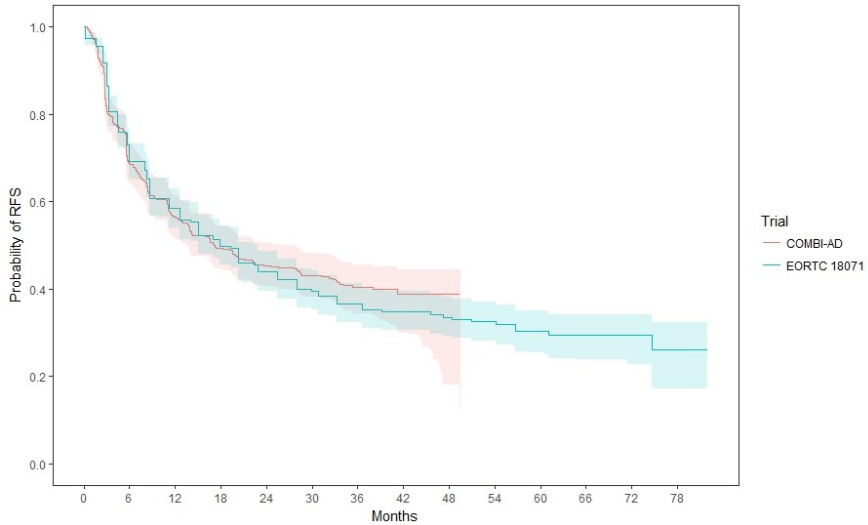
Comparison of RFS from COMBI-AD and EORTC 18071 placebo arms



Source: Figure 16 of the company submission

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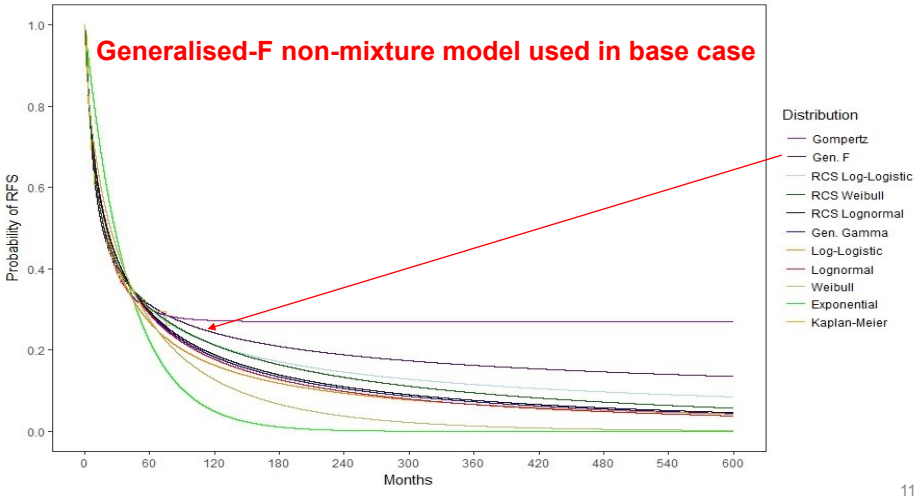
Modelling of RFS after observed period of COMBI-AD: Parametric functions fitted to placebo arm of EORTC 18071

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



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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%**

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Modelling of distant recurrence outcomes/costs

- Outcomes following a distant recurrence were applied as one-off total costs and QALYs at the point of entry into the DR health state
- Approach taken because outcomes associated with DR are related to the efficacy of metastatic treatments, not previous adjuvant therapy
- Total costs & QALYs were derived from 2 previous NICE appraisals in the first-line treatment of metastatic disease:
  - around half of patients with a DR had dabrafenib+trametinib in the model, so avoiding DR means large costs of dabrafenib+trametinib are avoided
  - assumes effectiveness of dabrafenib+trametinib for DR is not affected by having previously received it as an adjuvant treatment
- Post DR OS not explicitly used in the model and was included only to assess the validity of the model predictions for OS vs those observed in COMBI-AD
- Post-DR OS from COMBI-AD during the observed period showed no statistically significant differences between-arms (p=0.27)

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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.

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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.

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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	[redacted]	[redacted]	COMBI-AD CSR	-
Total discounted costs (including PAS)	[redacted]	[redacted]	TA366 ERG report, TA396	**£142,699**
Total discounted QALYs	[redacted]	[redacted]	TA366, TA396	**3.23**

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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

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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

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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
- Model fits an OS curve to post-DR patients but only for validation purposes

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ERG comments on company's extrapolation of the 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

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ERG concerns leading to competing risk (CR) analysis

Unknown whether people with premature end of follow up (PEFU) have an equal risk of an event as those with complete follow up:

- There was imbalance between arms in PEFU numbers: RFS: [redacted]; OS: 47 & 62, in adjuvant & placebo arms respectively. Timings of PEFU differed. Non-melanoma deaths were unequal: 6 adjuvant, 16 placebo
- In KM analysis PEFUs are censored, altering numbers at risk which can influence curve shape. Imbalances may influence arms unequally and may skew estimates of treatment effect
- ERG' analysis, with PEFU as a CR, offers an alternative to censoring in exploring PEFU influence
- CR analysis may be used when occurrence of the event of interest (e.g. recurrence) is precluded by prior occurrence of a competing event (e.g. death)
- Use of PEFU as CR for recurrence is unusual but not unprecedented: consistent with company expert advisor who expected "some type of CR analysis"
- ERG analysis using PEFU as a CR suggests treatment effect in KM analysis may be slightly overestimated by ~10% for RFS and ~20% for OS
- Very small effect on cost effectiveness if CR analysis is used instead of KM with company's extrapolation using EORTC 18071

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ERG comments – curve selection

- Key uncertainty in the modelling is which curves should be applied and the extent to which they should be extrapolated
- 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
- Longer term 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) model and the ERG's flexible parametric fit and CR models suggest treatment will postpone recurrence and the cure rate will eventually converge with placebo, leading to a worsening of the cost-effectiveness estimate

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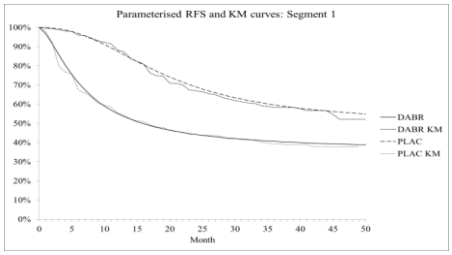
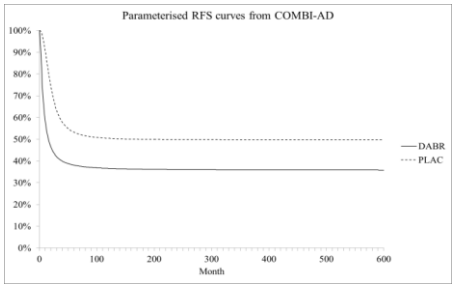
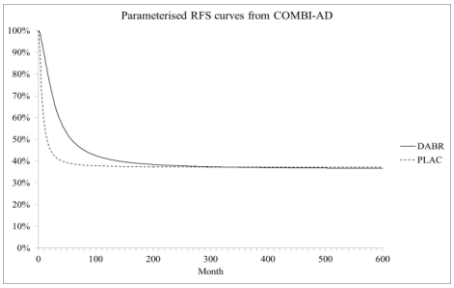
Company-explored RFS curves



Parameterised RFS and KM curve for segment 1



Base-case Log-Logistic (U) Mixture



Alternative Log-Logistic (R) Mixture

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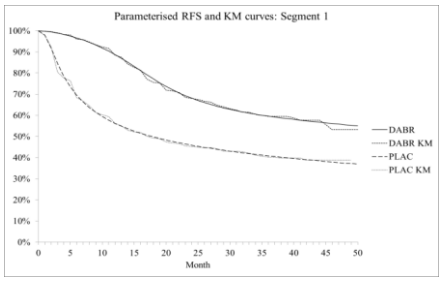
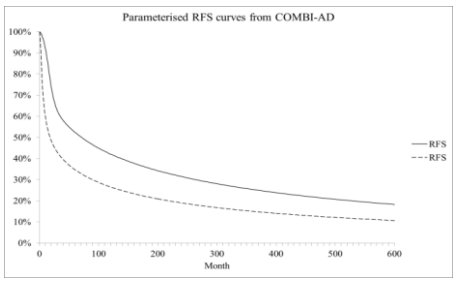
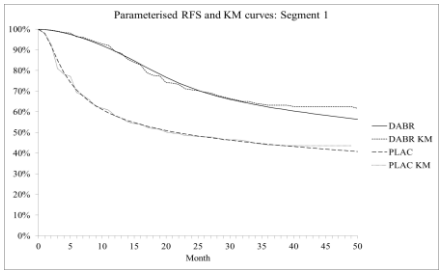
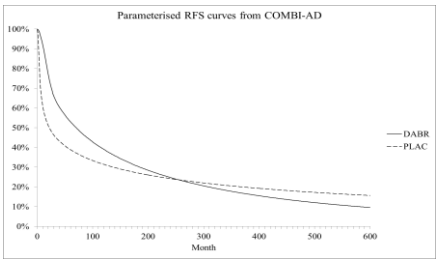
ERG alternative RFS curves





ERG flexible parametric fit





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ERG flexible competing risk parametric fit

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**
- Uncertainty about drug wastage during COMBI-AD - company's method may underestimate wastage, 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
  - ERG's estimates are based upon company data supplied at clarification but may overestimate wastage

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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

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ERG's exploratory analyses

ERG presents 4 sets of analyses, using:

- company log-logistic (U) cure model
- company log-logistic (R) model
- ERG's flexible parametric fit model
- ERG competing risks model

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ERG changes to the company's model

ERG also made the following changes to the model in its revised base case:

- Assumes that people who have had treatment have the same monitoring requirement as those remaining on treatment
- Assumes an additional quarterly OP appointment with treatment to account for dermatological monitoring
- Applies the proportions remaining on treatment during year 1 provided by the company at clarification
- Revises prescription drug costs based on information provided by the company at clarification on the number of packs of treatment dispensed
- Revises 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

Note: Revised base case assumes no EORTC-18071 extrapolation

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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)

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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

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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

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Key issues - cost effectiveness 1

- The key driver for additional QALYs with adjuvant therapy is staying in the recurrence free state and avoiding disseminated disease and death
- The key cost offsets for the adjuvant treatment are the costs of being in the disseminated disease state with further drug and administration costs

Given the main driver of the model is staying recurrence free what are the committee's view of the following:

- Is it appropriate to use data from the placebo arm of a study of adjuvant immunotherapy 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?

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Key issues - cost effectiveness 2

- 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
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- What are the committee's conclusions on possible underestimation of costs associated with adverse events and monitoring?
- Is the technology innovative?

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