National Institute for Health and Care Excellence

Draft for consultation

Melanoma: assessment and management

[G] Evidence review for the follow-up of people with melanoma

Health economic model report

NICE guideline <number>

Evidence reviews underpinning recommendations 1.9.1 to 1.9.13 and research recommendations in the NICE guideline

January 2022

Draft for Consultation

These evidence reviews were developed by Guideline Updates Team

Funding
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Contents

HE1 Methods

HE1.1 Model overview

The objective of this analysis was to compare the expected benefits, harms, and costs of computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) as an imaging approach in the follow up of patients with stage III melanoma. In addition, for patients with stage IIIA melanoma the expected benefits, harms and costs of a reduced number of imaging follow up appointments was compared to the current recommended follow up times.

HE1.1.1 Population(s)

The population of interest was patients with stage III melanoma who have started a course of adjuvant therapy. Patients who are *BRAF* mutant and *BRAF* wild type are modelled separately as such patients are eligible to receive different adjuvant therapies.

HE1.1.2 Interventions

The model assessed six different follow up regimes:

1. CT scan at the current recommended follow up times (four times in the first year, twice in years 2 and 3, and once in years 4 and 5).
2. PET-CT scans at the current recommended follow up times (four times in the first year, twice in years 2 and 3, and once in years 4 and 5).
3. Reduced follow up for patients with stage IIIA melanoma and current recommended follow up for patients with stage IIIB and IIIC melanoma using CT scans*.
4. Reduced follow up for patients with stage IIIA melanoma and current recommended follow up for patients with stage IIIB and IIIC melanoma using PET-CT scans*.

*Two different reduced follow up schedules were analysed, 2 years and 0 years (referring to the point at which patients stop receiving 6 monthly scans). Table HE001 shows the months which imaging is done for all the different follow up schedules.

Ultrasound of the nodal basin is another imaging technique; however, this was not included in this economic analysis for a number of reasons. Firstly, ultrasound is scanning a single area of the body whereas CT and PET-CT are scanning the whole body and therefore the imaging modalities are not comparable. Secondly, there was no randomly controlled data on the effectiveness of ultrasound and therefore there was limited confidence in the sensitivity and specificity produced by the included trials.

Table HE001: Follow up schedules for CT and PET-CT scans

Month	Standard follow up	Reduced follow up (2 years)	Reduced follow up (0 years)
3	Imaging	Imaging	Imaging
6	Imaging	Imaging	Imaging
9	Imaging	Imaging	Imaging
12	Imaging	Imaging	Imaging
15	-	-	-
18	Imaging	Imaging	-
21	-	-	-
24	Imaging	Imaging	Imaging
27	-	-	-

Month	Standard follow up	Reduced follow up (2 years)	Reduced follow up (0 years)
30	Imaging	-	-
33	-	-	-
36	Imaging	Imaging	Imaging
39	-	-	-
42	-	-	-
45	-	-	-
48	Imaging	Imaging	Imaging
51	-	-	-
54	-	-	-
57	-	-	-
60	Imaging	Imaging	Imaging

HE1.1.3 Type of evaluation, time horizon, perspective

The analysis measures outcomes as the expected number of quality adjusted life years (QALYs), and the results are presented using incremental cost-effectiveness ratios (ICERs) that express the cost per QALY gain of using a specific follow up regime compared to the next best alternative. For the sensitivity analysis net monetary benefit (NMB) is used to show which parameters affect the result. NMB used is at £20,000 and is therefore (20,000 x ∆QALY) - ∆Cost. The reason for using NMB is because it is easier to display a change in the most cost-effective option.

The model has a 20-year time horizon, to reflect all important differences in costs and outcomes between the follow up regimes being compared. A 20-year time horizon was used over a lifetime time horizon as there are no additional costs incurred by the intervention after 20 years, and, due to discounting, the number of QALYs gained is very low gained after 20 years. In addition, the difference in the total number alive between the two groups is negligible and therefore the number of QALYs gain by both groups will be very similar. . Each follow up regime compared in the model uses imaging as part of follow-up for 5 years and therefore the 20-year time horizon is long enough to capture all imaging appointments as well as any recurrences associated with the original melanoma diagnosis.

The analysis was conducted from the perspective of the NHS and Personal Social Services in the United Kingdom.

HE1.1.4 Discounting

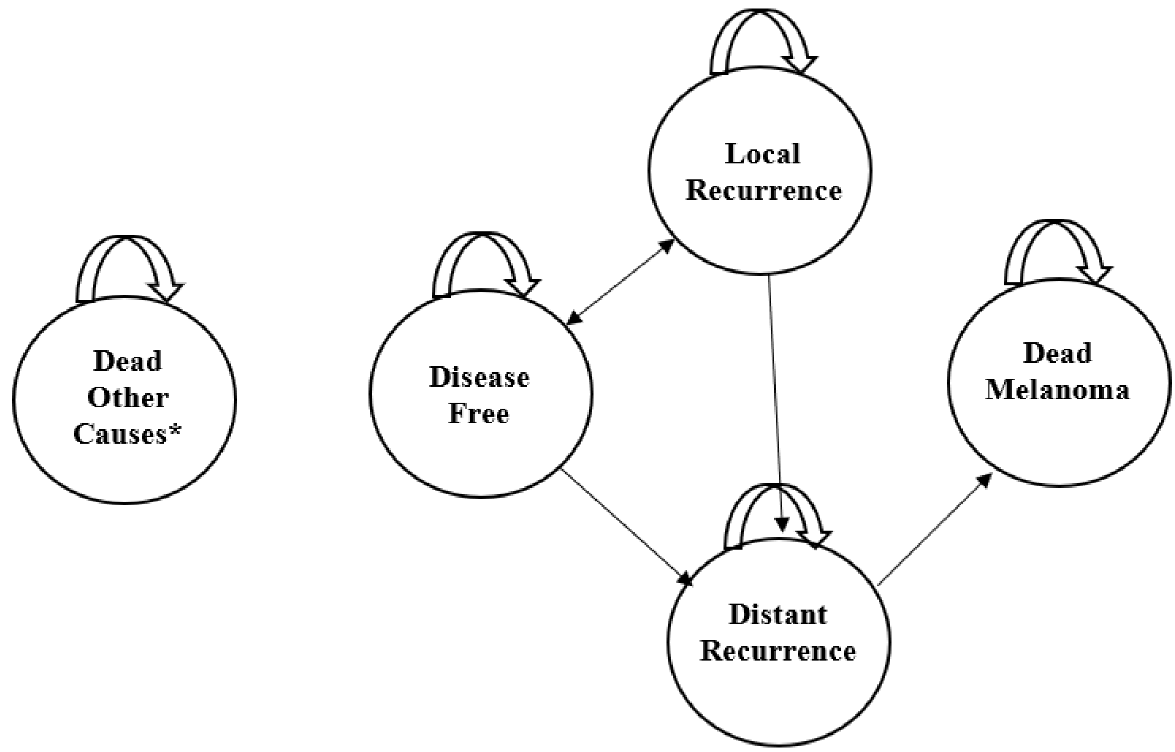
The analysis discounts all future costs and QALYs at a rate of 3.5% per year, as required by Developing NICE guidelines: the manual (2018).

HE1.2 Model structure

Two different Markov models were constructed in Microsoft Excel, one for patients with *BRAF* mutant stage III melanoma and the other for patients with *BRAF* wild type stage III melanoma. The two models were created separately as the patients receive different adjuvant treatment depending on their *BRAF* status and therefore the two different models have slightly different probabilities of melanoma recurrence. Figure HE001 provides a schematic depiction of the stage III model, which is the same for both *BRAF* mutant and *BRAF* wild type populations. Figure HE002 shows in more detail the movement of patients with local and distant recurrence. Table HE002 provides a list of the health states and an associated definition. Each model was split into stage IIIA, IIIB and IIIC, defined according to the American Joint Committee on Cancer (AJCC) 7th edition (American Joint Committee on cancer 2009), because each substage is associated with different probabilities of recurrence and survival. The reason for using the AJCC 7th edition (American Joint Committee on cancer 2009) rather than the 8th edition (American Joint Committee on cancer 2016) was due to the two studies used for recurrence using the 7th edition. The 8th edition (American Joint Committee on cancer 2016) included another substage, IIID, this was not included in this analysis, this is unlikely to have a large impact on the results as the number of patients falling into stage IIID is small, 36 out of 1,089 stage III melanomas diagnosed in 2018 (Unpublished data provided by a committee member). The split also had the advantage of being able to test a different follow up schedule for stage IIIA patients. The committee hypothesised that as stage IIIA patients have a lower probability of recurrence that fewer follow-up imaging appointments over the five years could be cost-effective compared to current recommended follow times, and that it would be clinically inappropriate to consider reduced follow up schedules for stage IIIB and IIIC patients.

Table HE002: Modelled health states

Health state	Definition
Disease Free	Patient has no evidence of melanoma
Local recurrence, not discovered	Patient has a local recurrence but has not been discovered by the patient or clinician or imaging
Local recurrence, patient discovered	Patient has a local recurrence that has been discovered by the patient or through a clinician examination but not with imaging
Local recurrence, imaging discovered	Patient has a local recurrence that has been discovered by imaging during a regular follow up appointment.
Distant recurrence, not discovered	Patient has a distant recurrence but has not been discovered by the patient or clinician or imaging
Distant recurrence, patient discovered	Patient has a distant recurrence that has been discovered by the patient or through a clinician examination but not with imaging
Distant recurrence, imaging discovered	Patient has a distant recurrence that has been discovered by imaging during a regular follow up appointment.
Dead, Melanoma	Died from melanoma
Dead, Other causes	Died from any cause that is not melanoma



This is a simplified version, local recurrence and distant recurrence are split into 'Patient discovered', 'Imaging discovered' and 'Not discovered' as shown in Figure HE002.
*Patients can transition to Death Other Causes from any non-dead health state

Figure HE001: Structure of original cost–utility model

The models start with patients receiving adjuvant therapy for the first year, which is available for all patients diagnosed with stage III melanoma, and therefore the patients receive imaging according to the protocols of the relevant adjuvant trials, which is imaging every three months. The patients receiving current recommended follow up times then receive imaging every six months for years 2 and 3 then annual imaging for years 4 and 5. For the patients on a reduced follow up schedule the patients either received imaging every six months for year 2 and annual for years 3 to 5 (2 years) or annual for years 2 to 5 (1 year) as shown in Table HE001. In addition to imaging, the patients received a clinical review every 3 months for the first three years of follow up and then every six months for the following two years. It was assumed that patients with *BRAF* mutant melanoma received dabrafenib plus trametinib as adjuvant therapy and then were eligible to receive either pembrolizumab, nivolumab or ipilimumab plus nivolumab if they experienced a distant recurrence. Patients with *BRAF* wild type melanoma received pembrolizumab as adjuvant therapy and then were eligible to receive either nivolumab or ipilimumab plus nivolumab if they experienced a distant recurrence. While there are multiple available adjuvant treatments, dabrafenib plus trametinib was chosen for *BRAF* Mutant and pembrolizumab for *BRAF* Wild Type as these are currently recommended by NICE, and because there was available Kaplan Meier curves for recurrence that was split into stage IIIA, IIIB and IIIC for both of these treatments. The committee felt that these two treatments were very common as adjuvant treatments and the outcomes for the patients were likely to be comparable to the other treatments available.

All patients start in the disease-free health state. Patients can then transition into any other health state except for "Dead, Melanoma".

- If the patient was in "Local recurrence, not discovered" then their recurrence is considered to be asymptomatic and cannot be detected by patient or clinician examination alone, it is assumed that the imaging has not detected the recurrence either. Patients in this health state can progress to distant disease, the recurrence can be found by imaging, the patient becomes symptomatic or the patient can die from all causes except from melanoma.

- If the patient has a local recurrence that has been found by the patient, clinician, or through imaging then the patient receives surgery. If the surgery was successful, then the patient moves back to the disease-free health state. If the surgery was unsuccessful, then the patient moves into the distant disease health state as it was assumed that the patient’s melanoma metastasised.
- It was assumed that a proportion of patients in the ‘Disease free’ health state would have received a false positive result. Within the model the patients remains in the ‘Disease free’ health state however, the number of patients receiving this false positive was recorded so the additional cost of a false positive could be applied.
- If the patient were in “Distant disease, not discovered” then the recurrence is also considered to be asymptomatic and cannot be detected by patient/clinician examination alone. Patients in this health state can remain with distant disease or die from melanoma.
- If the patient were in “distant disease, patient discovered” or “distant disease, imaging discovered”, then the patient receives one of the available systemic treatments and remains in the distant disease health state and the patient cannot be cured until they die from melanoma.
- All patients could also move to death from other causes from any living health state in the model.

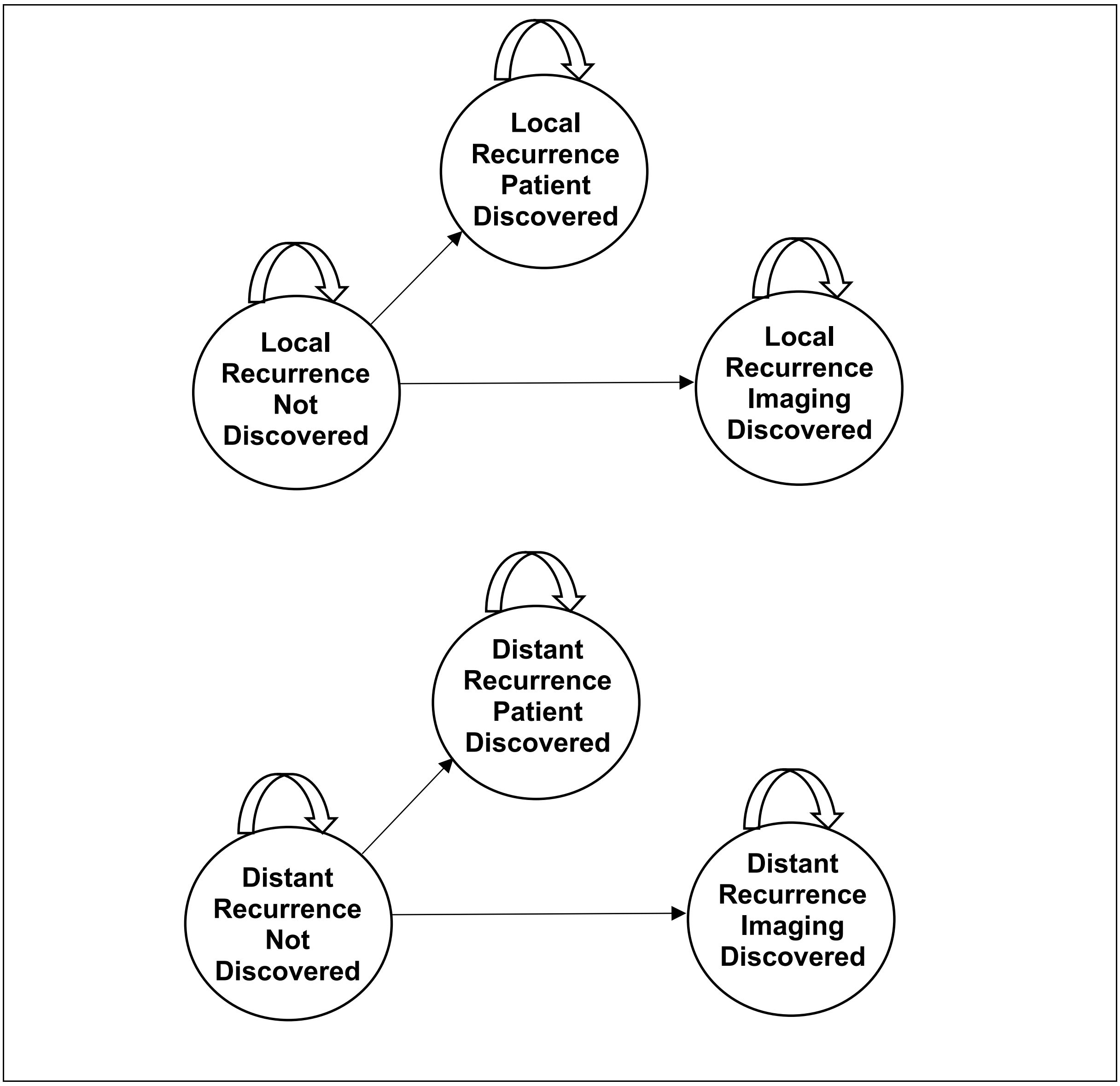


Figure HE002: Structure of local and distant recurrence

Within the model costs come from the CT or PET-CT scan, the clinical appointment, false positive results, surgery, restaging, treatment for recurrence, and terminal care. The cost for CT scans, PET-CT scans, MRI scans, surgery and clinician appointments came from the National Schedule of NHS costs 2018/19 We used 2018/19 rather than 2019/2020 due to the COVID-19 outbreak and thought that the 2019/2020 data is less likely to represent usual care in the NHS, for example only more severe treatments were likely to be completed and therefore, higher costs as a result. The cost for treatments for recurrence came from the British National Formulary (BNF) as the costs were not available in the other sources searched (NHS Commercial Medicines Unit's Electronic Market Information Tool and the Drug Tarriff) and the cost for palliative care came from the relative Technology Appraisals (TAs) of systemic treatments for advanced melanoma. Further information on costs is in HE1.4.4.

Patients received QALYs from being disease free, having unsuccessful surgery, not identified local recurrence, not identified distant recurrence, treatment for recurrence, and death. Further information on QALYs is located in HE1.4.3.

HE1.3 Model parameterisation

Identifying sources of parameters

The sensitivity and specificity of CT and PET-CT and the probabilities of a patient's recurrence being symptomatic came from two systematic reviews conducted for following up patients with melanoma (see below). The remaining parameters were identified through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

When searching for quality of life, resource-use and cost parameters, we conducted searches in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry, the NHS Economic Evaluation Database (NHS EED) and the existing TAs.

We asked the committee to identify papers of relevance for parameter values and their opinion if no values could be identified. We reviewed the sources of parameters used in the published CUAs identified in our systematic review for all review questions, this included an existing model from the previous iteration of the guideline; during the review, we also retrieved articles that did not meet the formal inclusion criteria but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, we obtained data from unpublished sources; further details are provided below.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should come from the UK population).
- All other things being equal, we preferred more powerful studies (based on sample size and/or number of events).
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

HE1.4 Parameters

HE1.4.1 Cohort parameters

HE1.4.1.1 Starting demographics and characteristics

The two models use slightly different cohort starting characteristics based on the mean age and proportion of males reported in the adjuvant therapy trials used to estimate the probabilities of recurrence. The cohort of patients in the *BRAF* mutant model started at 57 years of age and 64% of them were male, this was in line with the characteristics of trial participants reported in Dummer 2020 which was used to estimate the probability of recurrence for patients receiving dabrafenib and trametinib as adjuvant therapy. The cohort of patients in the *BRAF* wild type model started at 54 years of age and 63% of them were male, this was in line with the characteristics of trial participants reported in Eggermont 2020 which was used to estimate the probability of recurrence for patients receiving pembrolizumab as adjuvant therapy.

The proportion of patients in each melanoma substage was the same in both models. The proportion in stage IIIA, IIIB and IIIC was 0.36, 0.422 and 0.218 respectively. These proportions were sourced from the East of England Cancer Registry (2009), this was the same source as the previous NG14 model. More up to date values are based on the AJCC 8th edition which include stage IIID which is not included in the model due to a lack of data for adjuvant therapy recurrence rates for stage IIID. Therefore, the value from the East of England Cancer Registry was used.

HE1.4.1 Probability of recurrence

The two models, *BRAF* mutant and *BRAF* wild type, used different probabilities of recurrence depending on the adjuvant therapy the patient received. We assumed that all patients who were *BRAF* mutant received dabrafenib and trametinib and all patients who were *BRAF* wild type received pembrolizumab. While it is possible that both sets of these patients could receive different adjuvant treatments, we assumed all patients in each model would receive the same treatment for simplicity. The reason that these two treatments were chosen was because the recurrence curves were available for each of stage IIIA, stage IIIB and stage IIIC. We used the Kaplan Meier curves reported by Dummer 2020 of relapse-free survival to estimate the probabilities of recurrence for each of the three substages of patients who were treated with dabrafenib and trametinib. While relapse free survival has both relapse and death as an event within the data, these were the best available data on relapse. The committee also felt that the number of patients who died in this trial is likely to be low as the patients were being followed up so it would be unlikely for issues to be missed. The committee acknowledged that some patients would have died from other causes but felt that this would likely to be low and therefore it was best to use this data. Similarly, the Kaplan Meier curves reported by Eggermont 2020 of relapse-free survival were used to estimate the probabilities of recurrence for each of the three substages of patients who were treated with pembrolizumab. As Dummer 2020 only followed patients for five years and Eggermont 2020 only followed patients for three years we needed to predict the probabilities of recurrence beyond the trial follow up periods. The process for estimating these probabilities of recurrence was the same for dabrafenib and trametinib and pembrolizumab. The six Kaplan Meier curves of relapse-free survival (i.e., one for each substage and each treatment) were taken from the two studies and digitized using Engauge Digitizer (Mitchell et al.), this data was then imported into Stata (Statcorp) which was used to predict the curve into the future. Within Stata, the ipsfc command was used to get the individual patient data then the parametric survivor functions were applied. Five different parametric survivor functions were explored to identify the distribution that best fitted the observed data from the trial and also resulted in an appropriate extrapolation past the trial follow up period. These included the exponential, Weibull, Gompertz, lognormal and log-logistic models. Within the two cost-effectiveness models it was possible to change the parametric survivor function that was used to derive the three-monthly probabilities of recurrence to see how the choice of parametric model used to represent the recurrence data affected the results. The alternative survival curves are explored in the sensitivity analysis.

***BRAF* mutant analysis**

For the *BRAF* mutant model (adjuvant treatment with dabrafenib and trametinib), the distribution that was identified to best fit the observed data and result in appropriate extrapolations beyond the trial follow up period was the lognormal distribution for stage IIIA and the Gompertz distribution for stage IIIB/IIIC patients. The lognormal distribution was chosen for stage IIIA because it had the lowest Akaike's Information Criterion (AIC) at 136 and Bayesian Information Criterion (BIC) at 141 (Table HE003). We also visually inspected the survivor function curves (Figure HE003) to ensure the chosen curve appropriately represented the rates of recurrence that would be observed in clinical practice beyond the trial follow up period.

Table HE003: *BRAF* Mutant, Stage IIIA, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	140	142
Weibull	140	144
Gompertz	142	146
Lognormal	136	141
Log-logistic	138	143

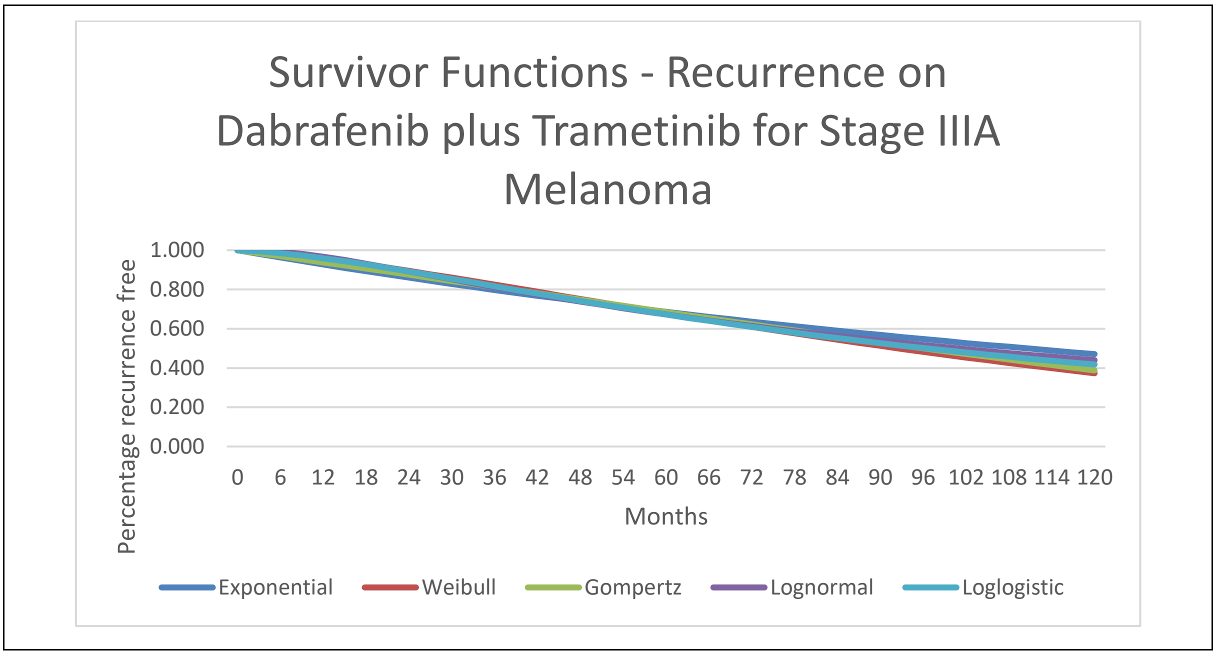


Figure HE003: Survivor Function, Recurrence on Dabrafenib plus Trametinib for Stage IIIA Melanoma

The Gompertz distribution was chosen for stage IIIB because it had the second lowest AIC at 376 and BIC at 383 (Table HE004). We also visually inspected the survivor function curves as before to ensure that the chosen curve appropriately represented the rates of recurrence that would be observed in clinical practice beyond the trial follow up period (Figure HE004). The committee felt that there is a point at which the probability of a recurrence becomes virtually zero and the extrapolation beyond the trial follow up using the Gompertz distribution best aligned with this assumption which was the reason it was chosen over the lognormal distribution.

Table HE004: *BRAF* Mutant, Stage IIIB, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	390	393
Weibull	391	397
Gompertz	376	383
Lognormal	374	381
Log-logistic	382	388

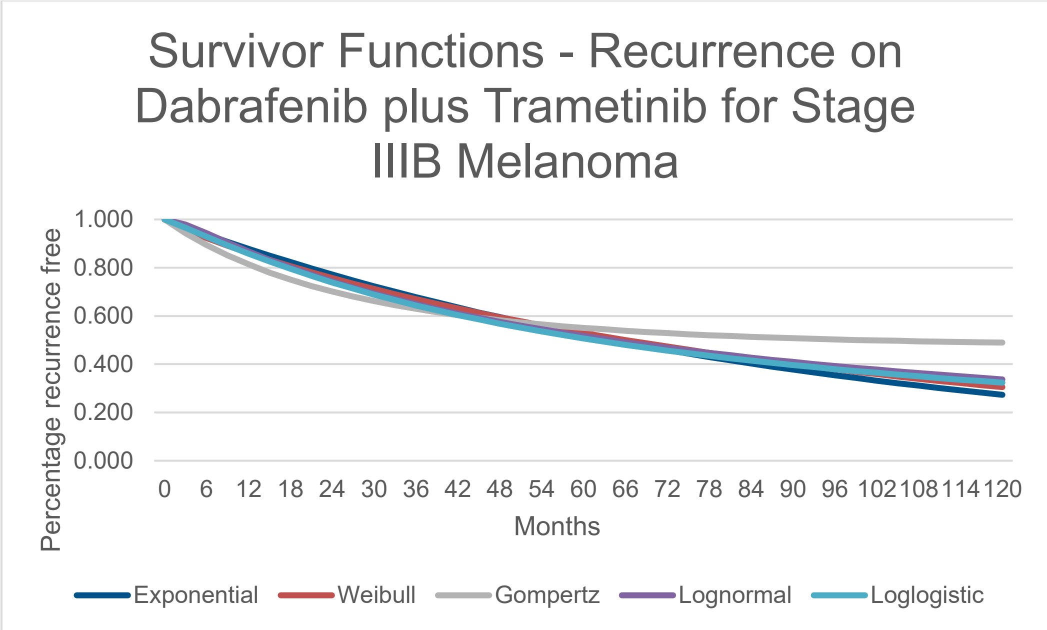


Figure HE004: Survivor Function, Recurrence on Dabrafenib plus Trametinib for Stage IIIB Melanoma

The Gompertz distribution was chosen for stage IIIC. We also visually inspected the survivor function curves as before to ensure that the chosen curve appropriately represented the rates of recurrence that would be observed in clinical practice beyond the trial follow up period (Figure HE005). Similar to stage IIIB, the committee felt that there is a point at which the probability of a recurrence becomes virtually zero. Even though it did not have the best fit statistics (Table HE005), the extrapolation beyond the trial follow up using the Gompertz distribution best aligned with this assumption which was the reason it was chosen over lognormal and log-logistic distributions. .

Table HE005: *BRAF* Mutant, Stage IIIC, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	450	453
Weibull	452	458
Gompertz	444	450
Lognormal	437	444
Log-logistic	441	448

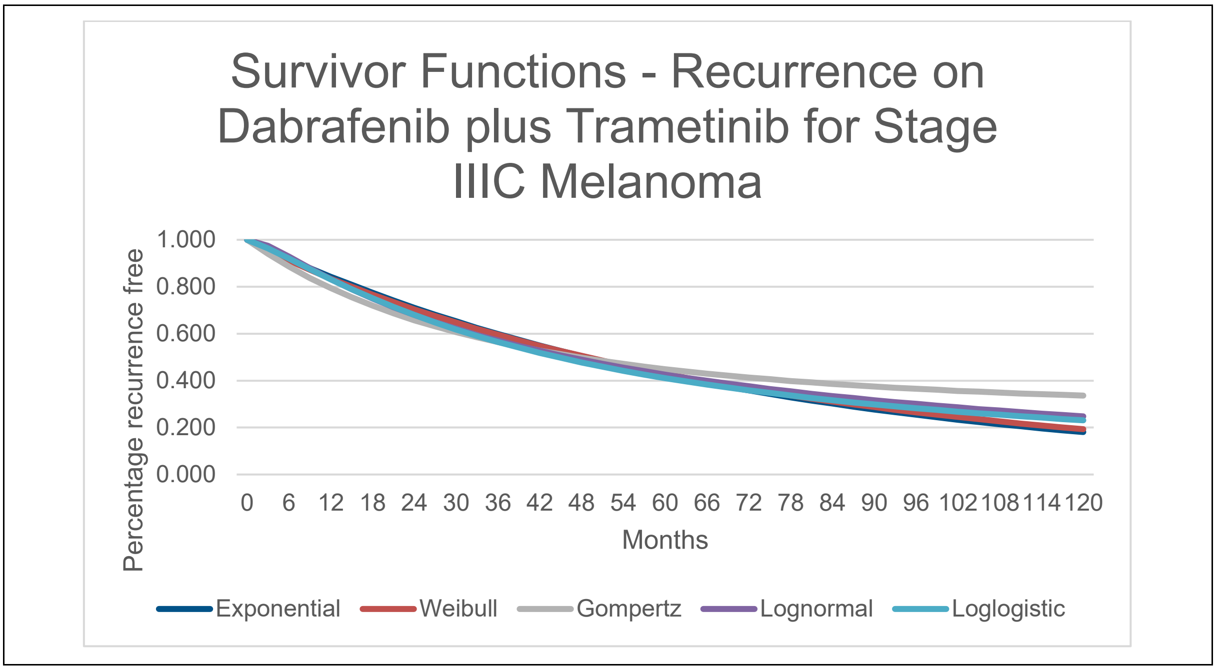


Figure HE005: Survivor Function, Recurrence on Dabrafenib plus Trametinib for Stage IIIC Melanoma

BRAF wild type analysis

For the *BRAF* wild type model (adjuvant treatment with pembrolizumab), the exponential distribution and Gompertz distribution were identified to best fit the observed data and result in appropriate extrapolations beyond the trial follow up period for stage IIIA and stage IIIB/IIIC patients respectively. The exponential distribution was chosen for stage IIIA because it had the lowest AIC at 111 and BIC at 113 (Table HE006). We also visually inspected the survivor function curves as before (Figure HE006) to ensure the chosen curve appropriately represented the rates of recurrence that would be observed in clinical practice beyond the trial follow up period.

Table HE006: *BRAF* Wild Type, Stage IIIA, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	111	113
Weibull	113	117
Gompertz	113	117
Lognormal	113	117
Log-logistic	113	117

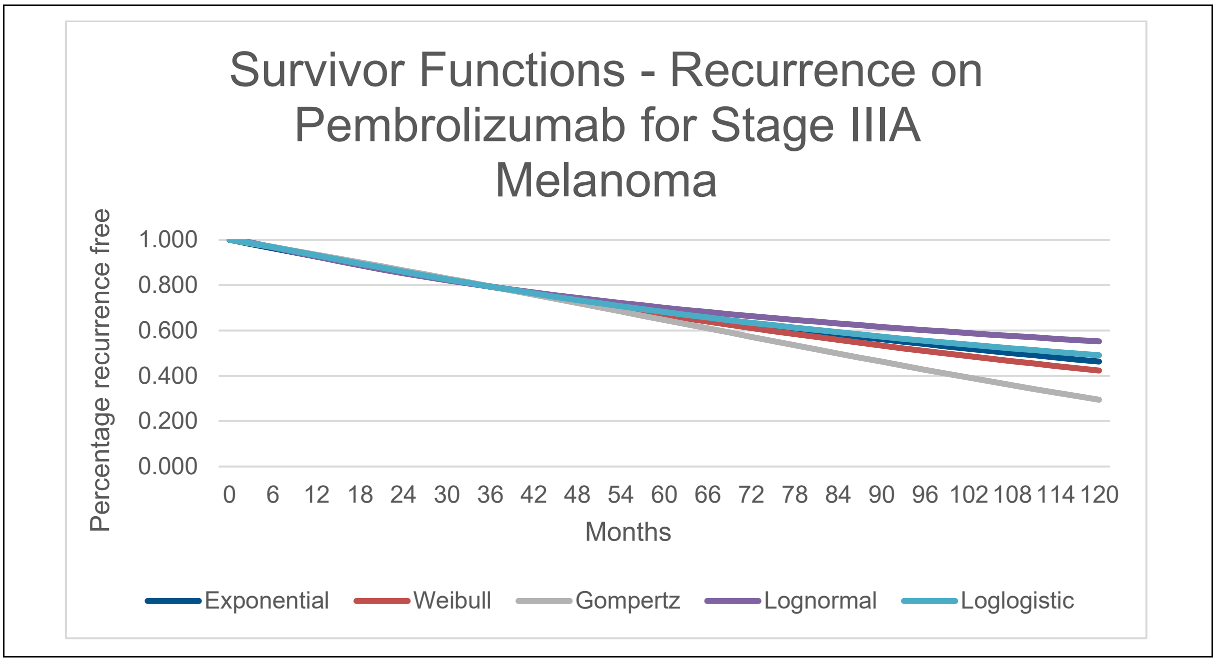


Figure HE006: Survivor Function, Recurrence on Pembrolizumab for Stage IIIA Melanoma

The Gompertz distribution was chosen for stage IIIB because it had one of the lowest AIC at 554 and BIC at 561 (Table HE007). We also visually inspected the survivor function curves as before to ensure that the chosen curve appropriately represented the rates of recurrence that would be observed in clinical practice beyond the trial follow up period (Figure HE007Figure HE004). The committee felt that there is a point at which the probability of a recurrence becomes virtually zero and the extrapolation beyond the trial follow up using the Gompertz distribution best aligned with this assumption which is why it was chosen over lognormal distribution.

Table HE007: *BRAF* Wild Type, Stage IIIB, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	577	581
Weibull	561	568
Gompertz	554	561
Lognormal	554	561
Log-logistic	558	565

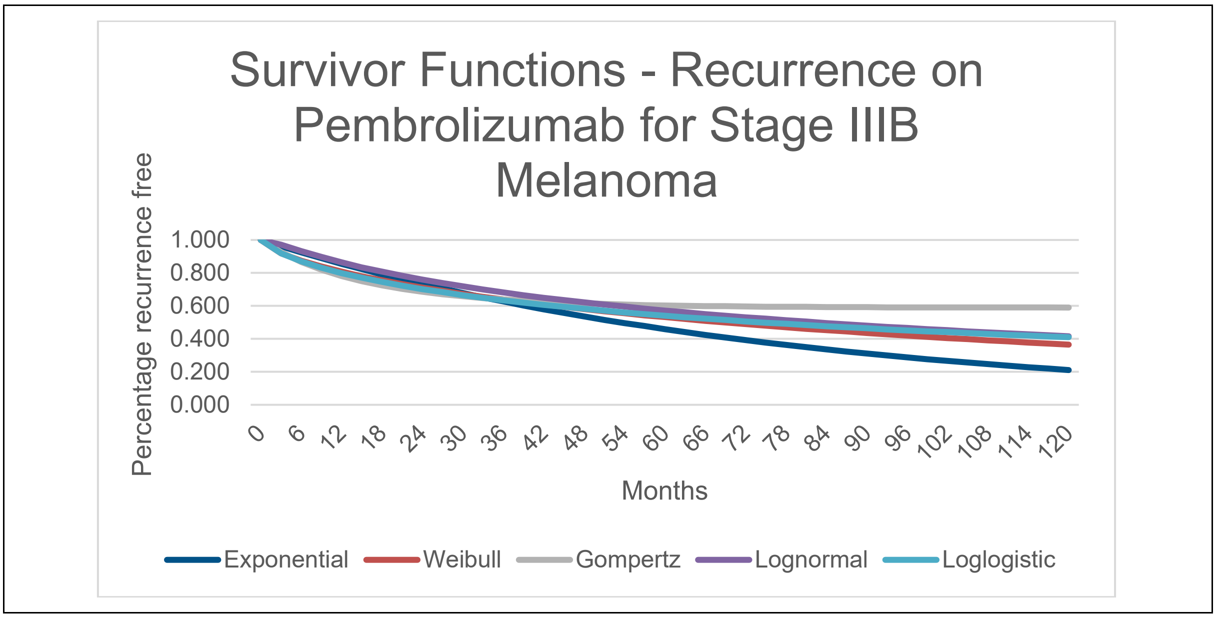


Figure HE007: Survivor Function, Recurrence on Pembrolizumab for Stage IIIB Melanoma

The Gompertz distribution was chosen for stage IIIC because it had the lowest AIC at 545 and BIC at 552 (Table HE008). We also visually inspected the survivor function curves as before to ensure that the chosen curve appropriately represented the rates of recurrence that would be observed in clinical practice beyond the trial follow up period (Figure HE008). Similar to stage IIIB, the committee felt that there is a point at which the probability of a recurrence becomes virtually zero and- the extrapolation using the Gompertz distribution best aligned with this assumption.

Table HE008: *BRAF* Wild Type, Stage IIIC, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	588	592
Weibull	559	566
Gompertz	545	552
Lognormal	547	553
Log-logistic	553	560

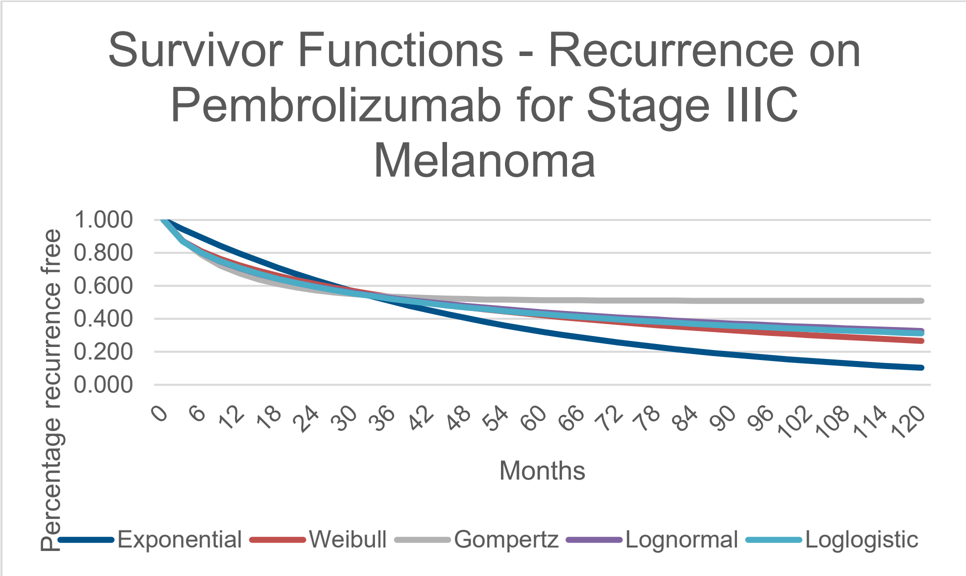


Figure HE008: Survivor Function, Recurrence on Pembrolizumab for Stage IIIC Melanoma

Probability of progression (Local to distant recurrence)

A proportion of patients with local recurrence would progress to distant disease for the model. No published data could be found that was specific to each substage, therefore, this parameter was based on committee opinion. The committee believed that 75% of patients progressed from local recurrence to distant recurrence in one cycle (i.e. 3 months) for stage IIIA, 80% for stage IIIB and 85% for stage IIIC. This was applied to patients who had had an unsuccessful surgery for local recurrence or patients who had undiagnosed local recurrence.

Site of first recurrence

If a patient gets a recurrence the model requires the proportion which are local and which are distant. The proportion for local was 31.7% and for distant was 68.3% which was obtained from Lim 2018. Lim 2018 was used as it was the only paper found that gave the proportion of local recurrences and distant recurrences that was required for the model.

HE1.4.3 Mortality

Background Mortality

Patients in every health state can die of causes other than melanoma and therefore overall background mortality is modelled. Overall background mortality was sourced from the ONS lifetables 2017-19, this was the latest available data when the models were built. There were multiple different mortalities used in the models.

Probability of death with an undiagnosed recurrence

Within the model the probability of dying when the patient has an undiagnosed recurrence is different to the background death rate, this is due to the patient not receiving the required treatment. The value used in the model was the same as the value used in the previous iteration. A more up to date value was searched for but could not be found. Therefore, the probability of death, in a 3 month period (one cycle of the model), with undiagnosed local recurrence was 6.7% and the probability of death with undiagnosed distant recurrence was 26.1%. These values were calculated from Meyers 2009.

Mortality after distant recurrence

For the *BRAF* mutant model, possible treatments after distant recurrence were pembrolizumab, nivolumab or ipilimumab plus nivolumab due to the available data. For nivolumab plus ipilimumab and nivolumab, we used treatment-specific Kaplan Meier curves of overall survival for the subgroup of *BRAF* mutant patients reported by Larkin 2019. In the *BRAF* Mutant model, for pembrolizumab we used the Kaplan Meier curve of overall survival reported by Robert 2019.

For the *BRAF* wild type model the possible treatments after distant recurrence were nivolumab or ipilimumab plus nivolumab and we used treatment-specific Kaplan Meier curves of overall survival for the subgroup of *BRAF* wild type patients reported by Larkin 2019, pembrolizumab was not used as if a patient has had it as adjuvant therapy they are unable to have it again as systemic therapy. Similar to the recurrence rates, the model evaluated patients longer than the follow up period of the trial, Larkin 2019 followed patients for 69 months and Robert 2019 were followed for 65 months. The process for estimating the three-monthly probabilities of death was the same as the approach used to estimate the probabilities of recurrence. The five OS curves were taken from the two studies and digitized using Engauge Digitizer (Mitchell et al.), this data was then imported into Stata (Statacorp) which was used to predict the curve beyond the follow up period of the trial. Within Stata the ipsfc command was used to get the individual patient data then the parametric survivor functions were applied. Five different parametric survivor functions were explored to identify the distribution that best fitted the observed data from the trial and also resulted in an appropriate extrapolation past the trial follow up period. These included the exponential, Weibull, Gompertz, lognormal and log-logistic models.

For *BRAF* mutant model, the lognormal distribution was identified to best fit the observed data and result in appropriate extrapolations beyond the trial follow up period for ipilimumab plus nivolumab, nivolumab and pembrolizumab. The lognormal distribution was chosen for ipilimumab plus nivolumab because it had the lowest AIC at 285 and BIC at 291 (Table HE009Table HE008). We also visually inspected the survivor function curves as before to ensure the chosen curve appropriately represented the overall survival that would be observed in clinical practice beyond the trial follow up period (Figure HE009**Figure HE008**).

For both the *BRAF* mutant and *BRAF* wild type models, there are a number of tunnel states to enable a patient diagnosed with a recurrence to be modelled from the beginning of the treatment curve and therefore have the same probability of death as month 0 in the graphs below. For example, if a patient is diagnosed at month 90 with a distant recurrence they would then have the probability of death from the overall survival curves at month 0 not month 90.

Table HE009: *BRAF* Mutant, Ipilimumab and Nivolumab, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	291	293
Weibull	293	298
Gompertz	290	295
Lognormal	285	291
Log-logistic	286	291

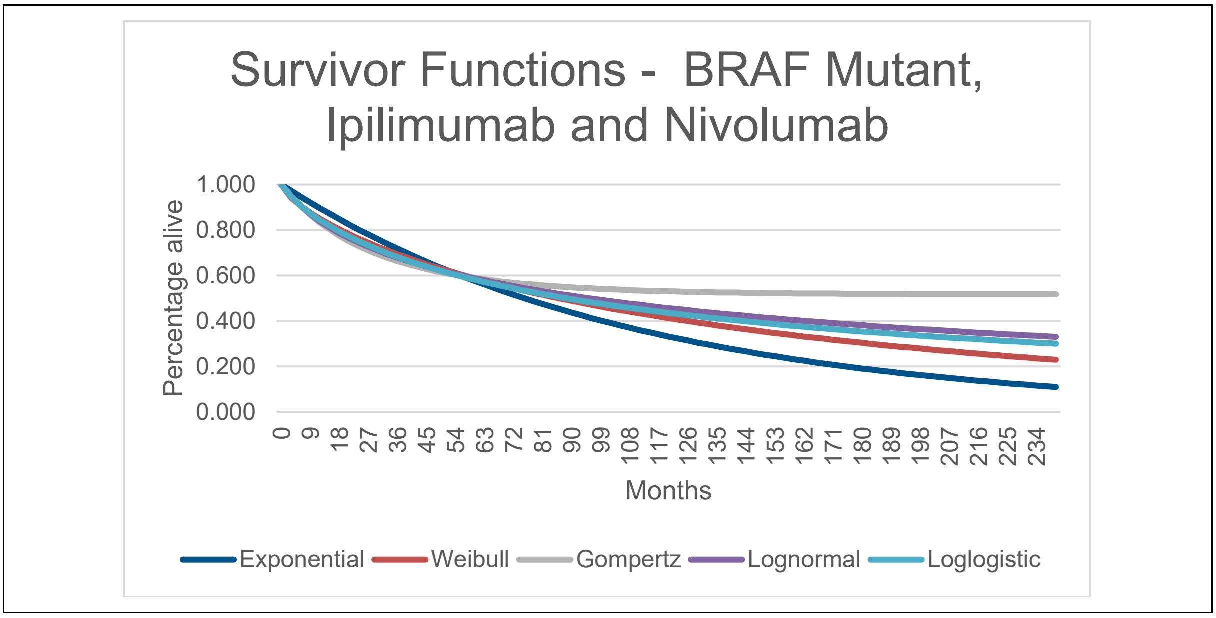


Figure HE009: Survivor Function, Ipilimumab and Nivolumab, *BRAF* Mutant

The lognormal distribution was chosen for nivolumab because it had the lowest AIC at 374 and BIC at 381 (Table HE010Table HE009Table HE008). We also visually inspected the survivor function curves as before to ensure the chosen curve appropriately represented the overall survival that would be observed in clinical practice beyond the trial follow up period (Figure HE010**Figure HE008**).

Table HE010: *BRAF* Mutant, Nivolumab, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	390	393
Weibull	391	397
Gompertz	376	383
Lognormal	374	381
Log-logistic	382	388

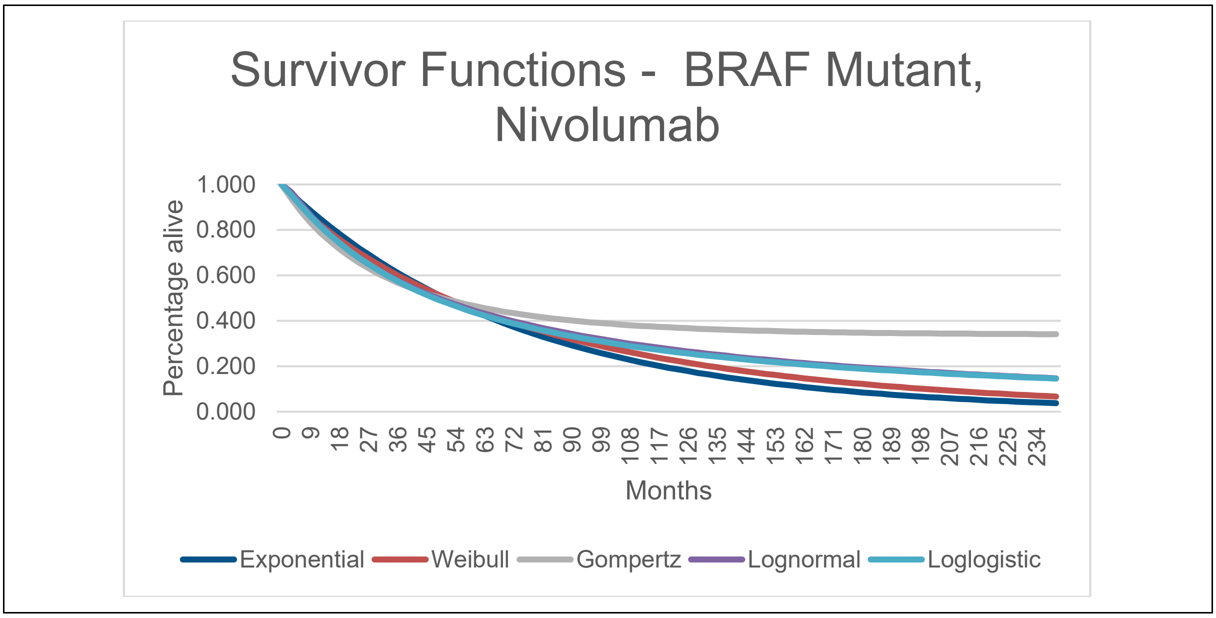


Figure HE010: Survivor Function, Nivolumab, *BRAF* Mutant

The lognormal distribution was chosen for pembrolizumab because it had the lowest AIC at 437 and BIC at 444 (Table HE011Table HE008). We also visually inspected the survivor function curves as before to ensure the chosen curve appropriately represented the overall survival that would be observed in clinical practice beyond the trial follow up period (Figure HE011**Figure HE008**).

Table HE011: *BRAF* Mutant, Pembrolizumab, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	450	453
Weibull	452	458
Gompertz	444	450
Lognormal	437	444
Log-logistic	441	448

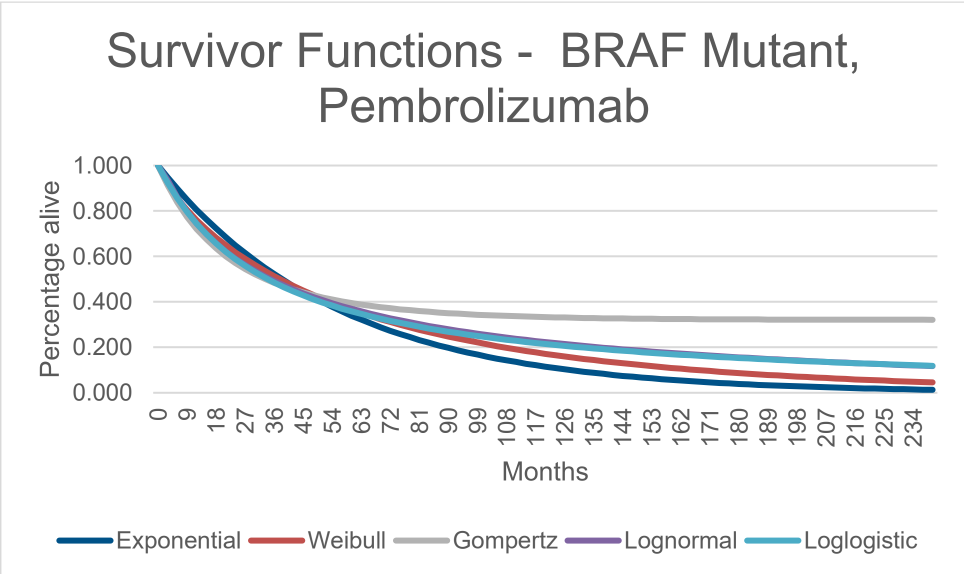


Figure HE011: Survivor Function, Pembrolizumab, *BRAF* Mutant

For *BRAF* wild type model, the log-logistic and lognormal distributions were identified to best fit the observed data and result in appropriate extrapolations beyond the trial follow up period for ipilimumab plus nivolumab and nivolumab respectively.

The log-logistic distribution was chosen for Ipilimumab and Nivolumab because it had the lowest AIC at 657 and BIC at 664 (Table HE012Table HE008). We also visually inspected the survivor function curves as before to ensure the chosen curve appropriately represented the overall survival that would be observed in clinical practice beyond the trial follow up period (Figure HE012**Figure HE008**).

Table HE012: *BRAF* Wild Type, Ipilimumab and Nivolumab, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	677	680
Weibull	672	678
Gompertz	659	666

Survivor Curve	AIC	BIC
Lognormal	661	667
Log-logistic	657	664

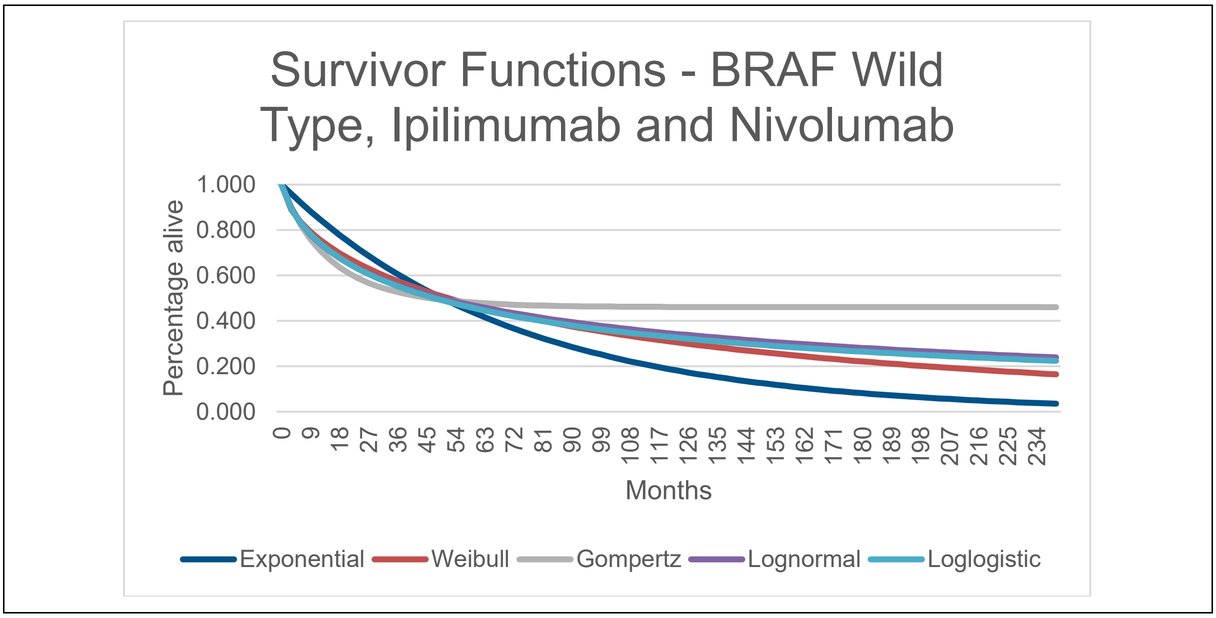


Figure HE012: Survivor Function, Ipilimumab and Nivolumab, *BRAF* Wild Type

The lognormal distribution was chosen for nivolumab because it had the second lowest AIC at 669 and BIC at 676 (Table HE010Table HE009Table HE008). We also visually inspected the survivor function curves as before to ensure the chosen curve appropriately represented the overall survival that would be observed in clinical practice beyond the trial follow up period (Figure HE010**Figure HE008**).The lognormal distribution was chosen over Gompertz because Gompertz plateaus at around 0.35 which the committee believed is not accurate of the overall survival that would be expected in clinical practice when patients receive nivolumab and therefore the distribution associated with the second lowest AIC and BIC were chosen.

Table HE013: *BRAF* Wild Type, Nivolumab, survivor curve fit statistics

Survivor Curve	AIC	BIC
Exponential	710	714
Weibull	685	692
Gompertz	661	668
Lognormal	669	676
Log-logistic	674	681

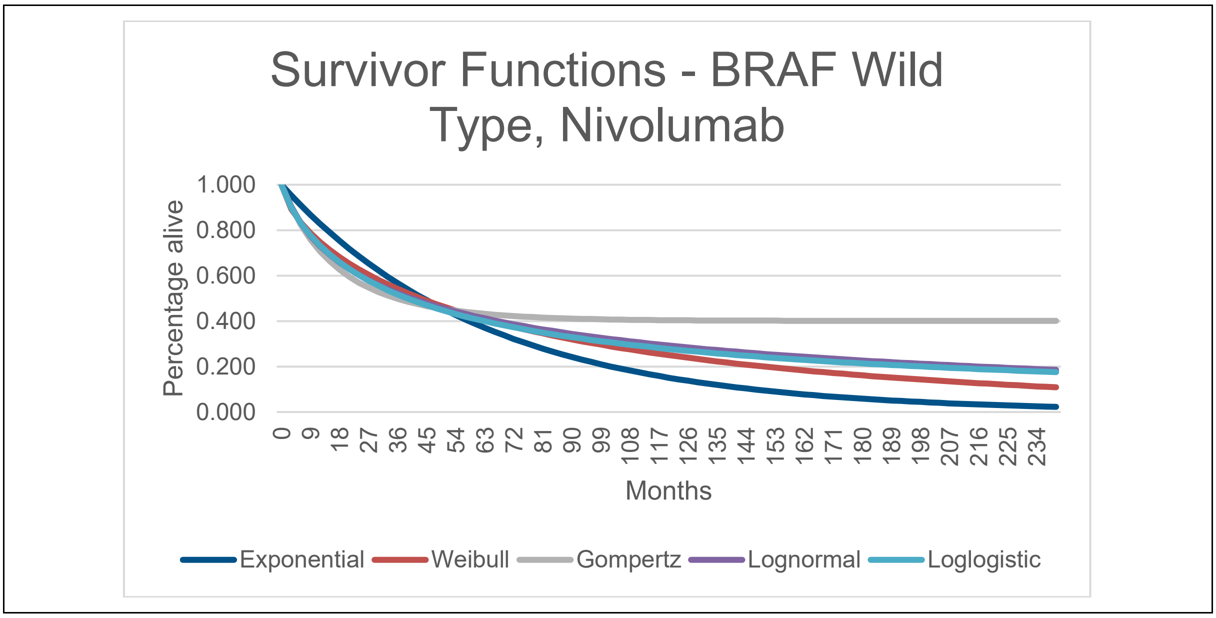


Figure HE013: Survivor Function, Nivolumab, *BRAF* Wild Type

Proportion on treatment for distant recurrence

After a patient has a distant recurrence there are different options of treatment dependent on the adjuvant treatment the patient received. It was assumed that the patients who were *BRAF* mutant received Dabrafenib plus Trametinib as adjuvant therapy and therefore it was assumed that the patients received ipilimumab plus nivolumab, nivolumab or pembrolizumab as systemic therapy for advanced melanoma (Table HE014). It was assumed that the patients who were *BRAF* Wild Type received pembrolizumab as adjuvant therapy and therefore, it was assumed that the patients received ipilimumab plus nivolumab or nivolumab as systemic therapy (Table HE014). The proportions of patients on the different treatments, for both *BRAF* Mutant and *BRAF* Wild Type, were taken from the SACT database (Systemic Anti-cancer therapy 2020).

Table HE014: Proportion on treatment for distant recurrence

Description	Value	Source
***BRAF* Mutant**		
Pembrolizumab	0.4760	SACT Database
Nivolumab	0.3323	SACT Database
Ipilmumab plus Nivolumab	0.1917	SACT Database
***BRAF* Wild Type**		
Nivolumab	0.6341	SACT Database
Ipilmumab plus Nivolumab	0.3659	SACT Database

HE1.4.2 Diagnostic accuracy and probability of symptomatic recurrence

The sensitivity and specificity of CT and PET-CT (Table HE015) for identifying melanoma recurrence were supplied by the clinical review from review question 6.2 (G RQ 6.1-6.4 combined). For CT there was only one study that estimated the sensitivity and specificity, and these values were used in both of the models. However, for PET-CT the clinical review estimated two different sensitivities and specificities using meta-analyses of the identified studies. One set of estimates included all the studies found in the clinical review, whereas the other set of estimates excluded all the studies with a high risk of bias. Within the model we used the set of sensitivity and specificity estimates that included all the studies identified in the clinical review. However, a sensitivity analysis was conducted that used the sensitivity and specificity estimates from the meta-analysis of studies that excluded those of high risk of bias.

Table HE015: Sensitivity and Specificity of CT and PET-CT

Description	Value
CT Sensitivity	0.670
CT Specificity	0.940
PET-CT Sensitivity	0.893
PET-CT Specificity	0.931

Patients with a symptomatic recurrence within the models identified their recurrence without imaging, either by themselves or a clinician discovered it at an appointment. Different values of the probability of a patient being symptomatic (for both *BRAF* models) were used for stage IIIA (0.6897), IIIB (0.4839) and IIIC (0.5429), sourced from Ibrahim 2020 that was identified in the clinical review for review question 6.1. Ibrahim 2020 was chosen because it reported that the imaging frequency was every six months and therefore the same as years 2 and 3 in the model. This is the probability of being symptomatic in each cycle of the model, this means that patients can become symptomatic over time. As a patient may not recur for a couple of years, they would only become symptomatic some time after this, there are also a number of patients would will never be symptomatic.

HE1.4.3 Quality of life

Table HE016: Utility values

Description	Value (per cycle)	Source
Disease Free	0.89	Askew 2011
Local recurrence	0.836	TA544
Distant recurrence	0.5	NG14
Dead	0	N/A
Nivolumab	0.7625	TA400
Pembrolizumab	0.7	TA366

The health-state utility values used within the two models were identified from multiple sources (Table HE016). The utility value used for the disease-free health state was sourced from a surveillance study, Askew 2011, which was 0.89 based on the EQ-5D-3L in America. The utility value for the local recurrence health state was sourced from a NICE Technology Appraisal (TA544) based on EQ-5D-3L data collected in a worldwide trial. The same value was used for both symptomatic and asymptomatic people because no further information on differing health states could be found. The asymptomatic patients received the same quality of life decrement as the symptomatic patients because no evidence could be found on the difference in decrement between the two populations. It was felt that using the symptomatic decrement in these patients was more appropriate than assuming they were equivalent to those who are disease free, since although they did not have symptoms alerting them to the recurrence they would still be less well than those who are disease free. No further health state utility value could be found for the distant recurrence without treatment health state and therefore the value from the model built in NG14 was used. Health values for people on treatment (patients in the distant recurrence, patient discovered and distant recurrence, imaging discovered health states) could be found but within the models some people have an unknown distant recurrence and therefore a different utility value associated with it. The utility value for the death health state is, by definition, zero. The utility value for the Nivolumab treatment health state was sourced from another NICE Technology Appraisal (TA400), based on EQ-5D data collected in a worldwide trial. TA400 was chosen over TA384 because TA384 has different utility values depending on how long after treatment the person is this is not included in our model whereas TA400 has one value for progressed disease. A utility value for the Ipilimumab and Nivolumab could not be found therefore, it was assumed that the value was the same as the Nivolumab health state. Finally, in the *BRAF* mutant model there was also a Pembrolizumab treatment health state, this utility value was sourced from a NICE Technology Appraisal (TA366), based on EQ-5D data collected in a worldwide trial. TA366 was chosen over TA357 because the people in TA366 had not previously been treated with ipilimumab whereas people in TA357 had been treated with ipilimumab.

Each of the utility values have been taken from different studies. While this is not ideal it was felt that these values were the most suited to the health states in the model and there were no available studies that had all or more than one utility values required for this model. It was felt that this was a more appropriate approach over using values from the same trial that may be less relevant to the population in the model.

HE1.4.4 Cost and healthcare resource use identification, measurement and valuation

Where possible, we drew resource-use information from the primary evidence-base identified in our systematic review of clinical evidence (see G 6.1-6.4 combined chapters). In the absence of such data, we attempted to locate published economic evaluations or costing studies providing relevant information. We filled any remaining gaps with estimates from the experts on the guideline committee.

We obtained unit costs for each of the resource use elements from a number of standard sources.

- For drugs prescribed in secondary care, we use prices from the NHS Commercial Medicines Unit’s Electronic Market Information Tool (eMIT; [September 2021]), where available. Otherwise, we use the NHS Prescription Services’ Drug Tariff (May 2021) or, where no cost is available from these sources, the BNF (March 2021)
- We use NHS National Cost Collection data [2018/19] (previously known as NHS Reference Costs) as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information. We used 2018/19 rather than 2019/2020 due to the COVID-19 outbreak and thought that the 2019/2020 data is less likely to represent usual care in the NHS, for example only more severe treatments were likely to be completed and therefore, higher costs as a result.
- Where we cannot source an appropriate unit cost from these sources, we may use values from a relevant published study, in which case we inflate them to current prices using HCIS inflation indices from Unit Costs for Health and Social Care (PSSRU; 2020).

HE1.4.4.1 Direct costs of interventions

The cost of a CT and a PET-CT was obtained from the NHS National Cost Collection. All the different adult scans were collected, and a weighted value was calculated using the number of patients who received the scan. Scans for patients aged 18 and younger were excluded as the population in the analysis are adults, and the costs for children and young people are often higher. The value found for CT was £97.15 (Table HE017) and the value for PET-CT (Table HE018) was £520.37. A weighted cost was estimated by the number of patients who received the intervention. Both contrast enhanced and non-contrast enhanced CT were included in the mean cost of CT. Ultimately, the committee decided to recommend contrast enhanced CT, and so we conducted a scenario analysis that included only these costs, resulting in a weighted average cost of £109.61 per scan.

1 **Table HE017: CT costs**

CT Description	Number of patients	Cost
Computerised Tomography Scan of One Area, without Contrast, 19 years and over	165005	£77.95
Computerised Tomography Scan of One Area, without Contrast, 19 years and over	645761	£85.18
Computerised Tomography Scan of One Area, without Contrast, 19 years and over	16464	£59.97
Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	31379	£101.17
Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	202974	£108.20
Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	790	£77.77
Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	2075	£97.04
Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	22533	£105.37
Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	123	£85.39
Computerised Tomography Scan of Two Areas, without Contrast	8753	£87.03
Computerised Tomography Scan of Two Areas, without Contrast	46172	£93.91
Computerised Tomography Scan of Two Areas, without Contrast	323	£78.53
Computerised Tomography Scan of Two Areas, with Contrast	43747	£104.53
Computerised Tomography Scan of Two Areas, with Contrast	185566	£103.47
Computerised Tomography Scan of Two Areas, with Contrast	1193	£91.42
Computerised Tomography Scan of Three Areas, without Contrast	1396	£105.45
Computerised Tomography Scan of Three Areas, without Contrast	22644	£102.69
Computerised Tomography Scan of Three Areas, without Contrast	40	£84.32
Computerised Tomography Scan of Three Areas, with Contrast	26735	£112.54
Computerised Tomography Scan of Three Areas, with Contrast	330086	£115.56
Computerised Tomography Scan of Three Areas, with Contrast	1924	£88.23
Computerised Tomography Scan of more than Three Areas	14413	£44.90
Computerised Tomography Scan of more than Three Areas	68608	£124.43
Computerised Tomography Scan of more than Three Areas	184	£94.01
Weighted cost		**£97.15**

2 **Table HE018: PET-CT costs**

PET-CT Description	Number of patients	Cost
Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over	5002	£180.25
Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over	38091	£549.21
Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over	2	£397.01
Positron Emission Tomography with Computed Tomography (PET-CT) of Two or Three Areas, 19 years and over	879	£302.82
Positron Emission Tomography with Computed Tomography (PET-CT) of more than Three Areas, 19 years and over	61	£31.63
Positron Emission Tomography with Computed Tomography (PET-CT) of more than Three Areas, 19 years and over	3230	£775.51

PET-CT Description	Number of patients	Cost
Weighted cost		**£520.37**

HE1.4.4 Costs associated with health states

Patients had multiple costs associated with different health states beyond the cost of CT or PET-CT. One of the further costs was for the clinical reviews that happen every three months for the first three years and then every six months for the following two years. The cost was made up of three different costs from General surgery, Dermatology and Clinical Oncology (Table HE019) from NHS National Cost Collection, this was due to patients potentially having appointments with different departments depending on which is the most appropriate at each stage of their follow up and the closest available clinician. For example, just after having had surgery they might have a surgery follow up or during treatment after distant recurrence they might meet with clinical oncology. Some patients would also receive a false positive imaging result and it was assumed that these patients would receive a follow up appointment in which it would be discovered that it was a false positive and the patient would then continue their follow up schedule. While each of the consultants in Table HE019 would not treat only melanoma patients, it was not possible to find the percentage of patients they are treating. Therefore, it was felt that it would be more appropriate to use the total number of patients rather than a differing percentage for each consultant. It is unlikely that this would have a large effect on the results as the costs for each of the three consultants were very similar.

Table HE019: Follow-up clinical appointment costs

Follow-up clinical appointment Description	Number of patients	Cost
Consultant led, Non-Admitted Face-to-Face Attendance, Follow-up (General Surgery)	670161	£113.06
Consultant led Non-Admitted Face-to-Face Attendance, Follow-up (Dermatology)	1106048	£112.12
Consultant led Non-Admitted Face-to-Face Attendance, Follow-up (Clinical Oncology)	994250	£142.73
Weighted cost		£128.17

The patients who were diagnosed with a local recurrence received surgery as treatment with curative intent. The cost of this treatment would depend on the size and location of the recurrence therefore, a weighted average of different skin surgeries was used as shown in Table HE020. These costs were sourced from NHS National Cost Collection. Similar to the consultant costs, not all the skin procedures will be melanoma related however, it is not possible to find the number that were related. Therefore, the average of all the procedures was used, one way sensitivity analysis around this value to see if it has any impact on the result.

Table HE020: Surgery costs

Surgery Description	Number of patients	Cost
Multiple Major Skin Procedures	1873	£2551
Major Skin Procedures	13726	£2473
Intermediate Skin Procedures, 19 years and over	264264	£501
Minor Skin Procedures, 19 years and over	1428797	£215
Weighted cost		**£279.93**

Patients who were identified with a local recurrence or distant recurrence were re-staged, this involved having a follow up appointment, a Magnetic Resonance Imaging scan (MRI) and a CT or PET-CT scan depending on the follow up regime they were on. The average cost of MRI is shown in Table HE021.

Table HE021: MRI costs

MRI Description	Number of patients	Cost
Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	433274	£120.83
Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	995281	£142.67
Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	11822	£152.08
Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over	30109	£102.37
Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over	202917	£158.54
Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over	5981	£127.24
Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast	3214	£190.30
Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast	41586	£217.49
Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast	269	£174.23
Magnetic Resonance Imaging Scan of Two or Three Areas, without Contrast	31019	£131.24
Magnetic Resonance Imaging Scan of Two or Three Areas, without Contrast	85402	£145.79
Magnetic Resonance Imaging Scan of Two or Three Areas, without Contrast	1221	£103.69
Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast	1204	£173.02
Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast	22758	£206.36
Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast	186	£161.25
Magnetic Resonance Imaging Scan of more than Three Areas	5143	£177.92
Magnetic Resonance Imaging Scan of more than Three Areas	39931	£196.02
Magnetic Resonance Imaging Scan of more than Three Areas	135	£214.95
Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning	399	£300.92
Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning	4947	£264.60
Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning	131	£101.74
Weighted cost		£142.76

In the *BRAF* mutant model patients with a distant recurrence can be treated with either pembrolizumab, nivolumab or ipilimumab plus nivolumab. In the *BRAF* wild type model patients were treated with nivolumab or ipilimumab plus nivolumab. The prices for the three treatments were obtained from the BNF, the prices for one dose are in Table HE022 along with the number of doses in a treatment and the total cost. For nivolumab and pembrolizumab the same dose size is recommended for all the patients however, for Ipilimumab the dose depends on the weight of the patient. As no average weight was supplied in Eggermont 2020 and Dummer 2020, the average weight of the UK population was used (78.78kg in *BRAF* mutant and 78.64kg in *BRAF* wild type), this was weighted by the sex of the population (64% male in *BRAF* mutant and 63% in *BRAF* wild type). It was assumed that each patient received one course, which for Ipilimumab is a dose every three weeks for four doses, for nivolumab is a dose every two weeks for six doses and for pembrolizumab is a dose every three weeks for four doses. Therefore, all these are within the first cycle after being diagnosed with a distant recurrence. So, all the costs of systemic treatment was assigned to the cycle in which the patient is diagnosed and not assigned in the later cycles. It was assumed that each patient would receive one cycle of treatment, this was because some patients would find the treatment toxic and be unable to continue whereas others may be able to continue for considerably longer. It would be possible to model different treatment lengths however that would have involved adding more health states which would have made the model considerably more complicated, therefore it was decided not to add this. Sensitivity analysis was done around the cost of the different treatments to ensure this assumption would not have a significant effect on the results. The cost of each of the treatments also included the administration cost (NHS reference cost). These reference costs included the cost of delivering the chemotherapy either ‘simple’ for pembrolizumab or more ‘complex’ for nivolumab or ipilimumab. These administration costs were applied for each time a medication was given, if two medications were given at the same time then only one administration cost was applied.

Table HE022: Costs of systemic therapy for treating distance recurrences

Treatment	Cost per one dose	Administration cost	Number of doses in model	Total cost
Nivolumab	£2,633	£306.90	6	£17,639
Pembrolizumab	£2,630	£241.06	4	£11,484
Ipilimumab (*BRAF* Mutant)	£17,725	£306.90	4	£72,614
Ipilimumab (*BRAF* Wild type)	£17,694	£306.90	4	£71,392

The final cost in the model was the cost of palliative care, the cost was obtained by taking an average of all the NICE Technology Appraisals for all the systematic treatments for melanoma, this value was £10,011.84 (TA268, TA269, TA319, TA321, TA366, TA384, TA396, TA400, TA410, TA562). One way sensitivity analysis was done around this parameter to see how this uncertain value affected the results.

There are patient access schemes (PAS) for the three systemic therapies. These values will be tested in both *BRAF* models to see how they affect the result.

HE1.4.5 Other parameters

Efficacy surgery

Patients who had a local recurrence were assessed for surgery. No published data could be found on the proportion of patients that were suitable for surgery or the proportion of surgeries that were successful, therefore the committee was asked to give an estimate for these values. The committee believe that 90% of patients were suitable for surgery and 95% of surgeries are successful.

HE1.4.6 Summary

All parameters used in the model are summarised in Table HE023, including details of the distributions and parameters used in probabilistic analysis.

1 **Table HE023: All parameters in original cost–utility model**

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Discount rate (QALYs)	3.5%	N/A	N/A	NICE reference case
Discount rate (Costs)	3.5%	N/A	N/A	NICE reference case
Cycles per year	4	N/A	N/A	N/A
Time horizon (years)	20	N/A	N/A	N/A
Baseline (*BRAF* Mutant)				
Starting age	57	N/A	N/A	Dummer 2020
Sex (% male)	64	N/A	N/A	Dummer 2020
Weight (kg)	78.78	N/A	N/A	BBC
Baseline (*BRAF* Wild Type)				
Starting age	54	N/A	N/A	Eggermont 2020
Sex (% male)	63	N/A	N/A	Eggermont 2020
Weight (kg)	78.64	N/A	N/A	BBC
Disease Stage				
IIIA	0.360	Dirichlet		East of England Registry
IIIB	0.422	Dirichlet		East of England Registry
IIIC	0.218	Dirichlet		East of England Registry
Patient symptomatic				
Patient symptomatic (year 1, IIIA, per cycle)	0.6879	Beta	α=19.310 β=8.690	Ibrahim 2020
Patient symptomatic (year 1, IIIB, per cycle)	0.4839	Beta	α=14.516 β=15.484	Ibrahim 2020
Patient symptomatic (year 1, IIIC, per cycle)	0.5429	Beta	α=18.457 β=15.543	Ibrahim 2020
Patient symptomatic (year 2-5, IIIA, per cycle)	0.6879	Beta	α=19.310 β=8.690	Ibrahim 2020
Patient symptomatic (year 2-5, IIIB, per cycle)	0.4839	Beta	α=14.516 β=15.484	Ibrahim 2020
Patient symptomatic (year 2-5, IIIC, per cycle)	0.5429	Beta	α=18.457 β=15.543	Ibrahim 2020
Patient symptomatic (reduced follow up, 2 years, IIIA, per cycle)	0.6879	Beta	α=19.310 β=8.690	Ibrahim 2020
Patient symptomatic (reduced follow up, 1 year, IIIA, per cycle)	0.4839	Beta	α=14.516 β=15.484	Ibrahim 2020
Patient symptomatic (reduced follow up, 1 year, IIIA, per cycle)	0.5429	Beta	α=18.457 β=15.543	Ibrahim 2020
Probability of death				
Unidentified local recurrence, per cycle	0.0666	N/A	N/A	Meyers 2009
Unidentified distant recurrence, per cycle	0.2610	N/A	N/A	Meyers 2009

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Site of first recurrence				
Local	0.3171	Dirichlet		Lim 2018
Distant	0.6829	Dirichlet		Lim 2018
Probability of progression (Local to distant recurrence)				
IIIA, per cycle	0.75	N/A	N/A	Committee assumption
IIIB, per cycle	0.8	N/A	N/A	Committee assumption
IIIC, per cycle	0.85	N/A	N/A	Committee assumption
Proportion on treatment for distant recurrence (*BRAF* Mutant)				
Pembrolizumab	0.4760	N/A	N/A	SACT Database
Nivolumab	0.3323	N/A	N/A	SACT Database
Ipilmumab plus Nivolumab	0.1917	N/A	N/A	SACT Database
Proportion on treatment for distant recurrence (*BRAF* Wild Type)				
Nivolumab	0.6341	N/A	N/A	SACT Database
Ipilmumab plus Nivolumab	0.3659	N/A	N/A	SACT Database
Efficacy surgery				
Proportion suitable for surgery	90%	N/A	N/A	Committee assumption
Proportion of surgeries successful	95%	N/A	N/A	Committee assumption
PET-CT				
Sensitivity	0.893	Beta	α=160.974 β=19.288	Clinical review
Specificity	0.931	Beta	α=181.370 β=13.442	Clinical review
CT				
Sensitivity	0.670	Beta	α=38.848 β=19.134	Clinical review
Specificity	0.940	Beta	α=35.266 β=2.251	Clinical review
Costs				
CT scan	£97.15	N/A	N/A	NHS National Cost Collection
PET-CT scan	£520.37	N/A	N/A	NHS National Cost Collection
MRI scan	$142.76	N/A	N/A	NHS National Cost Collection
Follow-up appointment	128.17	N/A	N/A	NHS National Cost Collection
Surgery	£279.93	N/A	N/A	NHS National Cost Collection
Palliative care	£10,012	N/A	N/A	Relevant TAs
Nivolumab (240mg/24ml, 6 doses)	£15,798	N/A	N/A	British National Formulary

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Pembrolizumab (100mg/4ml, 4 doses)	£10,520	N/A	N/A	British National Formulary
Ipilimumab (50mg/10ml, 4 doses)	£72,000	N/A	N/A	British National Formulary
Utility values				
Disease Free	0.89	Beta	α=1019.935 β=126.059	Askew 2011
Local recurrence	0.836	Beta	α=677.383 β=132.884	TA544
Distant recurrence	0.5	Beta	α=0.5 β=0.5	NG14
Dead	0	N/A	N/A	N/A
Nivolumab	0.7625	N/A	N/A	TA400
Pembrolizumab	0.7	N/A	N/A	TA366

HE1.5 Summary of key assumptions

Key assumptions in this model are:

- Patients in the model have stages IIIA, IIIB or IIIC melanoma and have started adjuvant therapy.
- Patients who are *BRAF* mutant are first treated with Dabrafenib and Trametinib and if they have a distant recurrence, they can receive pembrolizumab, nivolumab or ipilimumab plus nivolumab.
- Patients who are *BRAF* wild type are first treated with pembrolizumab and if they have a distant recurrence, they can receive nivolumab or ipilimumab plus nivolumab.
- Patients receive a clinical review every 3 months during the first 3 years, every 6 months for 4-5 years (current follow-up)
- Patients receive imaging every 3 months for the first year, then every 6 months for the next 2 years of follow-up or a reduced follow up for stage IIIA
- Depending on the arm of the model patients receive either a CT scan or a PET-CT scan
- Patients who have a local recurrence are treated with surgery only.
- We assumed that 90% of local recurrences were suitable for surgery, those not suitable stay in the local recurrence health state
- We assumed that 95% of surgeries for local recurrences were successful and return to the disease-free health state
- For the probability of progression (local to distant recurrence), we assumed stage IIIA was 0.75, stage IIIB was 0.8 and stage IIIC was 0.85

HE1.6 Sensitivity analyses

HE1.6.1 Deterministic sensitivity analyses

We completed deterministic sensitivity analyses to discover the parameters which had the biggest impact on the results. In particular, we wanted to discover if changing any parameter would change the result of which follow up regime was the most cost effective. We did one way sensitivity analysis which showed which parameters had the largest impact on the results, this can be presented in a tornado diagram, using the net monetarily benefit (NMB). The ICER and NMB are both reported but the tornado diagram will only use the NMB as if there are any parameters that change the result then that can be shown on the same tornado diagram. If we were not able to obtain a standard deviation for the parameter, then ± 10 % was used as a variation around the mean.

There are also three parameters in the model ‘Probability of progression’ (local to distant recurrence) for each stage that depend on each other. So, it is expected that stage IIIC should have a higher probability than stage IIIB which is in turn higher than stage IIIA. Therefore, we completed a scenario analysis which varied the values together but kept a 5% difference between the values.

The committee were interested in recommending contrast enhanced CT and therefore a scenario analysis was completed using £109.61 instead of £97.15. This was to examine the effect on the results.

The differing survival curves were investigated in survival analysis, for both recurrence and mortality. Each of the survival curves were changed individually to see the effect on the results.

HE1.6.2 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We ran the probabilistic sensitivity analysis for 10,000 runs to ensure the results stabilised. We specified probability distributions for all input variables with the exception of drug acquisition costs, some utility values and committee assumptions. This was due to there being no data on the uncertainty around the parameters and adding an arbitrary standard deviation would increase the uncertainty and would not reduce it. The committee felt that including these values in the probabilistic sensitivity analysis would not be helpful. They felt that it would be more helpful to examine these parameters in one way sensitivity analyses. Further explanation on why specific parameters were excluded from the probabilistic sensitivity analysis is explained below. We decided the type of distribution with reference to the properties of data of that type (for example, we use beta distributions for probabilities that are bounded between 0 and 1). Where possible, we parameterised each distribution using dispersion data from the source from which the value was obtained; where no such data were available, we gave consideration to applying plausible ranges based on committee advice and the usual properties of similar data however, for the majority of parameters the committee felt that assigning a value would not be appropriate and therefore these parameters were excluded from the probabilistic sensitivity analysis.

There are some parameters in the model which were not included in the probabilistic sensitivity analysis. These were baseline data, probability of death, probability of progression, proportion of patients eligible for surgery, proportion of successful surgeries and proportion on different distant recurrent treatments. The baseline data for both the *BRAF* Mutant and *BRAF* Wild Type were not varied in the probabilistic sensitivity analysis. This was due to these values being sourced from the recurrence studies and therefore no data for a standard deviation or any way to source that data. The probability of death parameters was obtained from Meyers et al. 2009. Due to there being no standard error and no information on the distribution of the parameter it was decided to only do one way sensitivity analysis and no include the parameter in the probabilistic sensitivity analysis. Probability of progression was not included in the probabilistic sensitivity, this is because (as explained in the Deterministic sensitivity analyses section) the value of stage IIIA is dependent on the values of stage IIIB and IIIC. It is assumed that stage IIIA is less than stage IIIB and in turn less than stage IIIC. Therefore, a separate analysis was done which changed each value but kept the difference between stage IIIA and stage IIIB and then stage IIIB and stage IIIC at 5%. The proportion of patients who are eligible for surgery and the proportion of successful surgeries were both committee assumptions and therefore there was no standard deviation. It would be possible to use a uniform distribution however, we believe that doing this would not reduce the uncertainly and it would be more useful to investigate the uncertainty using one way sensitivity analysis.

There are three sources of costs for the model, from NHS reference costs, the British National Formulary (BNF) and from NICE Technology Appraisals. None had standard deviations associated with them in the primary sources so each was assessed separately to see if and which distribution could be applied to it. For NHS reference costs there were multiple ways that a standard deviation could be found. It would be possible to assess the different trusts that have supplied the data to the NHS reference costs and calculate a standard deviation between them. However, NHS reference costs have not published that data this year and therefore the data from last year would have to be assessed. It was felt that while it is unlikely that there will be much difference from previous years, as different trusts supply different data each year last year’s data would not necessarily be fully applicable to this year. As using this trust data would already be a proxy for the standard deviation, using last year’s data would be adding more uncertainty into the analysis. Therefore, it was decided not to use trust data. Another option for the NHS reference costs would be to use data over time. It would be possible to take the past 5 years of data and take a standard deviation from that data. However again this would be a proxy for the standard deviation, and it was felt that a standard deviation over time would be different to the standard deviation required for this analysis. Therefore, it was decided not to add the NHS reference costs into the probabilistic sensitivity analysis. This was felt to be unlikely to be a major limitation, as that data should represent the true costs paid across a large number of individuals (and therefore only be subject to limited sampling uncertainty) and is in line with the approach taken in many economic evaluations.

A further set of cost inputs was the cost of treatments for distant recurrence. There were limited options for getting a standard deviation for the drug costs and the BNF reports the direct drug value and there is unlikely to be much variation in cost. It was decided to exclude all the costs from the probabilistic sensitivity analysis. The final cost in the model was the cost of palliative treatment, this was obtained from the Technology Appraisals for the treatment of melanoma. None of the Technology Appraisals reported a standard deviation and like other parameters it was felt that introducing an arbitrary value would not help quantify the uncertainty around the result. It was felt that varying the palliative care parameter in one way sensitivity analysis was more useful in discovering the impact of the parameter.

For the utility values there was available standard deviation for ‘No evidence of disease’ and ‘Loco-regional recurrence’ and therefore this was included in the probabilistic sensitivity analysis. For ‘Distant recurrence’, ‘Nivolumab’ and ‘Pembrolizumab’ there was no available information on the standard deviation. Therefore, it was decided not to include these parameters in the probabilistic sensitivity analysis.

For all the parameters not included in the probabilistic sensitivity analysis it was felt that not including them in the probabilistic sensitivity analysis is unlikely to be a major limitation and one way sensitivity analysis was likely to investigate the uncertainty of the parameters. Full distributions are given in Table HE023. However, it is likely that because all the values were not included in the probabilistic sensitivity analysis it is likely that the probabilistic sensitivity analysis does not capture the full extent of the uncertainty around the results.

HE2 Results

HE2.1 Base-case cost–utility results

For both BRAF mutant and BRAF wild type, CT at the current follow up schedule is the most cost-effective option compared with PET-CT at any follow up schedule and with CT at both reduced follow up schedules (Table HE024, Table HE025, *Dom means that the option is dominated, is more costly and less effective than the comparison

Table HE026 and Table HE027). PET-CT is never a cost-effective option compared with CT as it does not give a large enough increase in QALYs compared to the increase in costs. See Table HE001 for the definition of 2 years and 0 years follow up schedules.

Table HE024: Base-case deterministic cost–utility results (*BRAF* Mutant, 2 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£126,338	8.88965				£51,455	£140,352
CT	£126,366	8.89157	£28	0.00192	£14,548	£51,466	£140,381
PET-CT (Reduced)	£128,538	8.93438	£2,172	0.04281	£50,744	£50,149	£139,493
PET-CT	£128,698	8.93695	£160	0.00257	£62,167	£50,041	£139,410

Table HE025: Base-case deterministic cost–utility results (*BRAF* Mutant, 0 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£126,099	8.82752				£50,452	£138,727
CT	£126,366	8.89157	£267	0.06405	£4,169	£51,466	£140,381
PET-CT (Reduced)	£128,115	8.87313	£1,749	-0.0184	Dom	£49,347	£138,079
PET-CT	£128,698	8.93695	£2,332	0.04538	£51,391	£50,041	£139,410

*Dom means that the option is dominated, is more costly and less effective than the comparison

Table HE026: Base-case deterministic cost–utility results (*BRAF* Wild Type, 2 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£113,360	9.35189				£73,677	£167,196
CT	£113,386	9.35341	£26	0.00153	£16,785	£73,682	£167,216
PET-CT (Reduced)	£115,299	9.39861	£1,914	0.04520	£42,332	£72,673	£166,659
PET-CT	£115,457	9.40066	£157	0.00205	£76,900	£72,556	£166,563

Table HE027: Base-case deterministic cost–utility results (*BRAF* Wild Type, 0 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£113,031	9.29820				£72,933	£165,915
CT	£113,386	9.35341	£355	0.05521	£6,432	£73,682	£167,216
PET-CT (Reduced)	£114,796	9.34600	£1,410	-0.00742	Dom	£72,124	£165,584
PET-CT	£115,457	9.40066	£2,071	0.04725	£43,830	£72,556	£166,563

*Dom means that the option is dominated, is more costly and less effective than the comparison

The cost utility planes at for both *BRAF* mutant and *BRAF* Wild Type are very similar. The dotted white lines are at a gradient of £20,000, so if there are two points on the line then the point further to the right is cost effective (using NICE's £20,000 willingness-to-pay threshold). For both the different reduced follow up schedules for both *BRAF* Mutant and *BRAF* Wild Type (Figure HE014, Figure HE015, Figure HE016 and Figure HE017) show that CT is the most cost effective option. For 0 years (Figure HE015 and Figure HE017), the graphs show that there is no point at which PET-CT reduced would be cost effective over CT.

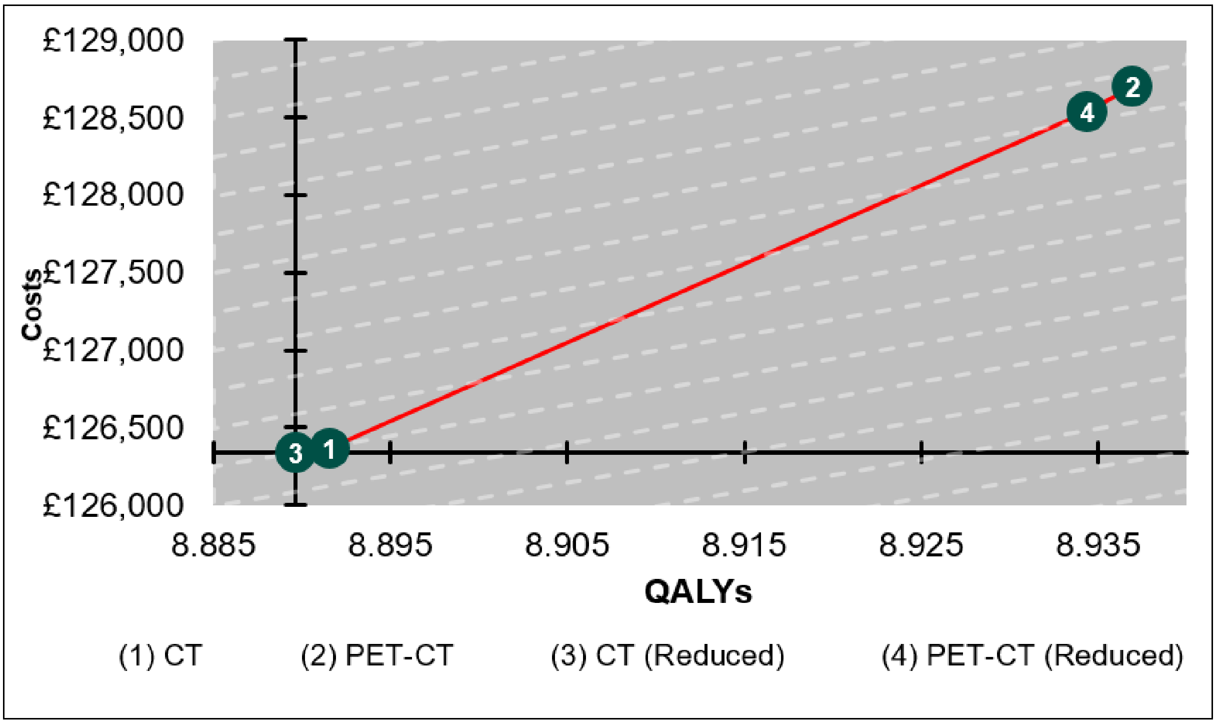


Figure HE014: Base-case deterministic results – cost–utility plane (*BRAF* Mutant, 2 years)

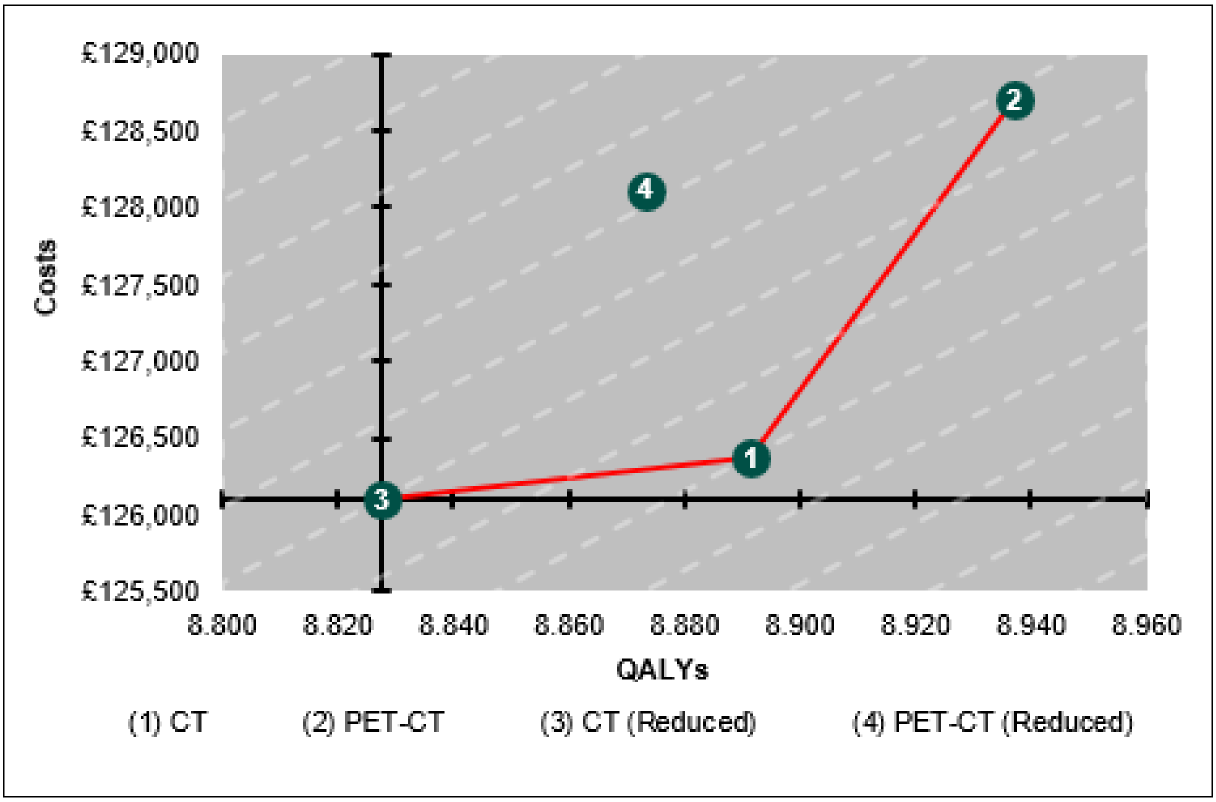


Figure HE015: Base-case deterministic results – cost–utility plane (*BRAF* Mutant, 0 years)

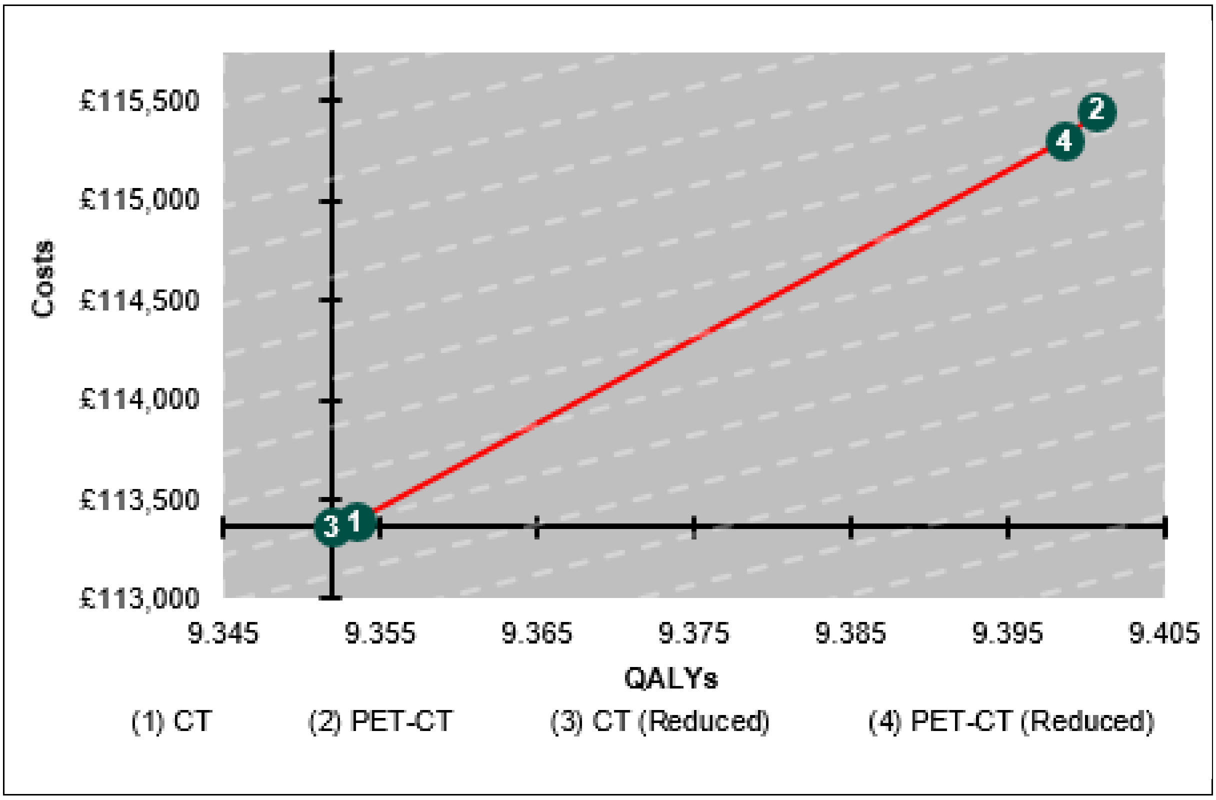


Figure HE016: Base-case deterministic results – cost–utility plane (*BRAF* Wild Type, 2 years)

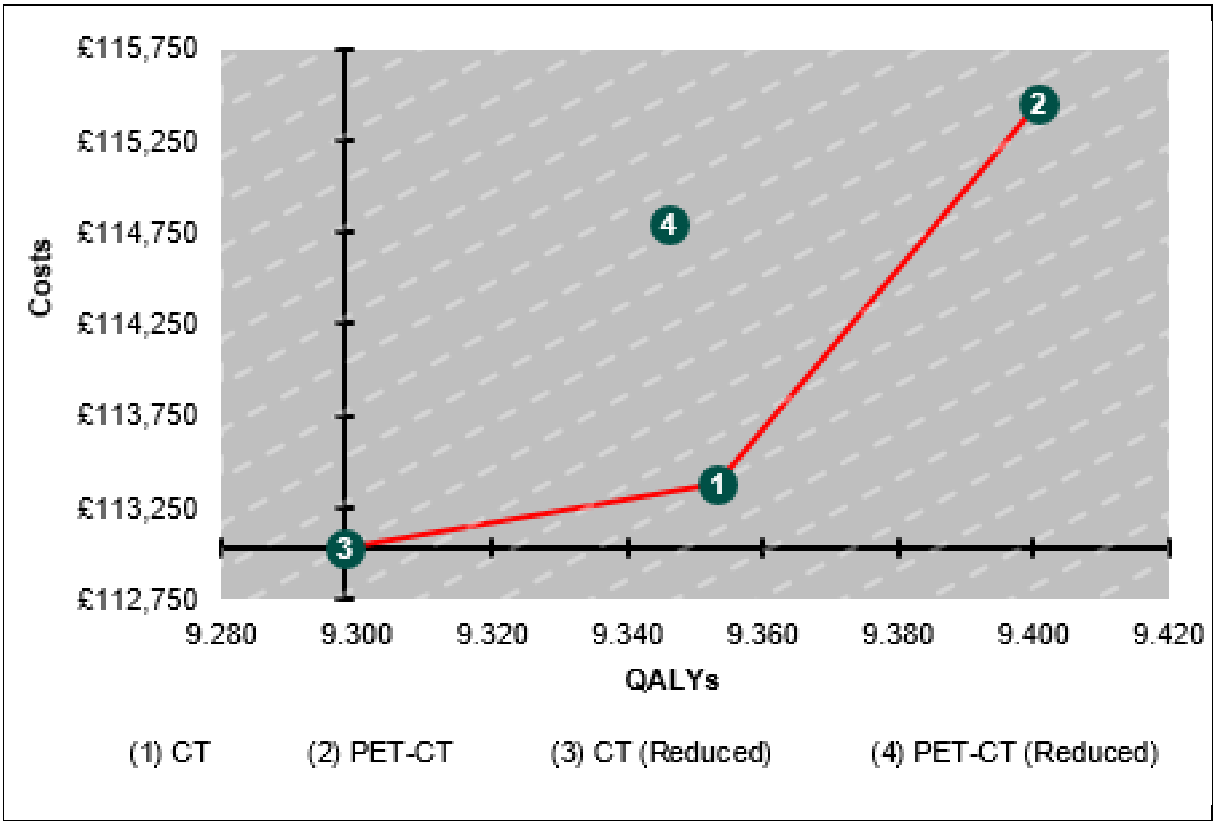


Figure HE017: Base-case deterministic results – cost–utility plane (*BRAF* Wild Type, 0 years)

HE2.2 Sensitivity analysis

HE2.2.1 Deterministic sensitivity analysis

CT, selected as the reference treatment as the most cost-effective option in the base case analysis, is compared to the other comparators in a series of pairwise comparisons to see whether a change in any parameters would change the choice of CT at the current follow up schedule as the preferred option.

The Tornado diagrams below display the Net Monetary Benefit (NMB) at £20,000 per QALY. This is because it is easier to see which parameter affect the results of the model when using NMB. When considering the ICER, a change in the difference in cost and QALYs between two interventions may lead to one being dominant or dominated over the other: these are not associated with numerical values and cannot be depicted in a tornado diagram. When using NMB if the parameter crosses zero it indicates that the results of the model has changed i.e. a different comparator has become cost effective.

All the tornado diagrams for each of the analyses discussed below are in Appendix A:.

HE2.2.1.1 *BRAF* mutant

For the *BRAF* Mutant model, the outcome of the sensitivity analyses were similar for with CT vs CT reduced follow up after 2 years (Figure HE022) and 0 years of 6 monthly scans (Figure HE025). In both scenarios, the two parameters that had the largest impact on the results were the percentage of patients with stage IIIA who were symptomatic for years 2 and above, and the percentage of patients who are symptomatic with the reduced follow up. This shows that if a patient is much more likely to be symptomatic at a reduced imaging frequency, then the reduced frequency may be the most cost-effective option. Unfortunately, there is no data on the increase in patients who are symptomatic at a lower imaging frequency. It would make sense that if the patient is being scanned more often then they are more likely to get symptoms. However, because the size of the change is unknown it could not be applied to the model. If the increase in symptomatic patients is small e.g. 0.05% then the results of the model does not change however, if the change is larger then CT at a reduced frequency is the most cost effective option.

For *BRAF* Mutant, with CT vs PET-CT, the only parameter that affected the results sufficiently to change the conclusion of the analysis was the sensitivity of CT (Figure HE023, Figure HE026). PET-CT only becomes cost effective if the sensitivity of CT is significantly reduced. It is unlikely that the true value of the sensitivity of CT is that low and therefore it is unlikely that PET-CT will ever be cost effective.

For *BRAF* Mutant, CT vs PET-CT reduced follow up after 2 years (Figure HE024) and 0 years of 6 monthly imaging (Figure HE027), the only parameters that affected the results was the sensitivity of CT. Similar to PET-CT, PET-CT reduced only becomes cost effective when the sensitivity of CT is significantly lower.

To investigate what happens to the results if the sensitivity of CT is significantly reduced, we ran the model with the sensitivity of CT at the lower end of its confidence interval, Table HE028 for reduced follow up after 2 years and Table HE029 for reduced follow up with 0 years of 6 monthly scans. When doing this we found that PET-CT at a reduced follow up was the most cost-effective option. However, as mentioned before, we believe that it is unlikely that the sensitivity of CT is that low especially as over the years radiographers have improved in reading the scans and the sensitivity is more likely to go up than down.

Table HE028: Reducing the sensitivity of CT, reported as ICERs (*BRAF* Mutant, 2 years)

Value at 0.54	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Cost	£127,319	£127,347	£128,538	£128,698
QALY	8.86329	8.86483	8.93438	8.93695
ICER	Reference	Ex. Dom	£17,155	£62,167

*Ex. Dom means that two or more comparators combined are less costly and more effective than this option.

Table HE029: Reducing the sensitivity of CT, reported in ICERs (*BRAF* Mutant, 0 years)

Value at 0.54	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Cost	£127,080	£127,347	£128,115	£128,698
QALY	8.80065	8.86483	8.87313	8.93695
ICER	Reference	£4,169	Ex. Dom	£18,727

*Ex. Dom means that two or more comparators combined are less costly and more effective than this option.

HE2.2.12 *BRAF* wild type

For *BRAF* Wild Type, CT vs CT reduced follow up after 2 years (Figure HE028) and 0 years of 6 monthly scans (Figure HE031). The two parameters that effected the results were the percentage of patients with stage IIIA who were symptomatic for years 2 and more, and the percentage of patients who are symptomatic with the reduced follow up. Similar to the *BRAF* Mutant model, if a patient is much more likely to be symptomatic at a reduced imaging frequency, then the reduce frequency may be the most cost-effective option. Unfortunately, there is no data on the increase in patients who are symptomatic at a lower imaging frequency. It would make sense that if the patient is being scanned more often then they are more likely to get symptoms. However, because the size of the change is unknown it could not be applied to the model. If the increase in symptomatic patients is small e.g. 0.05% then the results of the model does not change however, if the change is larger then CT at a reduced frequency is the most cost effective option

For *BRAF* Wild Type, CT vs PET-CT, the only parameter that effected the results was the sensitivity of CT (Figure HE029, Figure HE032). Similar to the *BRAF* mutant model, PET-CT only becomes cost effective if the sensitivity of CT is significantly reduced. It is unlikely that the true value of the sensitivity of CT is that low and therefore it is unlikely that PET-CT will ever be cost effective.

For *BRAF* Wild Type, CT vs PET-CT reduced follow up after 2 years (Figure HE030) and 0 years of 6 monthly imaging (Figure HE033),, the only parameter that effected the results was the sensitivity of CT. Similar to PET-CT, PET-CT reduced only becomes cost effective when the sensitivity of CT is significantly lower.

To investigate what happens to the results if the sensitivity of CT is significantly reduced, we ran the model with the sensitivity of CT at the lower end of its confidence interval, Table HE030 for reduced after 2 years and Table HE031 for 0 years of 6 monthly scans. When doing this we found that PET-CT at a reduced follow up was the most cost-effective option. However, as mentioned before, we believe that it is unlikely that the sensitivity of CT is that low especially as over the years radiographers have improved in reading the scans and the sensitivity is more likely to go up than down.

Table HE030: Reducing the sensitivity of CT, reported as ICERs (*BRAF* Wild Type, 2 years)

Value at 0.54	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Cost	£114,387	£114,414	£115,299	£115,457
QALY	9.32413	9.32535	9.39861	9.40066
ICER	Reference	Ex.Dom	£12,248	£76,900

*Ex. Dom means that two or more comparators combined are less costly and more effective than this option.

Table HE031: Reducing the sensitivity of CT (*BRAF* Mutant, 0 years)

Value at 0.54	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Cost	£144,058	£114,414	£114,796	£115,457
QALY	9.26995	9.32535	9.34600	9.40066
ICER	Reference	£6,413	Ex. Dom	£13,850

*Ex. Dom means that two or more comparators combined are less costly and more effective than this option.

There are Patient Access Scheme (PAS) costs for the three systemic treatments (ipilimumab plus nivolumab, nivolumab and pembrolizumab). These costs were used in the model however, it made no difference to the results, CT at the current follow up schedule was still the most cost effective option.

HE2.2.2 Scenario analysis

HE2.2.2.1 Probability of progression

Probability of progression was not included in the deterministic sensitivity analysis due to the implicit correlation between the three values for stage IIIA, stage IIIB and stage IIIC. The values were assumed by the committee with stage IIIA being 0.75, stage IIIB being 0.8 and stage IIIC being 0.85. Therefore, it was important to test how these values affect the result, this can be seen in Table HE032, Table HE033, Table HE034 and Table HE035. Table HE032, Table HE033 and Table HE035 show that CT at the current follow up schedule is always cost effective. In Table HE034 it shows for *BRAF* Wild type reduced after 2 years, there is potential that CT at a reduced follow up schedule could be cost effective. However, these results were only true if the values of the probability of progression were drastically reduced, and the committee felt that these values were not plausible in clinical practice.

Table HE032: Probability of progression sensitivity analysis, reported as ICERs (*BRAF* Mutant, 2 years)

IIIA, IIIB, IIIC	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
0.9, 0.95, 1	Reference	£13,274	£45,889	£57,420
0.85, 0.9 ,0.95	Reference	£13,639	£47,332	£58,773
0.8, 0.85, 0.9	Reference	£14,061	£48,942	£60,344
0.75, 0.8, 0.85	Reference	£14,548	£50,744	£62,167
0.7, 0.75, 0.8	Reference	£15,111	£52,765	£64,286
0.65, 0.7, 0.75	Reference	£15,766	£55,043	£66,755
0.6, 0.65, 0.7	Reference	£16,530	£57,620	£69,643
0.55, 0.6, 0.65	Reference	£17,428	£60,552	£73,043
0.5, 0.55, 0.6	Reference	£18,491	£63,909	£77,075
0.45, 0.5, 0.55	Reference	£19,763	£67,782	£81,905

Table HE033: Probability of progression sensitivity analysis, reported as ICERs (*BRAF* Mutant, 0 years)

IIIA, IIIB, IIIC	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
0.9, 0.95, 1	Reference	£3,945	Dominated	£46,555
0.85, 0.9 ,0.95	Reference	£4,168	Dominated	£48,551
0.8, 0.85, 0.9	Reference	£4,086	Dominated	£49,593
0.75, 0.8, 0.85	Reference	£4,169	Dominated	£51,391
0.7, 0.75, 0.8	Reference	£4,264	Dominated	£53,412
0.65, 0.7, 0.75	Reference	£4,370	Dominated	£55,693
0.6, 0.65, 0.7	Reference	£4,491	Dominated	£58,279
0.55, 0.6, 0.65	Reference	£4,628	Dominated	£61,227
0.5, 0.55, 0.6	Reference	£4,783	Dominated	£64,607
0.45, 0.5, 0.55	Reference	£4,961	Dominated	£68,515

Table HE034: Probability of progression sensitivity analysis, reported as ICERs (*BRAF* Wild Type, 2 years)

IIIA, IIIB, IIIC	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
0.9, 0.95, 1	Reference	£15,236	£36,369	£71,042
0.85, 0.9 ,0.95	Reference	£15,681	£38,160	£72,709
0.8, 0.85, 0.9	Reference	£16,193	£40,138	£74,648
0.75, 0.8, 0.85	Reference	£16,785	£42,332	£76,900
0.7, 0.75, 0.8	Reference	£17,471	£44,777	£79,518
0.65, 0.7, 0.75	Reference	£18,267	£47,514	£82,569
0.6, 0.65, 0.7	Reference	£19,196	£50,595	£86,139
0.55, 0.6, 0.65	Reference	£20,286	£54,086	£90,340
0.5, 0.55, 0.6	Reference	£21,577	£58,072	£95,320
0.45, 0.5, 0.55	Reference	£23,120	£62,660	£101,282

Table HE035: Probability of progression sensitivity analysis, reported as ICERs (*BRAF* Wild Type, 0 years)

IIIA, IIIB, IIIC	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
0.9, 0.95, 1	Reference	£6,089	Dominated	£37,869
0.85, 0.9 ,0.95	Reference	£6,190	Dominated	£39,657
0.8, 0.85, 0.9	Reference	£6,304	Dominated	£41,634
0.75, 0.8, 0.85	Reference	£6,432	Dominated	£43,830
0.7, 0.75, 0.8	Reference	£6,577	Dominated	£46,279
0.65, 0.7, 0.75	Reference	£6,741	Dominated	£49,024
0.6, 0.65, 0.7	Reference	£6,927	Dominated	£52,118
0.55, 0.6, 0.65	Reference	£7,138	Dominated	£55,629
0.5, 0.55, 0.6	Reference	£7,379	Dominated	£59,642
0.45, 0.5, 0.55	Reference	£7,654	Dominated	£64,270

HE2.2.2.2 Rate of recurrence and overall survival

The recurrence rate and overall survival used extrapolated data which involved an assumption on the form of the survival function, as shown in Figure HE003. Therefore, scenario analysis was done using all the other curves. As explained in **Error! Reference source not found.** the *BRAF* Mutant model used Lognormal for recurrence for stage IIIA, Gompertz for recurrence for Stages IIIB and IIIC and Lognormal for overall survival on either ipilimumab plus nivolumab, nivolumab and pembrolizumab. The *BRAF* Wild Type model used Exponential for recurrence for stage IIIA, Gompertz for recurrence for Stages IIIB and IIIC, Log-logistic for overall survival on ipilimumab plus nivolumab and Lognormal for overall survival on nivolumab.

As can be seen from Table HE036, Table HE037, Table HE038 and Table HE039 there are no differing parametric curves that change the result of CT at the current follow up being the most cost-effective option. Therefore, there is increased confidence that the choice of parametric curves for recurrence or overall survival does not impact the result of the economic model.

1 **Table HE036: Scenario Analysis (*BRAF* Mutant, 2 years)**

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Recurrence rate, Stage IIIA, Exponential	Reference	£17,858	£48,412	£74,993
Recurrence rate, Stage IIIA, Weibull	Reference	£18,041	£50,928	£74,753
Recurrence rate, Stage IIIA, Gompertz	Reference	£19,300	£49,774	£79,677
Recurrence rate, Stage IIIA, Log-logistic	Reference	£15,981	£50,574	£67,392
Recurrence rate, Stage IIIB, Exponential	Reference	£14,548	£59,469	£62,167
Recurrence rate, Stage IIIB, Weibull	Reference	£14,548	£57,611	£62,167
Recurrence rate, Stage IIIB, Lognormal	Reference	£14,548	£57,019	£62,167
Recurrence rate, Stage IIIB, Log-logistic	Reference	£14,548	£55,394	£62,167
Recurrence rate, Stage IIIC, Exponential	Reference	£14,548	£53,901	£62,167
Recurrence rate, Stage IIIC, Weibull	Reference	£14,548	£53,506	£62,167
Recurrence rate, Stage IIIC, Lognormal	Reference	£14,548	£52,842	£62,167
Recurrence rate, Stage IIIC, Log-logistic	Reference	£14,548	£52,480	£62,167
Overall survival, Ipilimumab and Nivolumab, Exponential	Reference	£14,295	£50,467	£61,178
Overall survival, Ipilimumab and Nivolumab, Weibull	Reference	£14,454	£50,738	£61,811
Overall survival, Ipilimumab and Nivolumab, Gompertz	Reference	£14,727	£50,775	£62,852
Overall survival, Ipilimumab and Nivolumab, Log-logistic	Reference	£14,508	£50,761	£62,013
Overall survival, Nivolumab, Exponential	Reference	£14,305	£50,667	£61,223
Overall survival, Nivolumab, Weibull	Reference	£14,408	£50,847	£61,636
Overall survival, Nivolumab, Gompertz	Reference	£14,944	£51,109	£63,715
Overall survival, Nivolumab, Log-logistic	Reference	£14,526	£50,890	£62,080
Overall survival, Pembrolizumab, Exponential	Reference	£14,140	£50,306	£60,553
Overall survival, Pembrolizumab, Weibull	Reference	£14,348	£50,757	£61,402

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Overall survival, Pembrolizumab, Gompertz	Reference	£15,144	£51,233	£64,485
Overall survival, Pembrolizumab, Log-logistic	Reference	£14,516	£50,893	£62,039

1

2 **Table HE037: Scenario Analysis (*BRAF* Mutant, 0 years)**

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Recurrence rate, Stage IIIA, Exponential	Reference	£4,199	Dominated	£49,609
Recurrence rate, Stage IIIA, Weibull	Reference	£4,394	Dominated	£52,079
Recurrence rate, Stage IIIA, Gompertz	Reference	£4,379	Dominated	£51,092
Recurrence rate, Stage IIIA, Log-logistic	Reference	£4,269	Dominated	£51,460
Recurrence rate, Stage IIIB, Exponential	Reference	£4,169	Dominated	£59,628
Recurrence rate, Stage IIIB, Weibull	Reference	£4,169	Dominated	£57,878
Recurrence rate, Stage IIIB, Lognormal	Reference	£4,169	Dominated	£57,320
Recurrence rate, Stage IIIB, Log-logistic	Reference	£4,169	Dominated	£55,784
Recurrence rate, Stage IIIC, Exponential	Reference	£4,169	Dominated	£54,376
Recurrence rate, Stage IIIC, Weibull	Reference	£4,169	Dominated	£54,003
Recurrence rate, Stage IIIC, Lognormal	Reference	£4,169	Dominated	£53,376
Recurrence rate, Stage IIIC, Log-logistic	Reference	£4,169	Dominated	£53,032
Overall survival, Ipilimumab and Nivolumab, Exponential	Reference	£4,182	Dominated	£51,081
Overall survival, Ipilimumab and Nivolumab, Weibull	Reference	£4,192	Dominated	£51,368
Overall survival, Ipilimumab and Nivolumab, Gompertz	Reference	£4,134	Dominated	£51,453
Overall survival, Ipilimumab and Nivolumab, Log-logistic	Reference	£4,180	Dominated	£51,400
Overall survival, Nivolumab, Exponential	Reference	£4,220	Dominated	£51,273
Overall survival, Nivolumab, Weibull	Reference	£4,228	Dominated	£51,464

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Overall survival, Nivolumab, Gompertz	Reference	£4,151	Dominated	£51,809
Overall survival, Nivolumab, Log-logistic	Reference	£4,197	Dominated	£51,525
Overall survival, Pembrolizumab, Exponential	Reference	£4,201	Dominated	£50,899
Overall survival, Pembrolizumab, Weibull	Reference	£4,230	Dominated	£51,367
Overall survival, Pembrolizumab, Gompertz	Reference	£4,122	Dominated	£51,962
Overall survival, Pembrolizumab b, Log-logistic	Reference	£4,195	Dominated	£51,526

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2 **Table HE038: Scenario Analysis (*BRAF* Wild Type, 2 years)**

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Recurrence rate, Stage IIIA, Weibull	Reference	£16,179	£42,981	£73,452
Recurrence rate, Stage IIIA, Gompertz	Reference	£17,886	£44,286	£77,889
Recurrence rate, Stage IIIA, Lognormal	Reference	£16,361	£41,491	£75,719
Recurrence rate, Stage IIIA, Log-logistic	Reference	£15,585	£42,315	£72,113
Recurrence rate, Stage IIIB, Exponential	Reference	£16,785	£48,255	£76,900
Recurrence rate, Stage IIIB, Weibull	Reference	£16,785	£44,807	£76,900
Recurrence rate, Stage IIIB, Lognormal	Reference	£16,785	£52,928	£76,900
Recurrence rate, Stage IIIB, Log-logistic	Reference	£16,785	£43,745	£76,900
Recurrence rate, Stage IIIC, Exponential	Reference	£16,785	£48,953	£76,900
Recurrence rate, Stage IIIC, Weibull	Reference	£16,785	£45,496	£76,900
Recurrence rate, Stage IIIC, Lognormal	Reference	£16,785	£44,488	£76,900
Recurrence rate, Stage IIIC, Log-logistic	Reference	£16,785	£44,443	£76,900
Overall survival, Ipilimumab and Nivolumab, Exponential	Reference	£16,209	£41,028	£74,424
Overall survival, Ipilimumab and Nivolumab, Weibull	Reference	£16,705	£42,164	£76,582

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Overall survival, Ipilimumab and Nivolumab, Gompertz	Reference	£17,424	£43,147	£79,581
Overall survival, Ipilimumab and Nivolumab, Lognormal	Reference	£16,860	£42,372	£77,221
Overall survival, Nivolumab, Exponential	Reference	£15,848	£40,413	£72,863
Overall survival, Nivolumab, Weibull	Reference	£16,485	£41,961	£75,654
Overall survival, Nivolumab, Gompertz	Reference	£17,764	£43,622	£81,006
Overall survival, Nivolumab, Log-logistic	Reference	£16,671	£42,274	£76,406

Table HE039: Scenario Analysis (*BRAF* Wild Type, 0 years)

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Recurrence rate, Stage IIIA, Weibull	Reference	£6,591	Dominated	£44,366
Recurrence rate, Stage IIIA, Gompertz	Reference	£7,238	Dominated	£45,764
Recurrence rate, Stage IIIA, Lognormal	Reference	£6,044	Dominated	£42,957
Recurrence rate, Stage IIIA, Log-logistic	Reference	£6,278	Dominated	£43,677
Recurrence rate, Stage IIIB, Exponential	Reference	£6,432	Dominated	£49,485
Recurrence rate, Stage IIIB, Weibull	Reference	£6,432	Dominated	£46,180
Recurrence rate, Stage IIIB, Lognormal	Reference	£6,432	Dominated	£54,035
Recurrence rate, Stage IIIB, Log-logistic	Reference	£6,432	Dominated	£45,160
Recurrence rate, Stage IIIC, Exponential	Reference	£6,432	Dominated	£50,195
Recurrence rate, Stage IIIC, Weibull	Reference	£6,432	Dominated	£46,966
Recurrence rate, Stage IIIC, Lognormal	Reference	£6,432	Dominated	£45,901
Recurrence rate, Stage IIIC, Log-logistic	Reference	£6,432	Dominated	£45,856
Overall survival, Ipilimumab and Nivolumab, Exponential	Reference	£6,312	Dominated	£42,498
Overall survival, Ipilimumab and Nivolumab, Weibull	Reference	£6,432	Dominated	£43,658

Parameter	CT (Reduced)	CT	PET-CT (Reduced)	PET-CT
Overall survival, Ipilimumab and Nivolumab, Gompertz	Reference	£6,325	Dominated	£44,688
Overall survival, Ipilimumab and Nivolumab, Lognormal	Reference	£6,407	Dominated	£43,876
Overall survival, Nivolumab, Exponential	Reference	£6,322	Dominated	£41,860
Overall survival, Nivolumab, Weibull	Reference	£6,498	Dominated	£43,437
Overall survival, Nivolumab, Gompertz	Reference	£6,293	Dominated	£45,185
Overall survival, Nivolumab, Log-logistic	Reference	£6,473	Dominated	£43,761

HE2.2.23 CT including contrast only

The cost of CT if all the scans that do not include contrast are excluded is £109.61. Table HE040, Table HE041, Table HE042 and Table HE043 show the results of using £109.61 instead of £97.15 for the cost of a CT scan. This shows that increasing the cost to contrast only CT still means that CT at the standard follow up schedule is still the most cost-effective option. While for the *BRAF* Mutant 2 year follow up ICER for CT is close to the £20,000 per QALY threshold, it is still below the threshold and therefore the preferred option.

Table HE040: Cost–utility results, CT contrast only (*BRAF* Mutant, 2 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£126,451	8.88965				£51,342	£140,239
CT	£126,483	8.89157	£32	0.00192	£16,584	£51,349	£140,265
PET-CT (Reduced)	£128,538	8.93438	£2,172	0.04281	£48,018	£50,149	£139,493
PET-CT	£128,698	8.93695	£160	0.00257	£62,167	£50,041	£139,410

Table HE041: Cost–utility results, CT contrast only (*BRAF* Mutant, 0 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£126,206	8.82752				£50,344	£138,619
CT	£126,483	8.89157	£276	0.06405	£4,314	£51,348	£140,265
PET-CT (Reduced)	£128,115	8.87313	£1,633	-0.0184	Dom	£49,347	£138,079
PET-CT	£128,698	8.93695	£2,216	0.04538	£48,820	£50,041	£139,410

*Dom means that the option is dominated, is more costly and less effective than the comparison

Table HE042: Cost–utility results, CT contrast only (*BRAF* Wild Type, 2 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£113,467	9.35189				£73,570	£167,089
CT	£113,497	9.35341	£29	0.00153	£19,255	£73,572	£167,106
PET-CT (Reduced)	£115,299	9.39861	£1,803	0.04520	£39,881	£72,673	£166,659
PET-CT	£115,457	9.40066	£157	0.00205	£76,900	£72,556	£166,563

Table HE043: Cost–utility results, CT contrast only (*BRAF* Wild Type, 0 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£113,133	9.29820				£72,831	£165,813
CT	£113,497	9.35341	£364	0.05521	£6,593	£73,572	£167,105
PET-CT (Reduced)	£114,796	9.34600	£1,299	-0.00742	Dom	£72,124	£165,584
PET-CT	£115,457	9.40066	£1,906	0.04725	£41,484	£72,556	£166,563

*Dom means that the option is dominated, is more costly and less effective than the comparison

HE2.2.3 Probabilistic sensitivity analysis

The probabilistic sensitivity results are shown in Table HE044, Table HE045, Table HE046 and Table HE047.

Both *BRAF* models with imaging reduced after 2 years (Table HE044 and Table HE046) show that CT is cost effective as the ICER is below NICE's willingness to pay threshold of £20,000 per QALY. For both models PET-CT and PET-CT reduced is over the willingness to pay threshold.

For both *BRAF* models with 0 years of 6 monthly scans (Table HE045 and Table HE047), CT is the most cost effective option. For these two models PET-CT reduced is dominated by CT, that means that CT is less expensive and more effective. PET-CT is not a cost effective option for 0 years because it is over the willingness to pay threshold.

The probabilistic results for all the different models are congruent to the deterministic results and all show the same option (CT at current follow up schedule) is the most cost effective option.

Table HE044: Probabilistic sensitivity cost–utility results (*BRAF* Mutant, 2 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£124,392	8.92807				£54,169	£143,450
CT	£124,421	8.93054	£29	0.00247	£11,640	£54,190	£143,495

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
PET-CT (Reduced)	£126,535	8.97458	£2,114	0.04404	£47,994	£52,957	£142,703
PET-CT	£126,696	8.97767	£161	0.00309	£52,068	£52,858	£142,635

Table HE045: Probabilistic sensitivity cost–utility results (*BRAF* Mutant, 0 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£124,064	8.86460				£53,228	£141,874
CT	£124,340	8.93086	£276	0.6626	£4,168	£54,277	£143,586
PET-CT (Reduced)	£126,030	8.91218	£1,690	-0.0187	Dom	£52,214	£141,335
PET-CT	£126,622	8.97786	£2,282	0.04700	£48,551	£52,935	£142,714

Table HE046: Probabilistic sensitivity cost–utility results (*BRAF* Wild Type, 2 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£115,686	9.31124				£70,539	£163,651
CT	£115,713	9.31326	£28	0.00202	£13,599	£70,552	£163,684
PET-CT (Reduced)	£117,491	9.36111	£1,777	0.04785	£37,145	£69,731	£163,343
PET-CT	£117,649	9.36360	£159	0.00249	£65,644	£69,623	£163,259

Table HE047: Probabilistic sensitivity cost–utility results (*BRAF* Wild Type, 0 years)

Strategy	Absolute		Incremental			Absolute net health benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
CT (Reduced)	£115,737	9.24034				£69,069	£161,473
CT	£116,099	9.29609	£361	0.05575	£6,480	£69,823	£162,784
PET-CT (Reduced)	£177,357	9.29186	£1,259	-0.0042	Dom	£68,480	£161,398
PET-CT	£118,022	9.34681	£1,923	0.05072	£37,920	£68,914	£162,382

A cost utility plane was created of each of the models, Figure HE034, Figure HE035, Figure HE036 and Figure HE037. All these figures were very similar which showed that there was a very small difference between the four comparators. A cost effectiveness acceptability curve was created for each of the models Figure HE018, Figure HE019, Figure HE020 and Figure HE021. For the 0 years model, there is a strong preference for CT at the current follow up rate for both *BRAF* models for the majority of willingness to pay thresholds. For the 2 years model, there is a preference for CT at the current follow up schedule above £15,000 willingness to pay threshold. However, the preference for CT over CT at a reduced follow up schedule is limited. When this was discussed with the committee, they felt that this was not enough evidence to reduce the number of follow up imaging appointments as the majority of evidence says CT at the current follow up schedule is the most cost effective option.

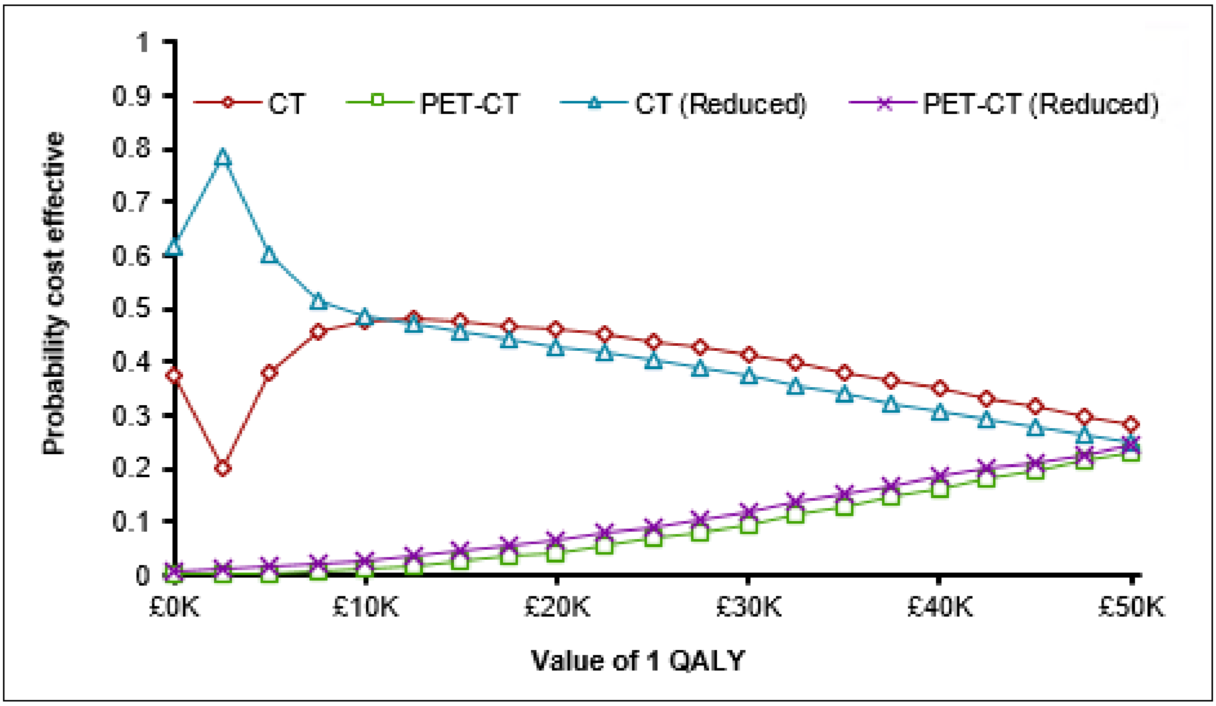

Figure HE018: Base-case Probabilistic results – cost–effectiveness acceptability curve (*BRAF* Mutant, 2 years)

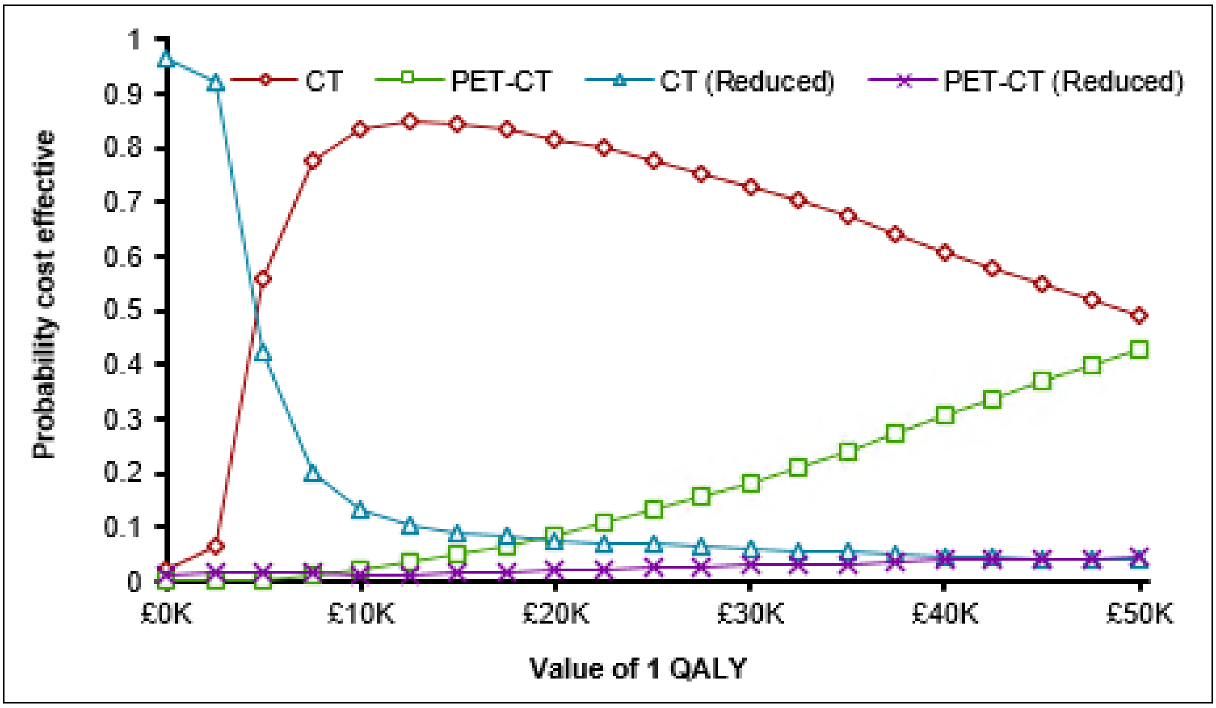

Figure HE019: Base-case Probabilistic results – cost–effectiveness acceptability curve (*BRAF* Mutant, 0 years)

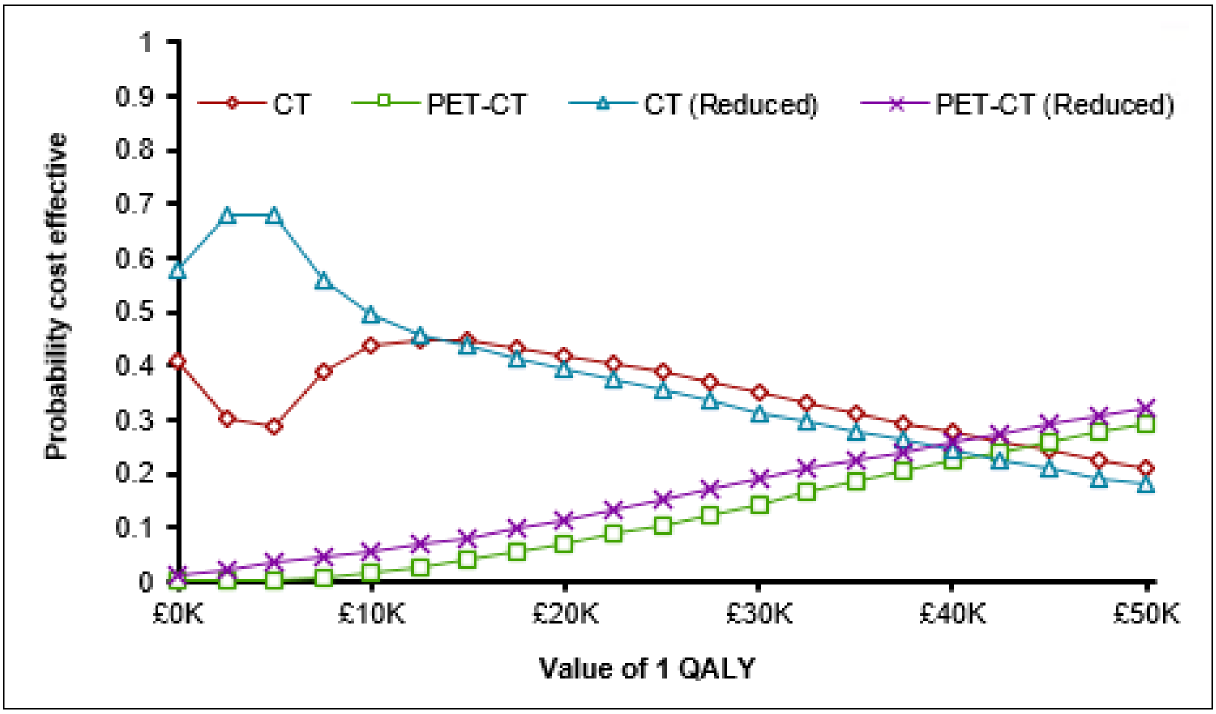

Figure HE020: Base-case Probabilistic results – cost–effectiveness acceptability curve (*BRAF* Wild Type, 2 years)

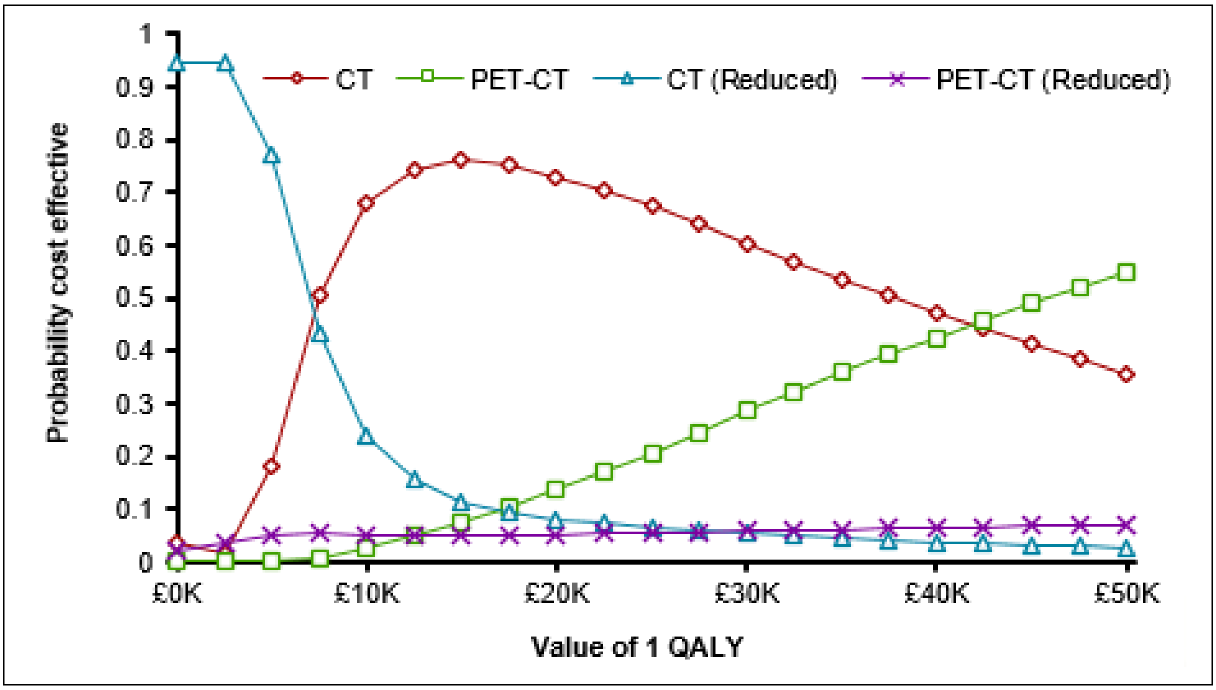

Figure HE021: Base-case Probabilistic results – cost–effectiveness acceptability curve (*BRAF* Wild Type, 0 years)

HE2.3 Discussion

HE2.3.1 Principal findings

The principle finding of the model was CT at the current follow up schedule is the most cost effective follow up regime for patients on adjuvant therapy with stage III melanoma, compared with PET-CT at all follow-up schedules that were explored and with CT at two different reduced follow-up schedules. The current follow up schedule is four scans in the first year while on adjuvant therapy, two scans in years 2 and 3 and one scan in years 4 and 5. PET-CT was not found to be cost effective because the cost of PET-CT is significantly more than CT and the increase in detection does not provide sufficient additional benefits. The reduction in follow up imaging was not cost effective compared with current imaging schedules for stage IIIA patients, as reducing the number of scans did not save a significant amount of money compared to the number of patients whose recurrences are missed. PET-CT (reduced at 0 years) was dominated by CT, which means that CT was less costly and more effective than PET-CT at 0 years.

HE2.3.2 Strengths of the analysis

The analysis considered groups of patients with each *BRAF* status separately and captured the treatment-specific recurrence rates applicable to each group. Therefore, it was possible within this analysis to find that different follow up schedules or modalities were cost effective in the different *BRAF* subgroups. The results ended up showing that the same follow up schedule was cost effective in both *BRAF* statuses. This will also make it easier in practice as clinicians will be able to use the same follow up with all patients with stage III melanoma, regardless of their *BRAF* status or substage.

One of the strengths of the analysis is that the results are robust to the majority of parameters explored. A change in only one particular parameter would result in PET-CT, either at the current follow up or reduced follow up, being cost effective compared with CT. Therefore, it is possible to be quite confident in not using PET-CT in the follow up of melanoma.

For the majority of parameters that did change the results, it was only when the value was at the very extreme of the confidence interval that the result changed. Therefore, there is further confidence that CT at the current follow schedule is the most cost-effective option.

The cost effectiveness acceptability curve shows that for all the different *BRAF* models and follow up schedules there is a large range of willingness to pay thresholds that CT is the most cost-effective option. The probability the CT is cost effective is at least 45% and against the 0 years it is over 70%, this increases the confidence using CT at the current follow up schedule is the most cost-effective option.

HE2.3.3 Weaknesses of the analysis

The analysis only investigates patients with stage IIIA, IIIB and IIIC melanoma and who have started a course of adjuvant therapy. Some patients, especially stage IIIA, may not have adjuvant treatment due to low recurrence rates and potentially severe side effects with adjuvant therapy. This means that they are not included in the analysis and potentially these patients would have a different recurrence rate and therefore a different follow up may be cost effective.

Another weakness of the analysis was that some of the parameters, for example the proportion of patients who are eligible for surgery, did not have published data and therefore the committee was asked for expert opinion. This means that there were no confidence intervals around the values and these parameters were not included in the probabilistic sensitivity analysis. However, one way sensitivity analyses were done around these parameters which showed that these parameters did not impact the results and therefore are not too concerned about the parameters not being included in the probabilistic sensitivity analysis.

The follow up treatment is only costed for one cycle of treatment, which is within one cycle of the model. This is an underestimate of the cost of treatment for recurrence however it is very unlikely that patients would stay on treatment until their death which would result in a large overestimate of the cost of treatment. It is difficult to know how long a patient would be on systemic treatment and therefore difficult to include it in the model. The committee felt that modelling the treatment for one cycle was more appropriate than to model the treatment until the patient's death.

A further potential limitation is that the recurrence curves will implicitly take into account the follow up schedule of the trials. If a recurrence is found in the trial, then it is 'identified' and therefore we do not know the rate of developing an undetected recurrence. However, this is an issue with the data, an unknown that we cannot quantify, and not something we can change.

HE2.3.4 Comparison with other CUAs

The only cost-effectiveness study found that compares CT and PET-CT was Krug et al. 2010, which found that PET-CT was a cost-effective option. However, there was multiple differences between our study and Krug et al. which is likely to be the reason behind the different results. The population in this study was different to our study as Krug et al. investigated patients with resected IIC and III melanoma. Another difference is that the PET-CT option in Krug et al. only scanned the chest looking for lung metastases and this was compared to a full body CT whereas our study compared full body PET-CT with full body CT. The patients in this trial also received a chest X-ray and blood tests and it is only those with suspicion of pulmonary metastases which are sent for a PET-CT or full body CT. The sensitivity and specificity of PET-CT and CT were very different in the two models, see Table HE048. The parameter that had the biggest impact on the model in Krug et al. was the specificity of PET-CT however none of the sensitivity or specificity of CT or PET-CT had a large effect on the results in our model. Krug el al. was also based in Belgium and therefore has a slightly different healthcare system to the United Kingdom.

Table HE048: Comparison of sensitivity and specificity of CT and PET-CT between our model and Krug et al.

Parameter	Our model	Krug et al
Sensitivity of CT	0.67	0.78
Specificity of CT	0.94	0.92
Sensitivity of PET-CT	0.89	0.94
Specificity of PET-CT	0.93	0.95

It is likely that Krug et al. found PET-CT cost effective because they were investigating patients who were at a much higher risk of a recurrence and therefore the much more likely to have a recurrence, therefore the benefit over cost of PET-CT was greater. The prices of CT and PET-CT in the Krug et al. study were very different to the values used in this analysis, this is likely due to Krug et al. being in Belgium and therefore the differing healthcare system having differing costs. As this analysis used values published by the NHS it is felt that they are more applicable for use within this guideline.

No studies could be found that investigated a reduced follow up compared to the current recommended follow up schedule. Therefore, it is not possible to compare how this analysis fits with other research into follow up schedules.

HE2.4 Conclusions

Using CT at a follow up schedule of four scans in the first year, two scans in years 2 and 3 and an annual scan in years 4 and 5 is the most cost effective follow up schedule compared to PET-CT for patients who had stage III melanoma and received adjuvant therapy. The results to robust to changes in many parameters, as explored through deterministic sensitivity analysis, and those that did result in a change in conclusions were not considered to be clinically feasible scenarios. The probabilistic sensitivity analysis also showed that CT had a high probability of being cost effective at the £20,000 willingness to pay threshold for all the models. Therefore, we can be very confident in the conclusion that CT at the current follow up schedule the most cost-effective option.

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Appendices

Appendix A: Tornado Diagrams

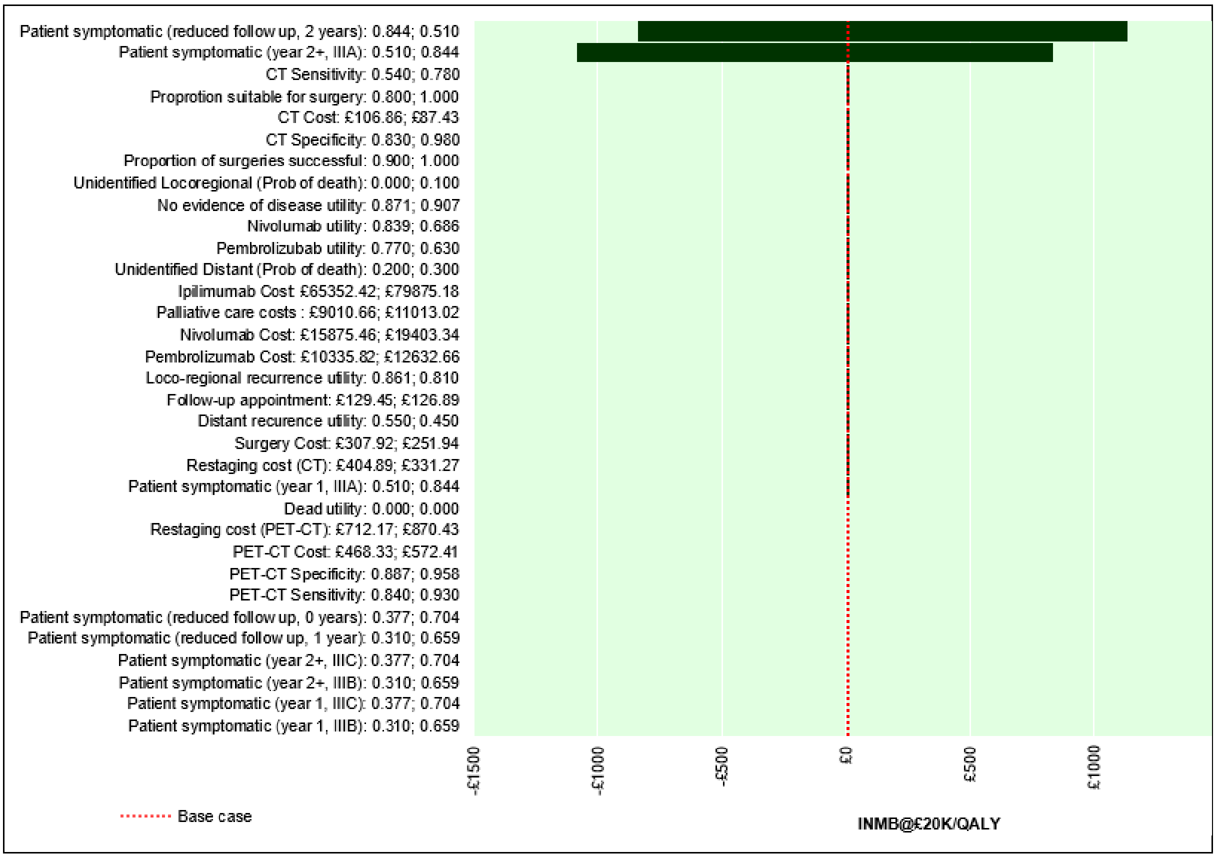

Figure HE022: Deterministic sensitivity analysis – tornado diagram (*BRAF* Mutant, CT vs CT reduced to annual scans after 2 years)

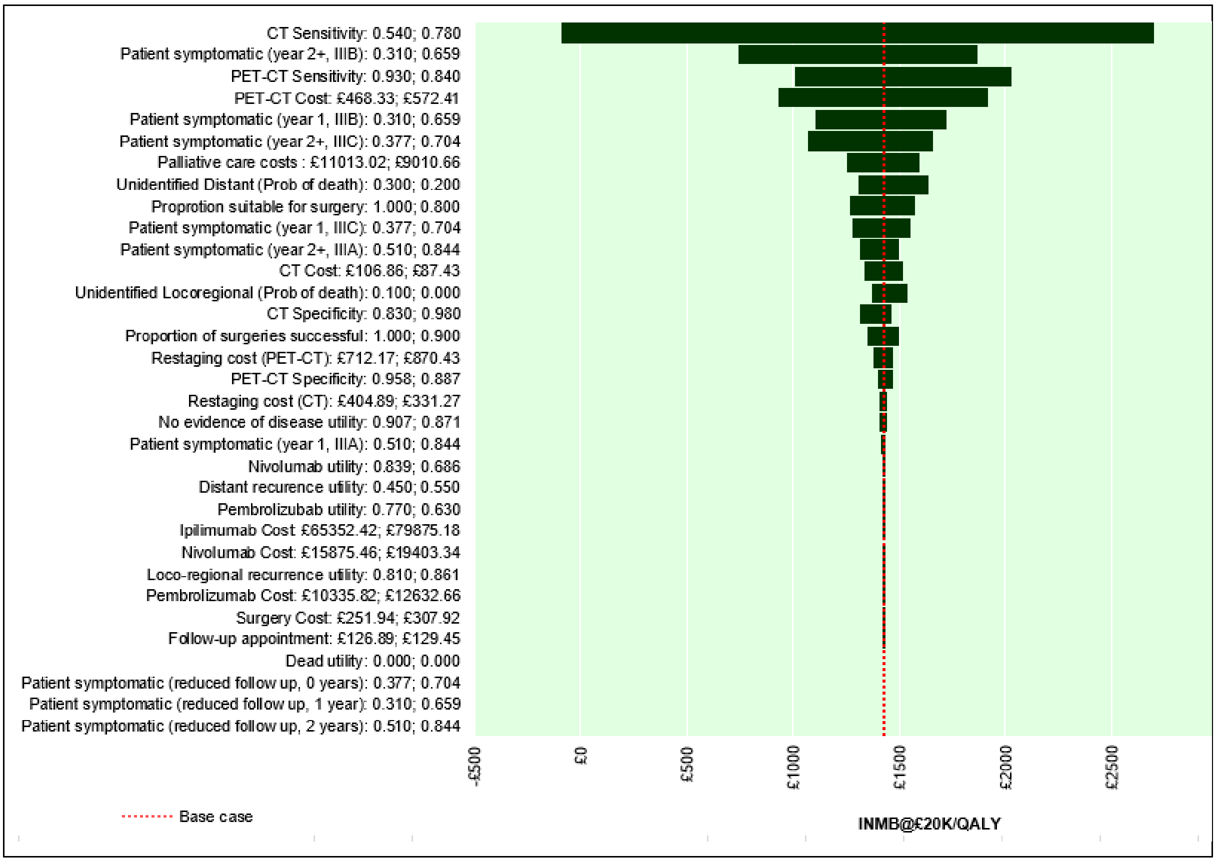

Figure HE023: Deterministic sensitivity analysis – tornado diagram (*BRAF* Mutant, 2 years, CT vs PET-CT)

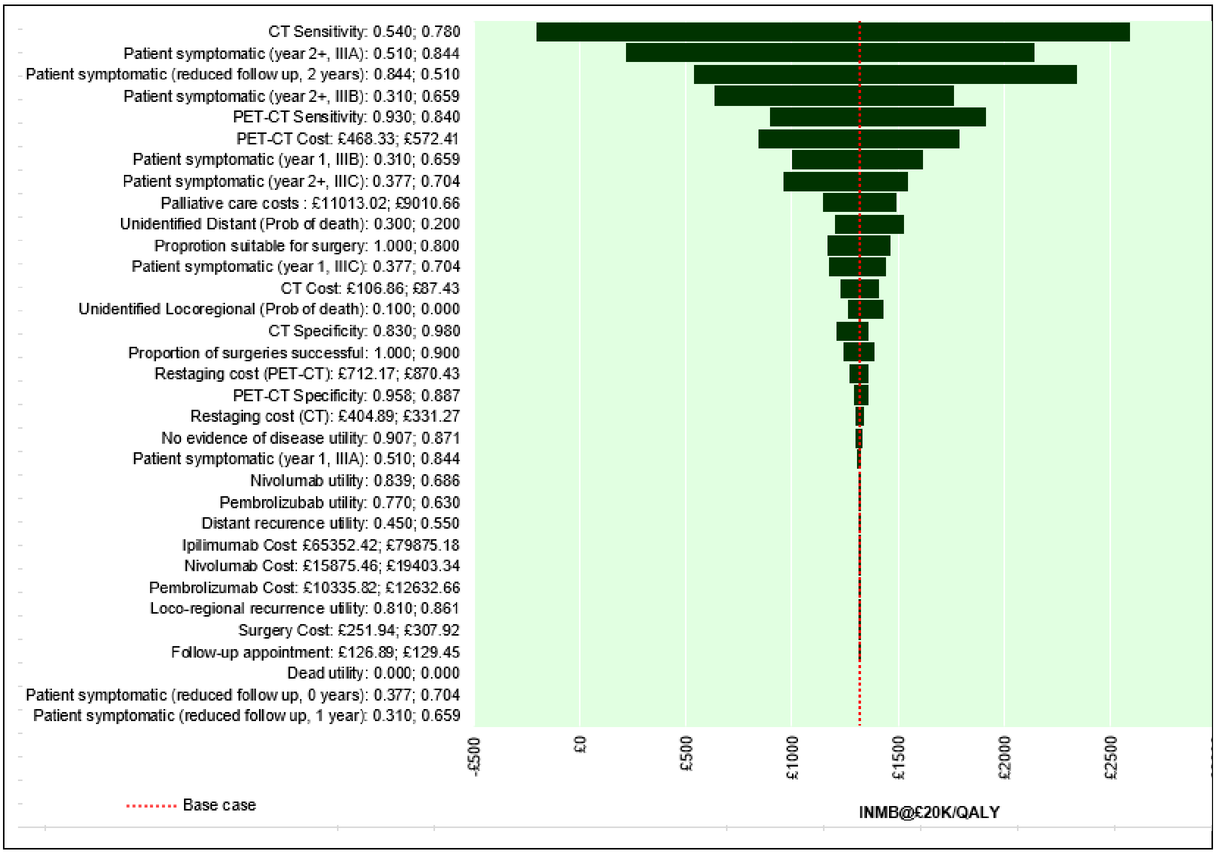

Figure HE024: Deterministic sensitivity analysis – tornado diagram (*BRAF* Mutant, CT vs PET-CT reduced to annual scans after 2 years)

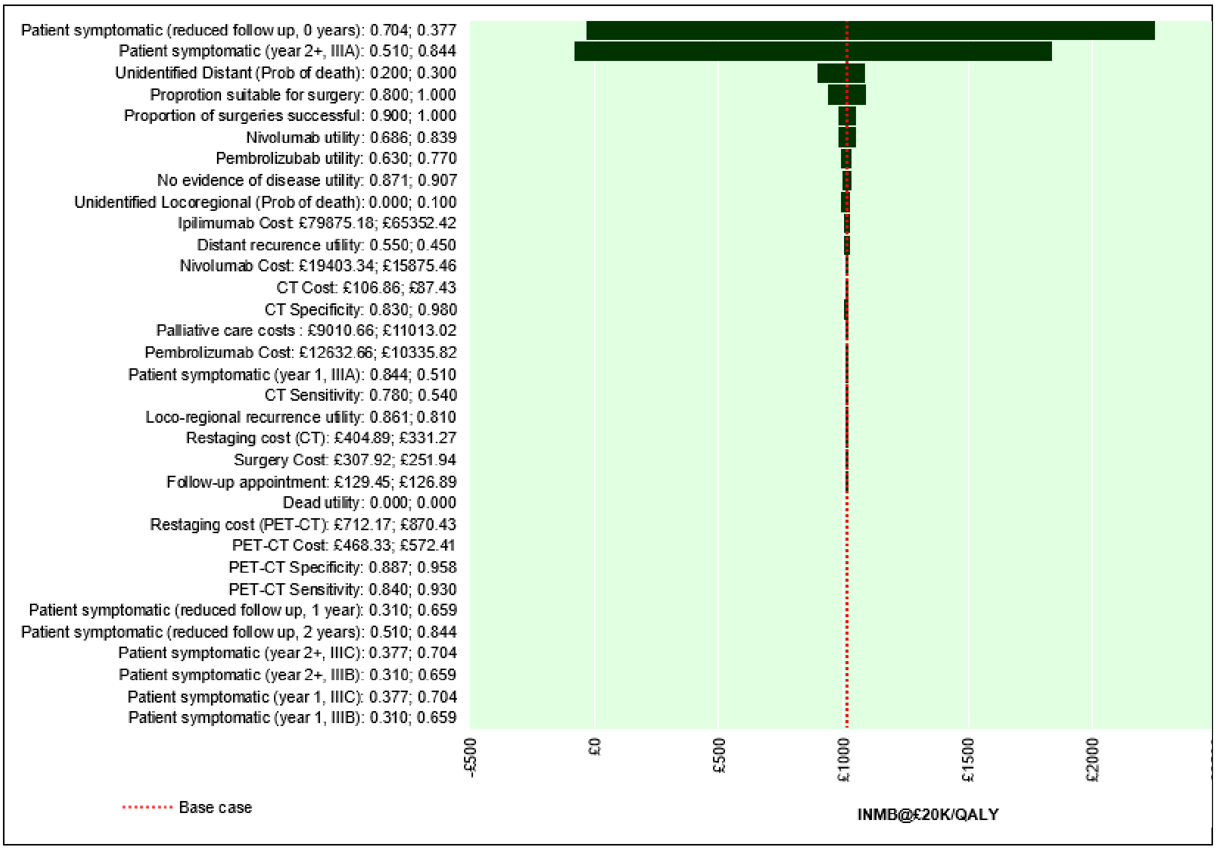

Figure HE025: Deterministic sensitivity analysis – tornado diagram (*BRAF* Mutant, CT vs CT reduced with 0 years of 6 monthly scans)

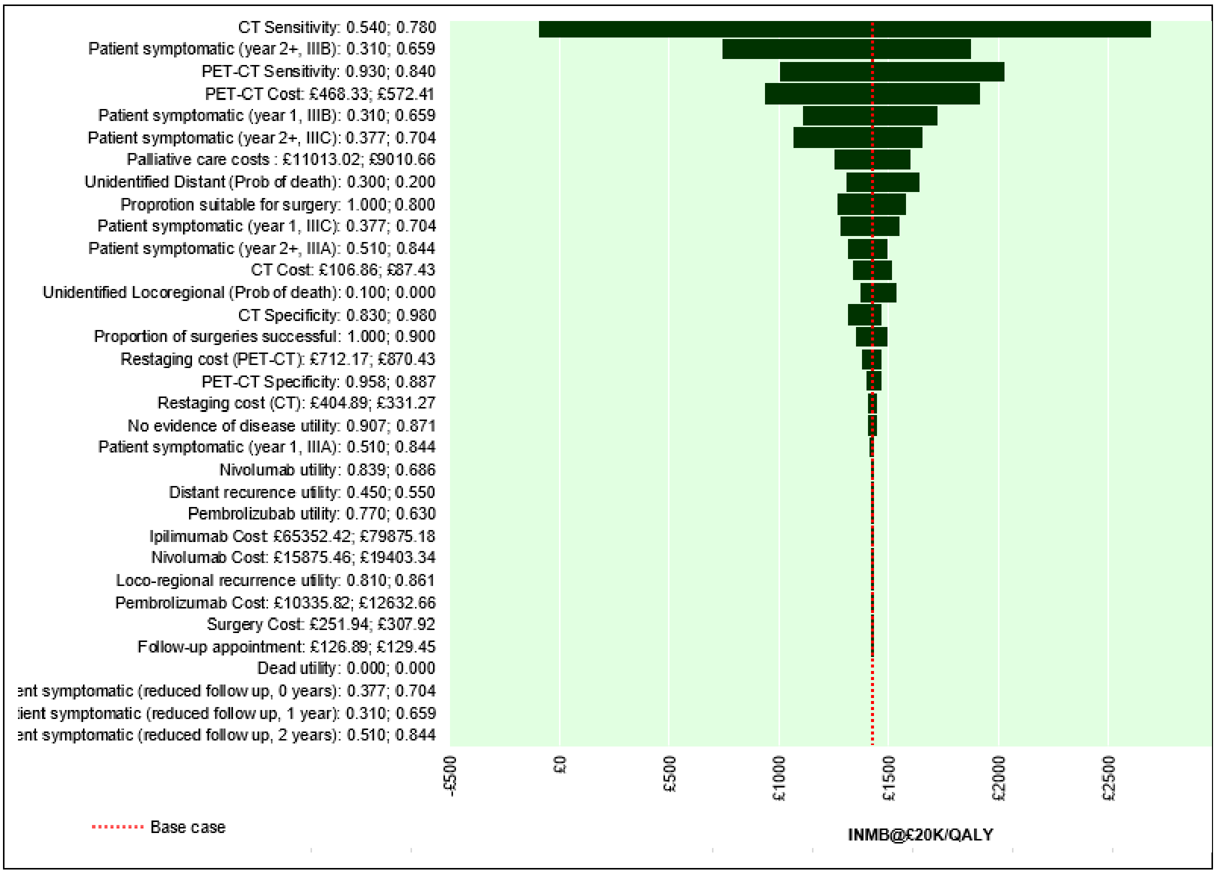

Figure HE026: Deterministic sensitivity analysis – tornado diagram (*BRAF* Mutant, 0 years, CT vs PET-CT)

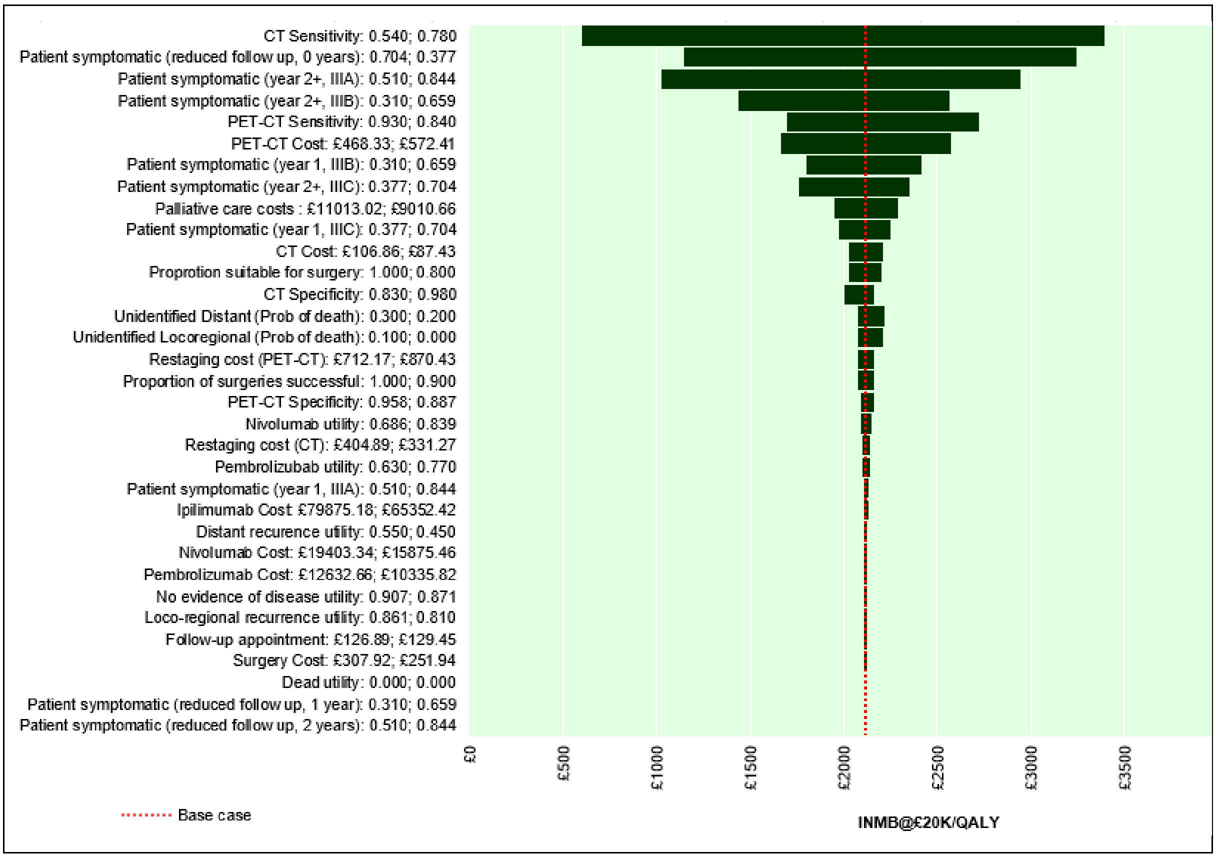

Figure HE027: Deterministic sensitivity analysis – tornado diagram (*BRAF* Mutant, 0 years, CT vs PET-CT reduced with 0 years of 6 monthly scans)

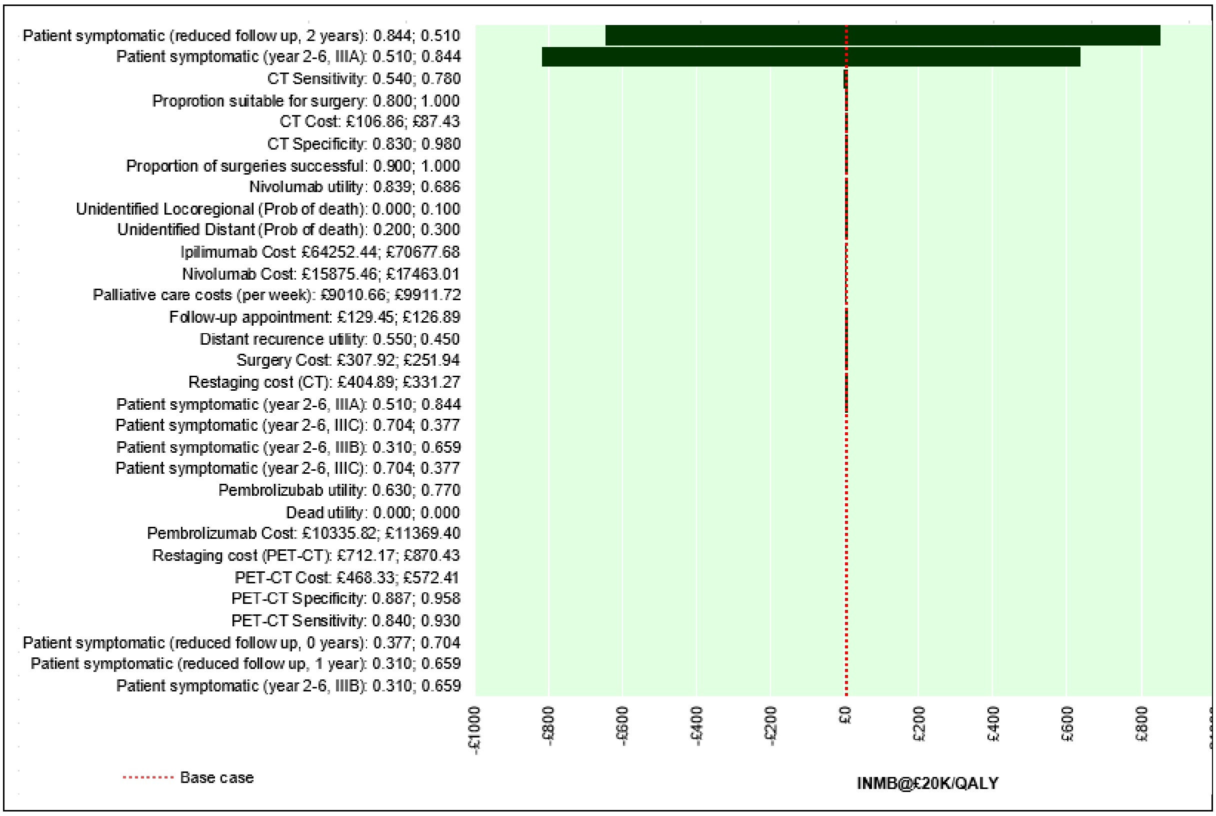

Figure HE028: Deterministic sensitivity analysis – tornado diagram (*BRAF* Wild Type, CT vs CT reduced to annual scans after 2 years)

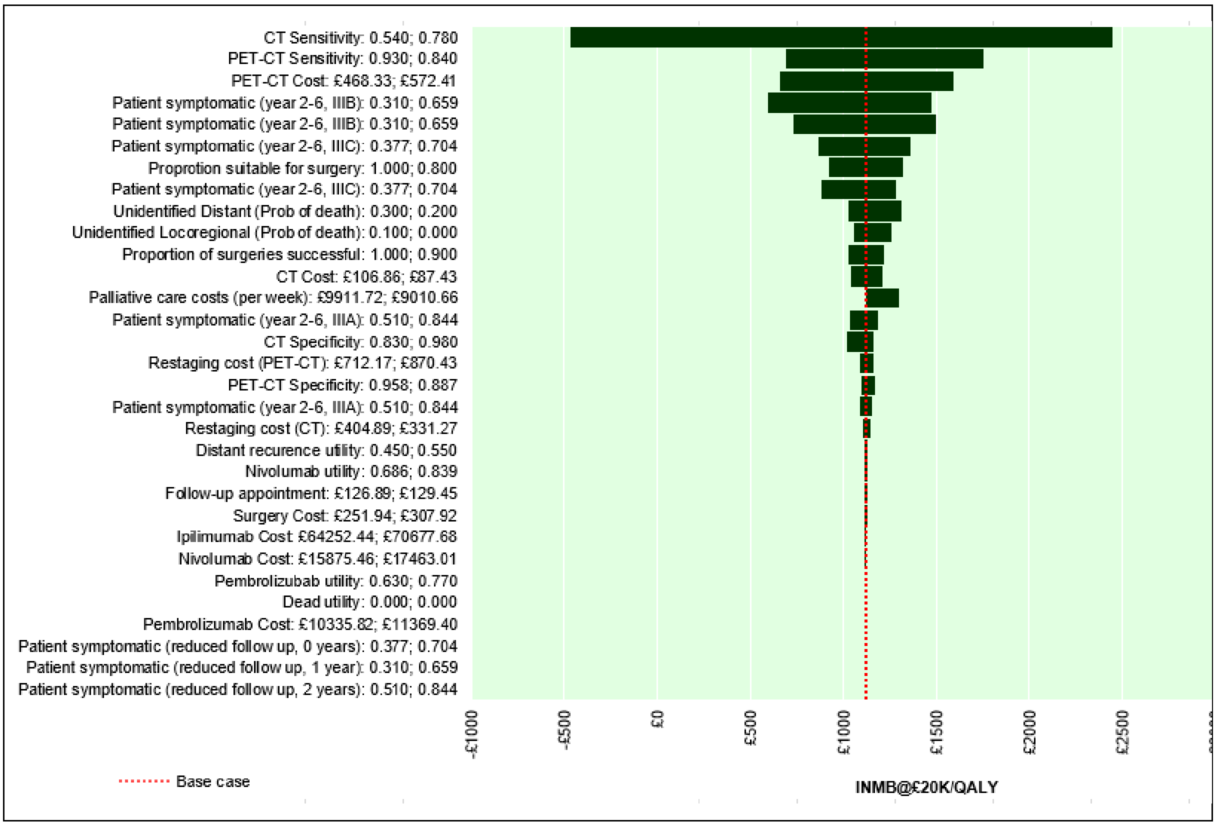

Figure HE029: Deterministic sensitivity analysis – tornado diagram (*BRAF* Wild Type, 2 years, CT vs PET-CT)

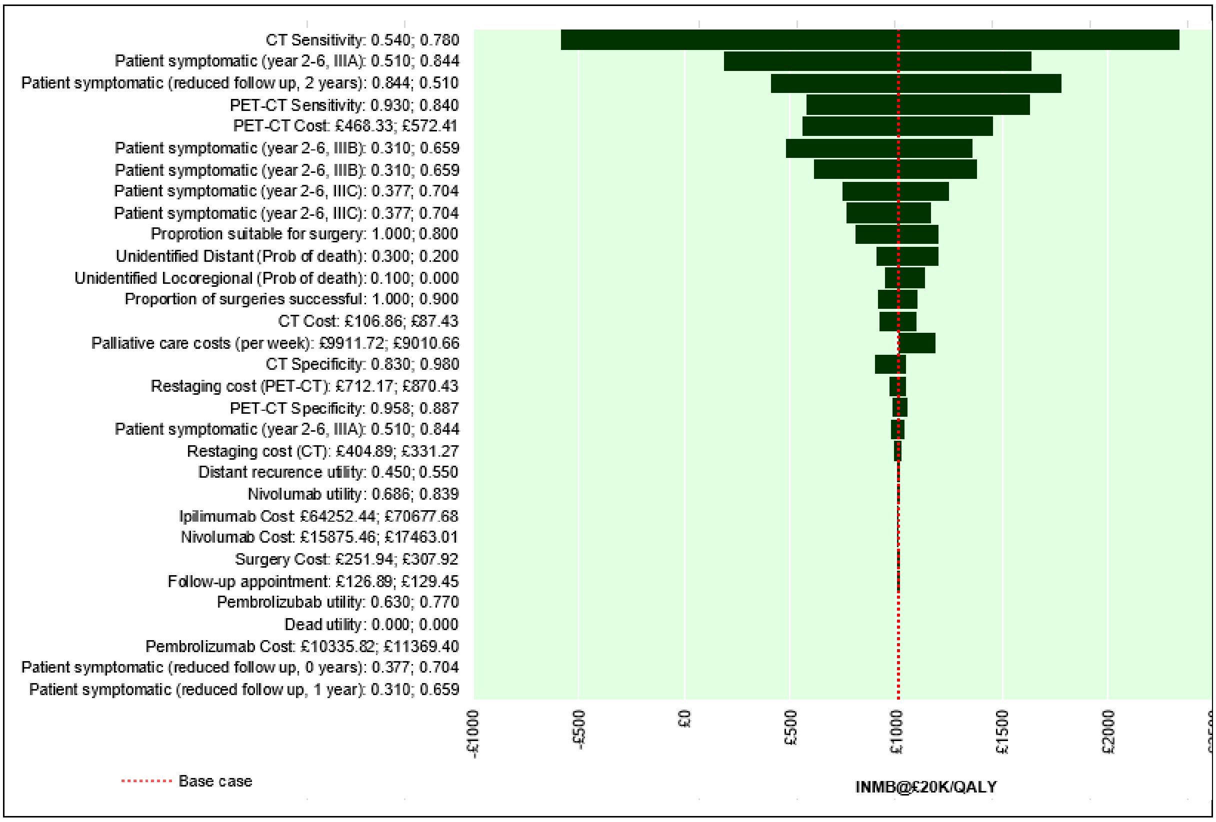

Figure HE030: Deterministic sensitivity analysis – tornado diagram (*BRAF* Wild Type, 2 years, CT vs PET-CT reduced to annual scans after 2 years)

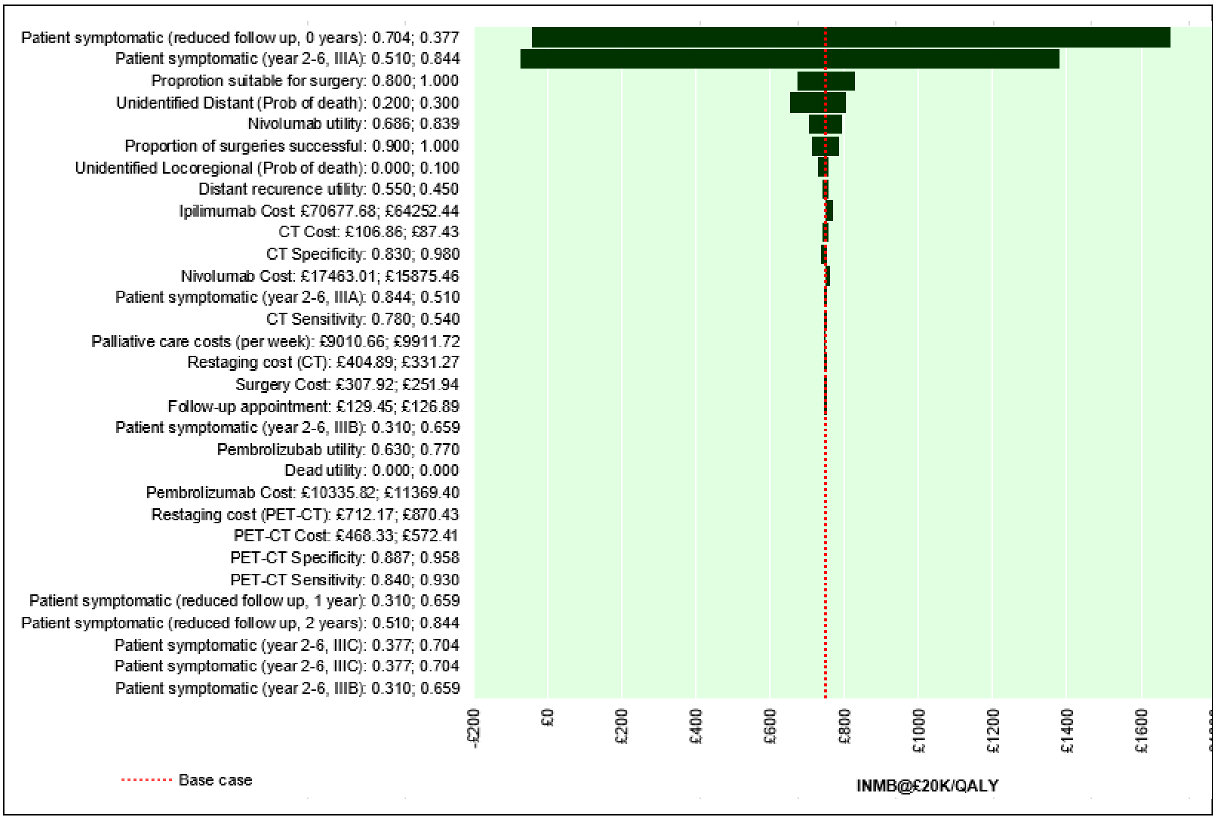

Figure HE031: Deterministic sensitivity analysis – tornado diagram (*BRAF* Wild Type, CT vs CT reduced with 0 years of 6 monthly scans)

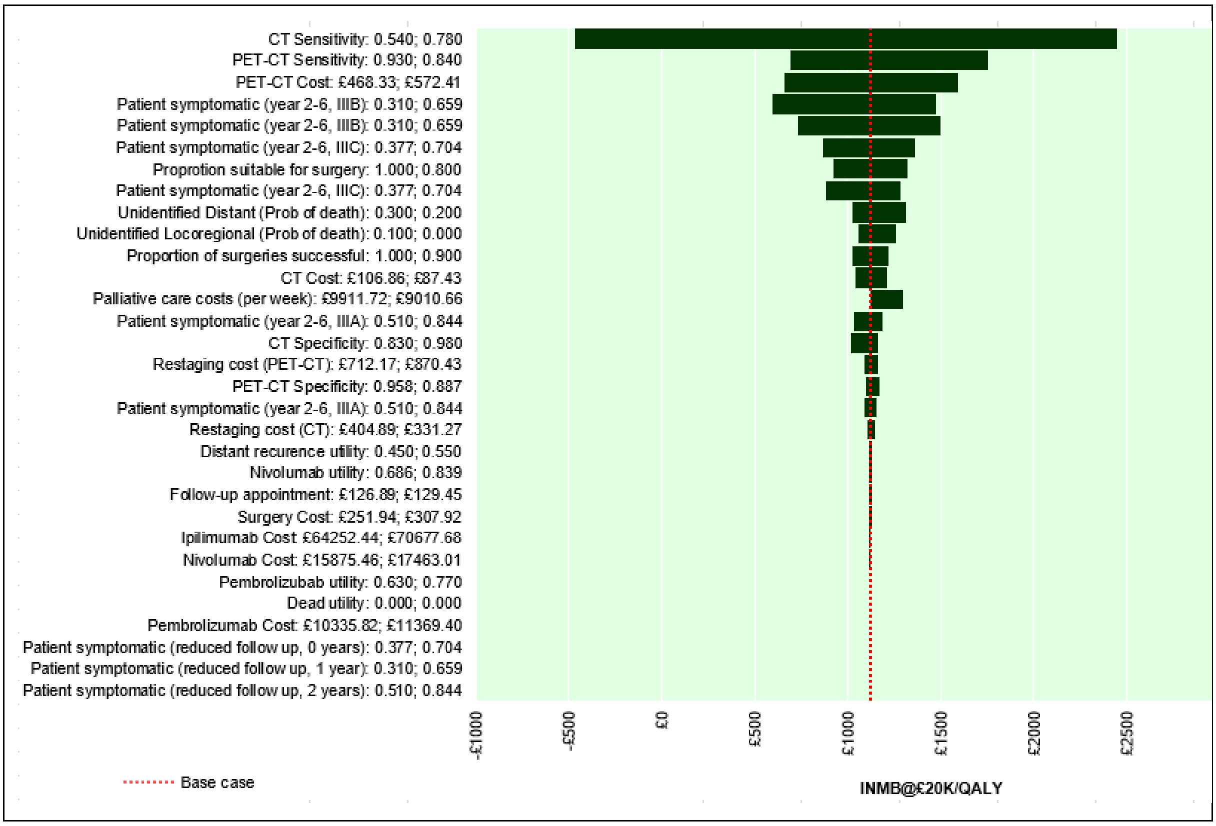

Figure HE032: Deterministic sensitivity analysis – tornado diagram (*BRAF* Wild Type, 0 years, CT vs PET-CT)

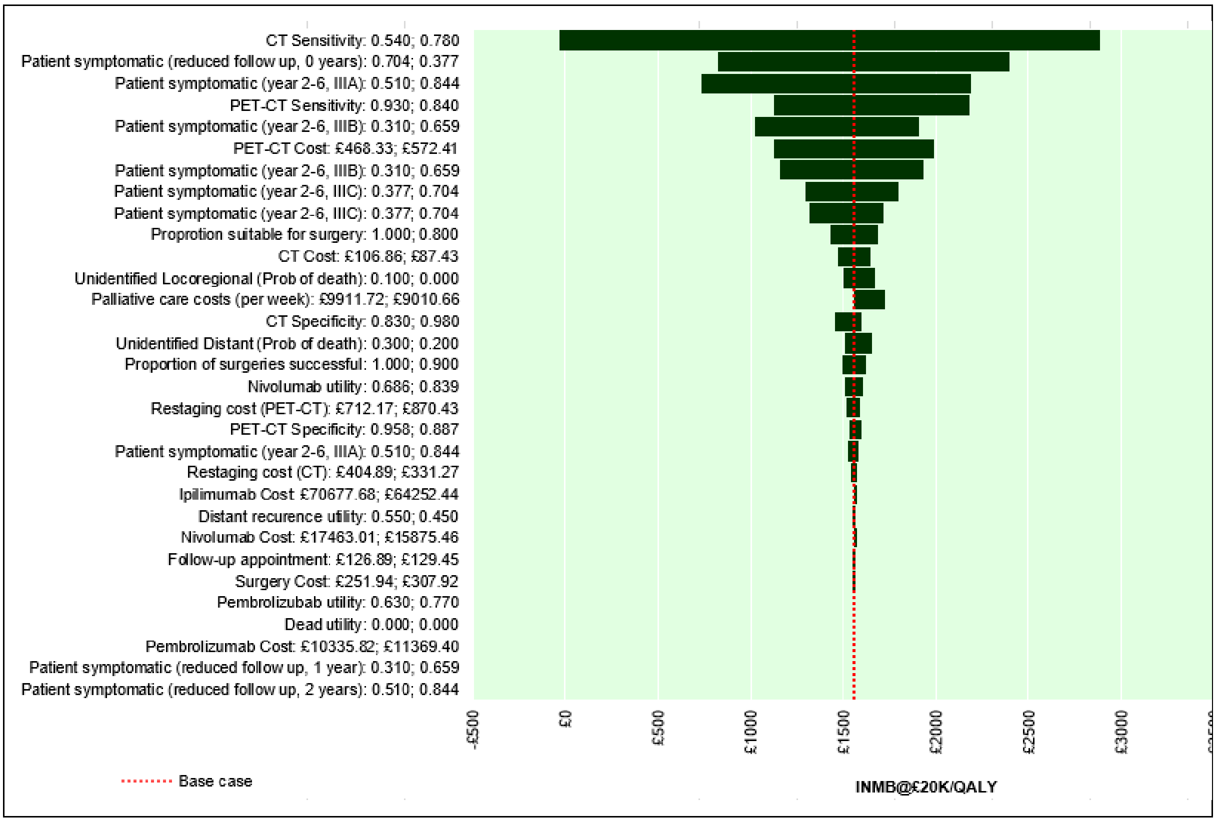

Figure HE033: Deterministic sensitivity analysis – tornado diagram (*BRAF* Wild Type, 0 years, CT vs PET-CT reduced with 0 years of 6 monthly scans)

Appendix B: Cost Utility planes

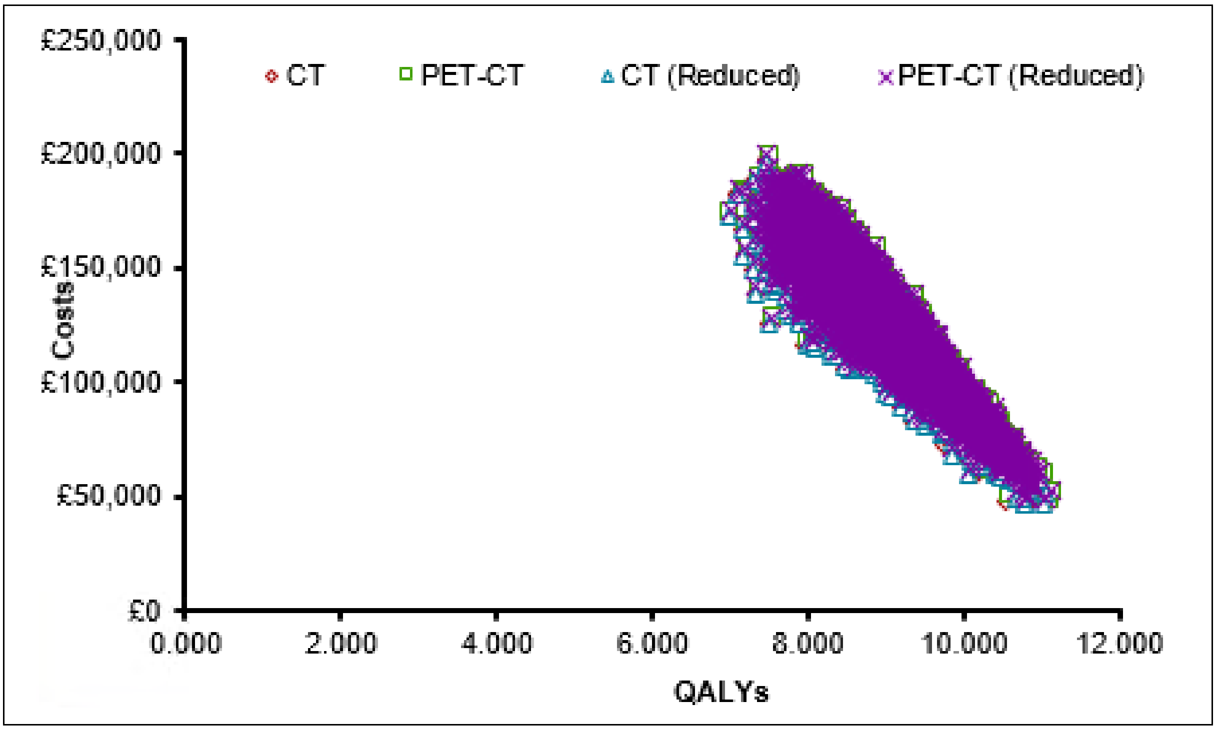

Figure HE034: Base-case Probabilistic results – cost–utility plane (*BRAF* Mutant, 2 years)

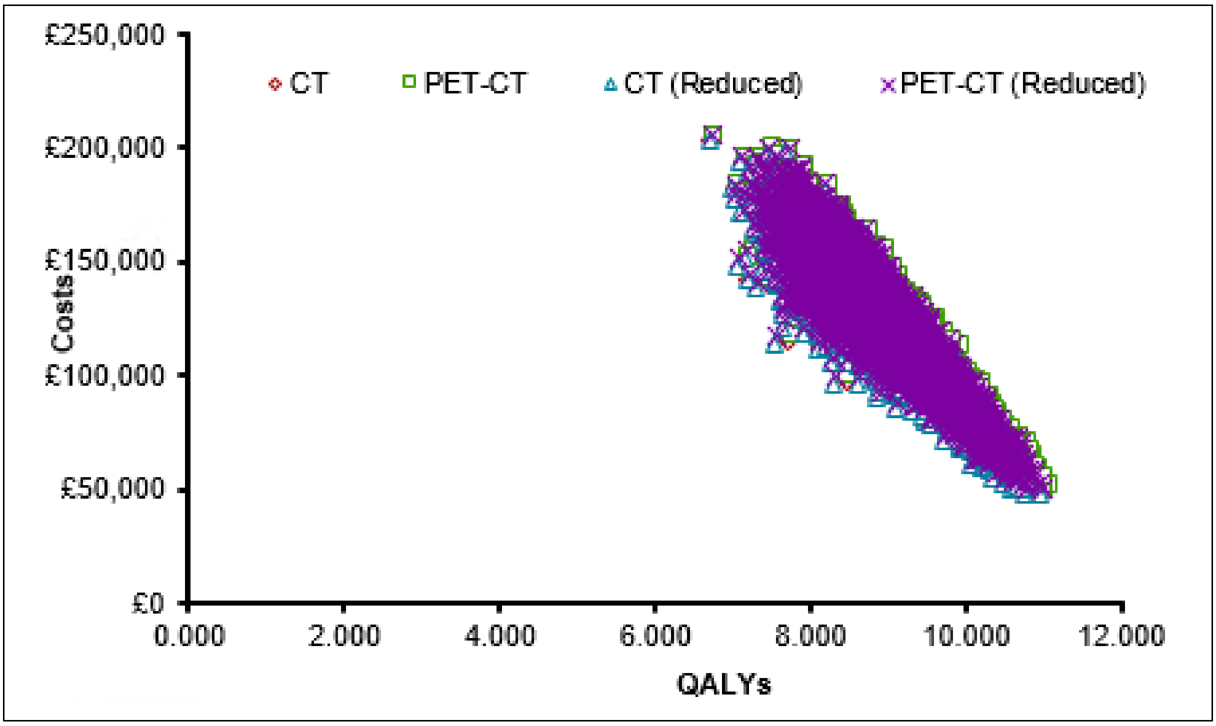

Figure HE035: Base-case Probabilistic results – cost–utility plane (*BRAF* Mutant, 0 years)

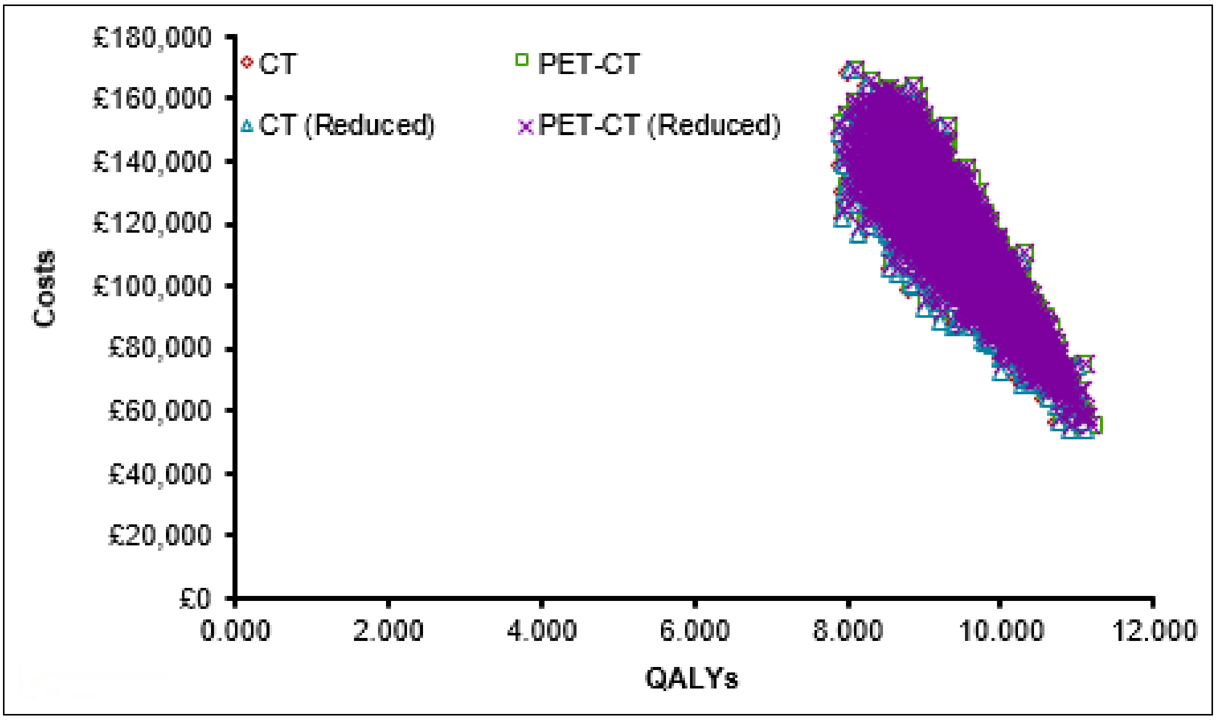

Figure HE036: Base-case Probabilistic results – cost–utility plane (*BRAF* Wild Type, 2 years)

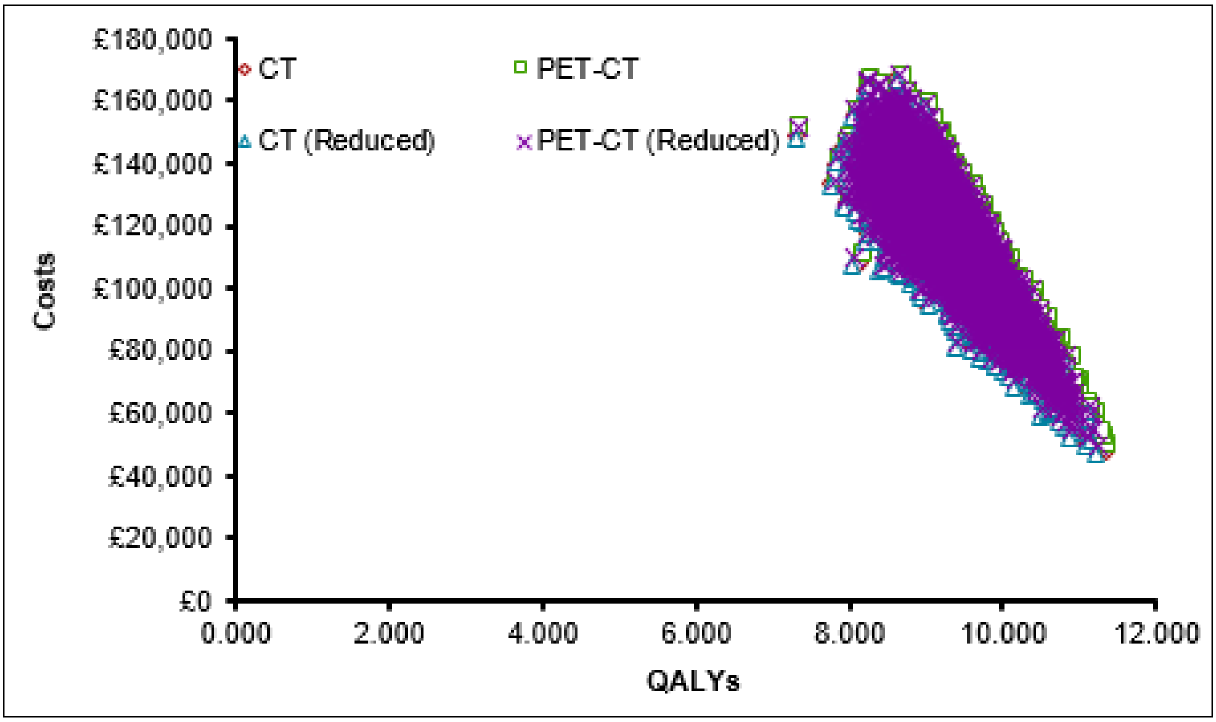

Figure HE037: Base-case Probabilistic results – cost–utility plane (*BRAF* Wild Type, 0 years)