National Institute for Health and Care Excellence

Final

Melanoma: assessment and management

[F] Evidence reviews for systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma Health economic model report

NICE guideline NG14

Evidence reviews underpinning recommendations 1.7.1 to 1.7.2 and 1.8.6 to 1.8.17 and research recommendations in the NICE guideline

July 2022

Final

National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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HE1 Methods

HE1.1 Model overview

The committee identified this review question for *de novo* economic modelling with the aim to reduce variation in clinical practice. This may arise due to the fact that there is currently no guidance on the optimal treatment sequence and the treatments that patients receive may be dependent on where they receive care. The objective of this analysis was to evaluate and compare the expected benefits, harms, and costs of the licensed systemic and localised anticancer treatments for first line use in advanced melanoma.

HE1.1.1 Population(s)

The population of interest was people with stage 4 and unresectable stage 3 melanoma.

A subgroup analysis was also explored in which only people with *BRAF* wild type melanoma were considered. It was not possible to conduct a subgroup analysis of people with *BRAF* mutant melanoma because only a small number of trials reported Kaplan Meier data in this subgroup and so a connected network could not be made, and it would not be possible to compare all relevant treatments for the subgroup in the network meta-analysis. The committee noted that *BRAF* status is not expected to be an effect modifier for treatment efficacy of immunotherapies (Larkin 2015, Puzanov 2020) so the effectiveness of these treatments was considered to be consistent across the mixed *BRAF* population. *BRAF* status determined the choice of comparator (both first line and second line), the treatment effect and, in a scenario analysis only, health state utility.

HE1.1.2 Interventions

The model assessed 5 strategies in the base case analysis:

1. Nivolumab
2. Pembrolizumab
3. Nivolumab and ipilimumab combination
4. Encorafenib and binimetinib combination
5. Dabrafenib and trametinib combination

Ipilimumab, dabrafenib and vemurafenib were also listed in the scope of this analysis, however these strategies were not considered in the economic model as although they have positive NICE technology appraisals the committee noted that they are no longer used as first line therapies in current practice as there are more recently approved drugs available that are more cost-effective than each of these treatments. The lack of usage is also supported by evidence from the SACT database.

For people with *BRAF* wild type melanoma, only immunotherapies are licensed because the mechanism of response in targeted therapies is specifically associated with the presence of a *BRAF* mutation, therefore in the subgroup analysis of people with *BRAF* wild type melanoma, the following strategies were considered:

- Nivolumab
- Pembrolizumab
- Nivolumab and ipilimumab combination

Table HE001: Modelled therapies

Strategy	Dosage	Treatment rules
Nivolumab	• 240mg every 2 weeks OR • 480mg every 4 weeks	-
Pembrolizumab	• 200mg every 3 weeks OR • 400mg every 6 weeks	-
Nivolumab + ipilimumab	• Nivo 1mg/kg every 3 weeks • Ipi 3mg/kg every 3 weeks	Ipi is only permitted to be given for 4 cycles
Encorafenib + binimetinib	• Enco 450mg per day • Bini 45mg twice per day	Only used in patients who are *BRAF* mutant
Dabrafenib + trametinib	• Dab 150mg twice per day • Tram 2mg per day	Only used in patients who are *BRAF* mutant

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 strategy compared to the next best alternative.

The model has a lifetime time horizon to reflect all important differences in costs and outcomes between the follow up regimes being compared.

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

HE1.2 Model structure

In our work for this review question, we reviewed NICE technology appraisals (TAs) for melanoma anticancer treatments. Companies have used two types of model structures in their submissions to NICE, partitioned survival models (TAs 562, 414, 410, 396, 366, 357, 321, 269, 268) or semi-Markov models (TAs 400, 384, 319). Though models of each type have been considered appropriate and well-structured by the Evidence Review Group (ERG), they each have their own limitations. Partitioned survival models are often limited by the time horizon the data cover, with assumptions required to extrapolate over a longer period. Markov models are limited in how they calculate transition probabilities from trial data, where modellers must either have access to individual patient level data or make significant assumptions regarding PFS events. Ultimately, we decided to build a partitioned survival model because:

1) The outcomes needed for a partitioned survival model, progression free survival (PFS) and overall survival (OS), are usually reported in the literature, thus we know data exists to build such a model.
2) A partitioned survival model is consistent with the majority of economic models submitted by the manufacturers providing us the benefit of having a large number of models for us to review when building our own.

The partitioned survival analysis has three mutually exclusive health states; progression-free, progressed, and dead. All patients start in the progression-free health state and can either progress or die, and only forward transitions are allowed in the model i.e. once progressed a patient cannot go back to progression-free.

The proportions in health states over time are informed by the survival data generated in the NMA. The model schematic is presented in Figure HE001.

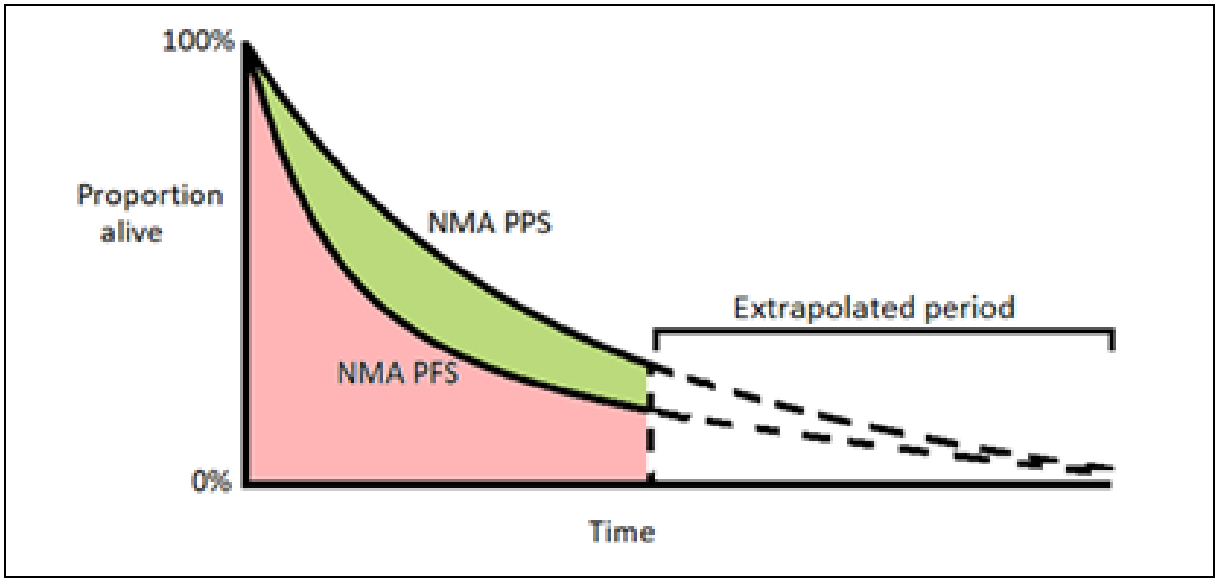

Figure HE001: Model schematic

The model includes costs associated with treatment, administration, adverse events, health state management, and palliative and terminal care. Further information on costs is located in HE1.4.7.

QALYs are accrued from health state membership and are lost due to adverse events associated with treatment. Further information on QALYs is located in HE1.4.6.

HE1.3 Model parameterisation

Identifying sources of parameters

The main sources of quality of life, resource use and cost parameters were existing NICE technology appraisals of the modelled treatments, and publicly available sources such as the NHS National Schedule of reference costs, and the Personal Social Services Research Unit: Unit costs of Health and Social Care.

For data on the modelled treatments, including time on treatment and second line therapies, we primarily used the clinical trial publications associated with each treatment. All parameters and any assumptions were informed and agreed by the committee.

Where possible, we drew resource use information from the NICE technology appraisals of the relevant treatments. Where the necessary data was unavailable, 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.

The approach to identifying unit costs for each of the resource use elements from a number of national sources was as follows:

- For drugs prescribed in secondary care, we use prices from the NHS Commercial Medicines Unit's Electronic Market Information Tool (eMIT; [December 2020]), 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 Parameters

HE1.4.1 Cohort parameters

HE1.4.1.1 Starting demographics and characteristics

The cohort of patients in the model started at 59 years of age and 60.9% of them were male, which were the average characteristics of the populations in the clinical trials of the modelled treatments (listed in Appendix A). Age and gender were included in the economic model to estimate general population mortality. The modelled cohort had an average weight of 80kg and an average body surface area of 1.93m², informed by the Break-3 clinical trial, and was included in the model in order to estimate treatment dosage for some comparators. The model included a mixed *BRAF* mutation population, with 32% of patients being *BRAF* mutant, and 68% being *BRAF* wild type as in CheckMate-067 reported in NICE TA400. Some parameter values were only reported by *BRAF* status and therefore it was necessary to include the proportion who were of each BRAF type in the model to estimate the mean parameter value for the overall population.

HE1.4.2 Survival analysis

HE1.4.2.1 NMA & extrapolation

To populate a partitioned survival model, two survival curves are required; progression-free survival and overall survival. A number of network meta-analyses (NMA) were conducted to allow for comparison between multiple treatments, and to maximise the data available for generating these survival curves.

A systematic review of RCTs for anticancer treatments used in advanced melanoma was performed to identify studies for inclusion in the NMA, detailed in Evidence Review F. Where available, the Kaplan-Meier (KM) curves from the included studies were digitised to recreate sets of individual patient data for OS and PFS by study treatment. We extracted OS and PFS data for the overall trial population for use in our base case analysis, and extracted OS and PFS by *BRAF* status where available,

Six models using different approaches to modelling time to event NMAs were considered; 1) cox proportional hazards (PH) model, 2) generalised gamma models, 3) piecewise exponential models, 4) fractional polynomial models, 5) Royston-Parmar flexible parametric models, and 6) restricted mean survival time (RMST) models. The Cox PH, RMST and

Royston-Parmar flexible parametric models were rejected due to an understanding that the other available models would provide superior fit and best use of available data (Freeman et al. (2018)). The Cox PH model was not fit as the PH assumption was tested and every network included trials where the PH assumption was not met. The RMST model was rejected as this model requires equal length follow-up and, given that the included trials varied in follow-up duration from 2 years to 5 years, large amounts of data would be discarded. Royston-Parmar models are in the same class as fractional polynomial models, and, given these models did not provide a better fit and dramatically increased the model complexity, it was considered valid to exclude the Royston-Parmar model. The remaining three NMA models (generalised gamma, piecewise exponential and fractional polynomial models) were fitted to the dataset. The best fitting curves and extrapolations from the NMA were selected by using a combination of model fit statistics and visual inspection, with the committee providing clinical insight on what the PFS and OS over time are expected to look like. The full methods and results of the NMA are detailed in the Network meta-analysis report.

Overall survival (base case population)

The committee felt that the generalised gamma models with treatment effects on the location and scale parameters were the more appropriate fit to the Kaplan-Meier data and gave a more realistic long-term extrapolation for overall survival. The piecewise exponential model was not considered appropriate as, on visual inspection, the shape did not fit to the dacarbazine (DTIC) KM data as well as that of the generalised gamma model. The generalised gamma model with two treatment effects was selected over the single treatment effect model using the model fit statistics and clinical opinion.

The generalised gamma survival function is:

$$S(t) = 1 - \Gamma_{(\sigma t)^Q}(\mu)$$

where σ, Q and μ are the scale, shape and location parameters, respectively. Figure HE002 illustrates overall survival over time for each of the included comparators.

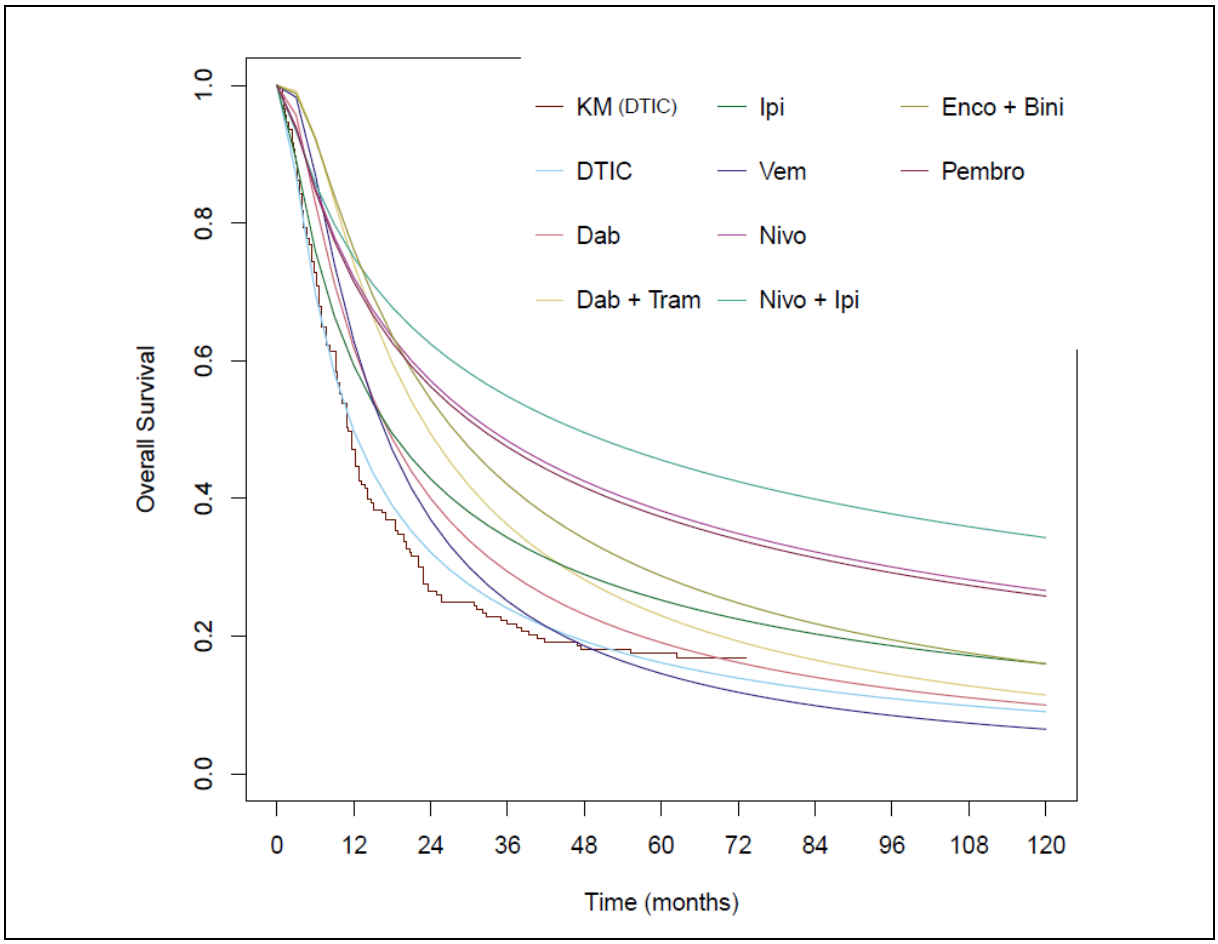

Figure HE002: Overall survival, generalised gamma model

Progression-free survival (base case population)

The committee felt that the piecewise exponential model with three time-intervals and cut points at 12 and 18 months were the more appropriate fit to the Kaplan-Meier data and gave a more realistic long-term extrapolation for progression-free survival. The generalised gamma model was not considered appropriate as, on visual inspection, the shape did not fit to the KM data as well as the piecewise model did. The three time-interval piecewise exponential model with cut points at 12 and 18 months was selected using an iterative process with the model statistics and feedback from clinical experts on the committee.

The general form of the exponential survival function is:

$$S(t) = \exp\{-\int_0^t \lambda du\} = e^{-\lambda t}$$

where λ is the rate parameter. Figure HE003 illustrates progression-free survival over time for each of the included comparators.

The committee noted that the PFS extrapolations for pembrolizumab were overly pessimistic, and they expected that they would be similar to that of nivolumab, given that they have the same mechanism of action, and that the shape of the curves should be similar. They considered that the PFS curve fits sufficiently well initially, but that after around 24 months the rate of decline is too great. Therefore, we have conducted a scenario analysis where after 24 months, the PFS hazard rate for pembrolizumab is set to be equal of that of nivolumab.

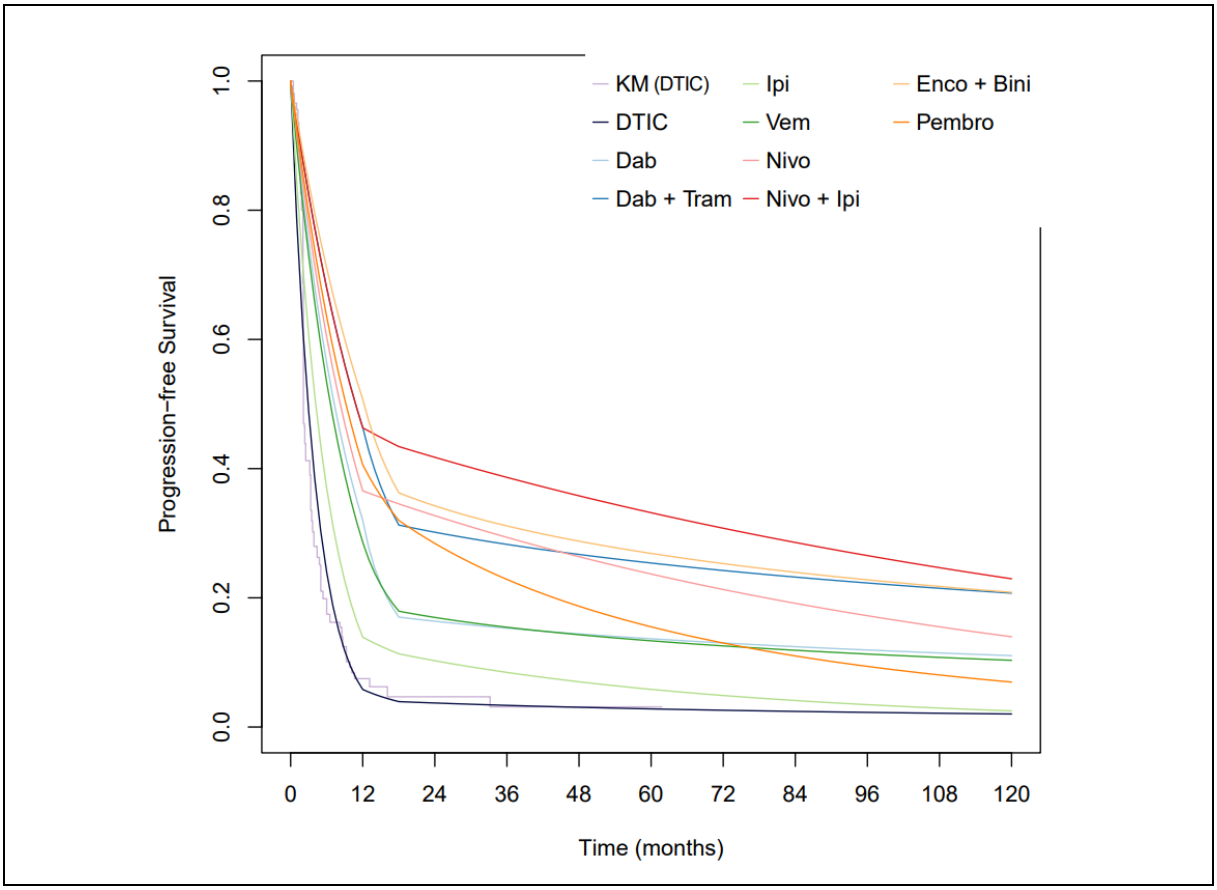

Figure HE003: Progression-free survival, piecewise model

The survival curves for the reference strategy, nivolumab, were generated by fitting generalised gamma and piecewise exponential models to the recreated patient level data for OS and PFS, respectively. The NMA model generates the treatment effects relative to nivolumab for the other strategies. The treatment effects for the two-parameter generalised gamma model are the location parameter, mu, and the scale parameter, sigma. The treatment effects for the three-interval piecewise model are lambda_1, lambda_2, and lambda_3, for each time interval. The coefficients for the overall survival and progression-free survival models are in Table HE023 and Table HE024, respectively.

BRAF wild type subgroup analysis

The *BRAF* wild type analysis only compared the immunotherapies (nivolumab, pembrolizumab, and ipilimumab in combination with nivolumab) since *BRAF*/MEK inhibitors are not indicated for *BRAF* wild type patients. The NMA was conducted for overall survival using only data for people with *BRAF* wild type melanoma only. This was identified from trials that enrolled people with *BRAF* wild type melanoma and reported OS and PFS data for those with *BRAF* wild type melanoma separately to those with *BRAF* mutant melanoma; subsequently, the included trials in the network were CheckMate-067 and KeyNote-006. It was not possible to conduct an NMA for progression-free survival in this subgroup since KeyNote-006, the only included trial that provides evidence for pembrolizumab, did not provide the aggregate data for this outcome stratified by *BRAF* status. The parameters for the nivolumab reference overall survival curve and the treatment effect hazard ratios for the

other therapies are presented in Table HE025. Further details of the NMA are detailed in the Network meta-analysis report.

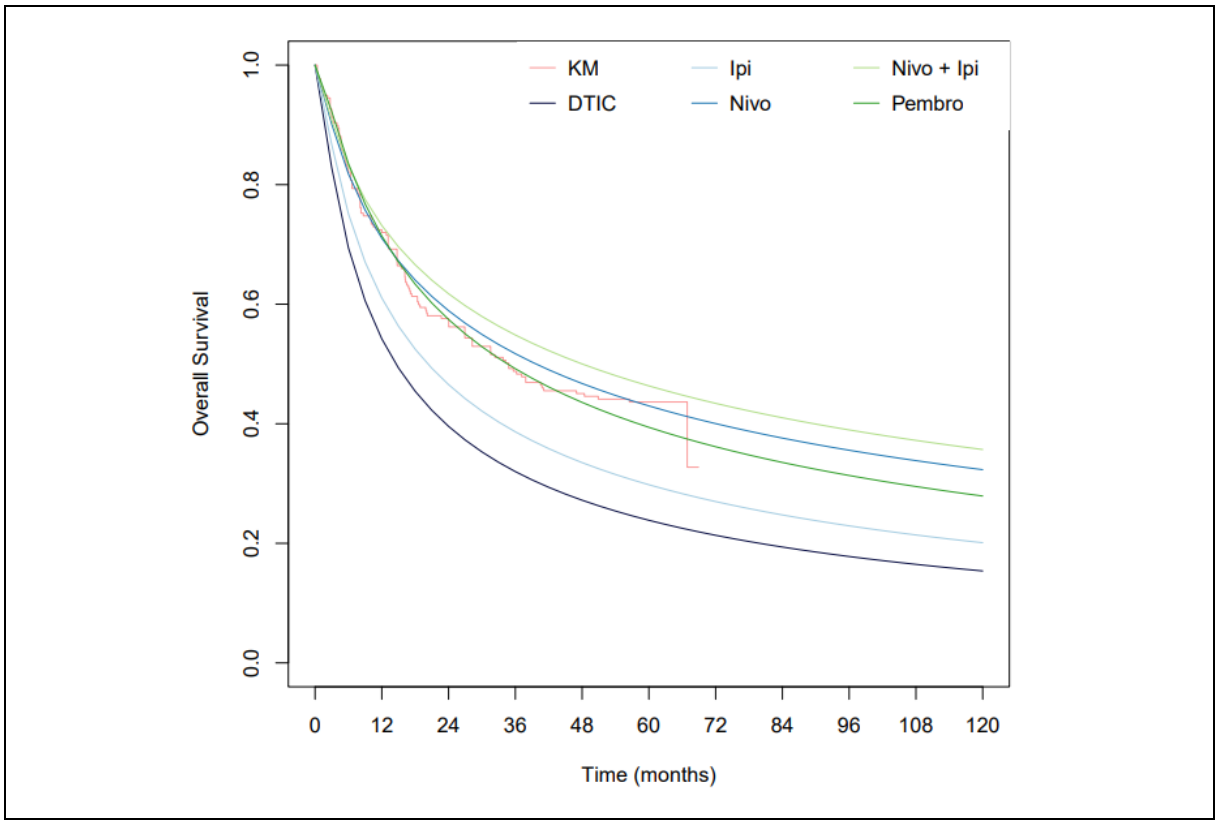

Figure HE004: Overall survival for *BRAF* wild type subgroup, generalised gamma model

The economic model for the *BRAF* wild type subgroup is largely the same as for the base-case, with modifications to parameters where *BRAF*/MEK inhibitors have been excluded. These modified parameters include the distributions of second line therapies, adverse event costs and health state utility values. Details of these modifications are provided in the relevant sections.

BRAF mutant subgroup analysis

An analysis was considered for the *BRAF* mutant subgroup, for a network including the same five comparators included in the base case analysis of the mixed population, and including only data for people with *BRAF* mutant melanoma in the NMA. The exclusion of certain trials which did not provide survival data by *BRAF* status meant that it was not possible to create a fully connected network of trials that is required to conduct the NMA, as detailed in the Network meta-analysis report, so an economic analysis could not be conducted for the *BRAF* mutant subgroup. However, the pooled analysis for the mixed population estimated for the base case analysis is considered to be sufficiently representative within this subgroup of people, since the *BRAF*/MEK inhibitors are already analysed in the target population for those therapies.

HE1.4.2.2 Treatment effect duration

On committee inspection of the survival curves from the NMA, it was noted that the predicted survival curves for the *BRAF*/MEK inhibitors did not seem plausible in the long term, and that it was unlikely that treatment effects of *BRAF*/MEK inhibitors would persist indefinitely given their mode of action. The committee explained how, with targeted treatments, cancer cells

can evolve and develop resistance on treatment, whereby the cancer cell circumnavigate the BRAF/MEK pathway to find another pathway to replicate/grow.

Further, the unadjusted OS and PFS curves for dabrafenib with trametinib crossed, which is not clinically possible and indicates that those curves are not plausible extrapolations. The curves for encorafenib+binimetinib and dabrafenib+trametinib were therefore adjusted based on committee clinical opinion and visual inspection, to gradually fit to the ipilimumab curves which were agreed to be the most plausible option. The ipilimumab curves used were those from Schadendorf et al. because these curves had 10 years of follow-up which is longer than reported in other studies and the committee believed the ipilimumab trajectory was the most plausible of the curves presented. Ipilimumab was selected to adjust the BRAF/MEK curves to as the committee considered that after having BRAF/MEK inhibitors, people are likely to receive immunotherapy as the second line treatment. We do not have data on the effectiveness of therapies second line. When used as second line, immunotherapies are not as effective as when used first line so to be conservative the committee chose the worst performing immunotherapy to adjust the survival curve (i.e. ipilimumab instead of ipilimumab+nivolumab, pembrolizumab or nivolumab).

These ipilimumab curves were digitised and parameterised using the generalised gamma and piecewise exponential models for OS and PFS, respectively. The treatment effect period was assumed to be 36 months and 24 months for encorafenib+binimetinib and dabrafenib+trametinib, respectively. A treatment effect adjustment factor was applied assuming that the change towards the ipilimumab survival prediction is gradual over 12 months, and this period was varied in scenario analysis to test the impact of this assumption. With the adjustment the OS curve for each therapy increased, and the PFS curve decreased.

The adjusted curves are presented alongside the unadjusted curves in Figure HE005.

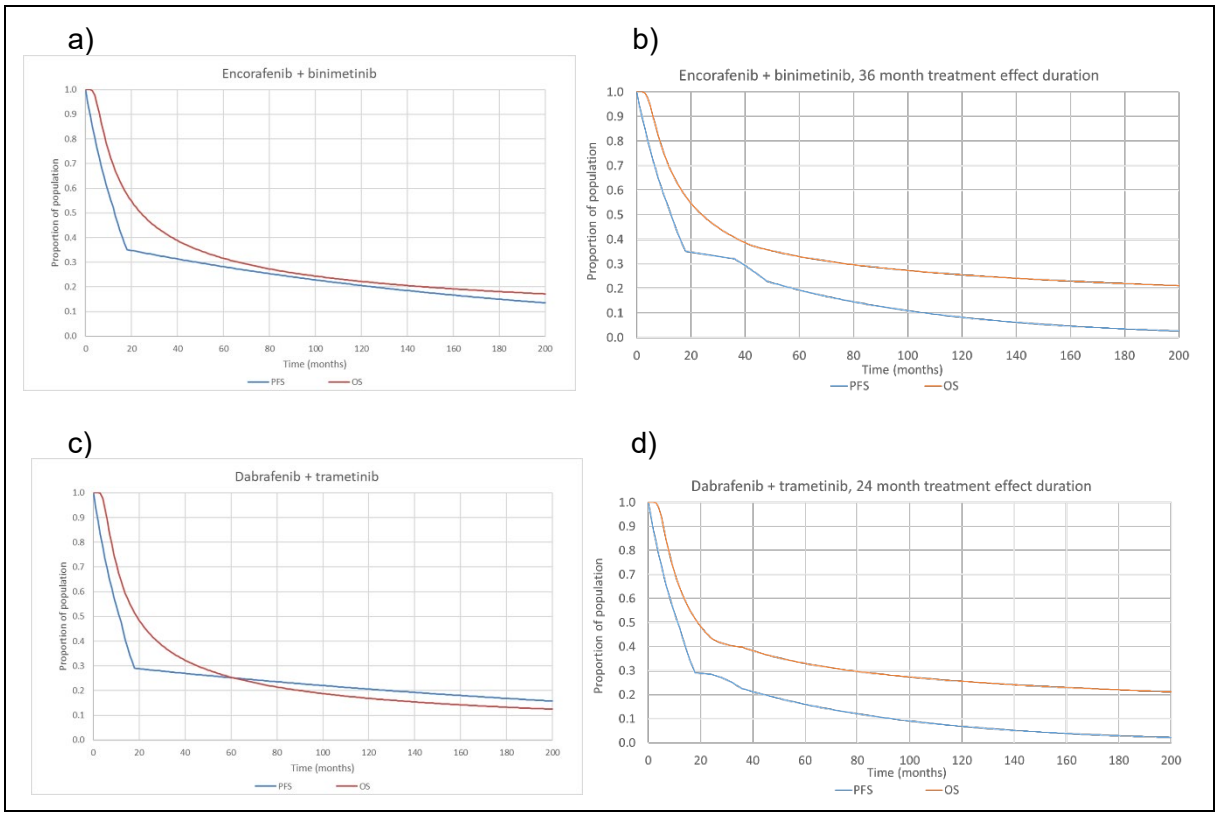

Figure HE005: Survival curves unadjusted (a, c) and adjusted (b, d) for expected duration of treatment effect

HE1.4.2.3 General population mortality adjustment

Since the model has a lifetime time horizon, it is important to account for non-melanoma mortality rather than using only the extrapolations of the trial data. Using the National life tables for England, the progression-free and overall survival curves are adjusted so that survival predictions cannot be higher than the estimates for general population survival at any time point. In the base-case, general population mortality is applied from 10 years onwards because the committee considered that patients that survive for 10 years are generally considered to be cured and are unlikely to die from melanoma. These adjusted survival curves are presented alongside the unadjusted curves in Figure HE006. The unadjusted curves visibly overestimate survival, with over 20% of people with melanoma surviving past 100 years of age. The adjustment reduces the long-term survival estimates to be below the general population mortality. Scenario analyses were conducted to assess the uncertainty around when to apply this adjustment, details of which are included in HE1.5.1.

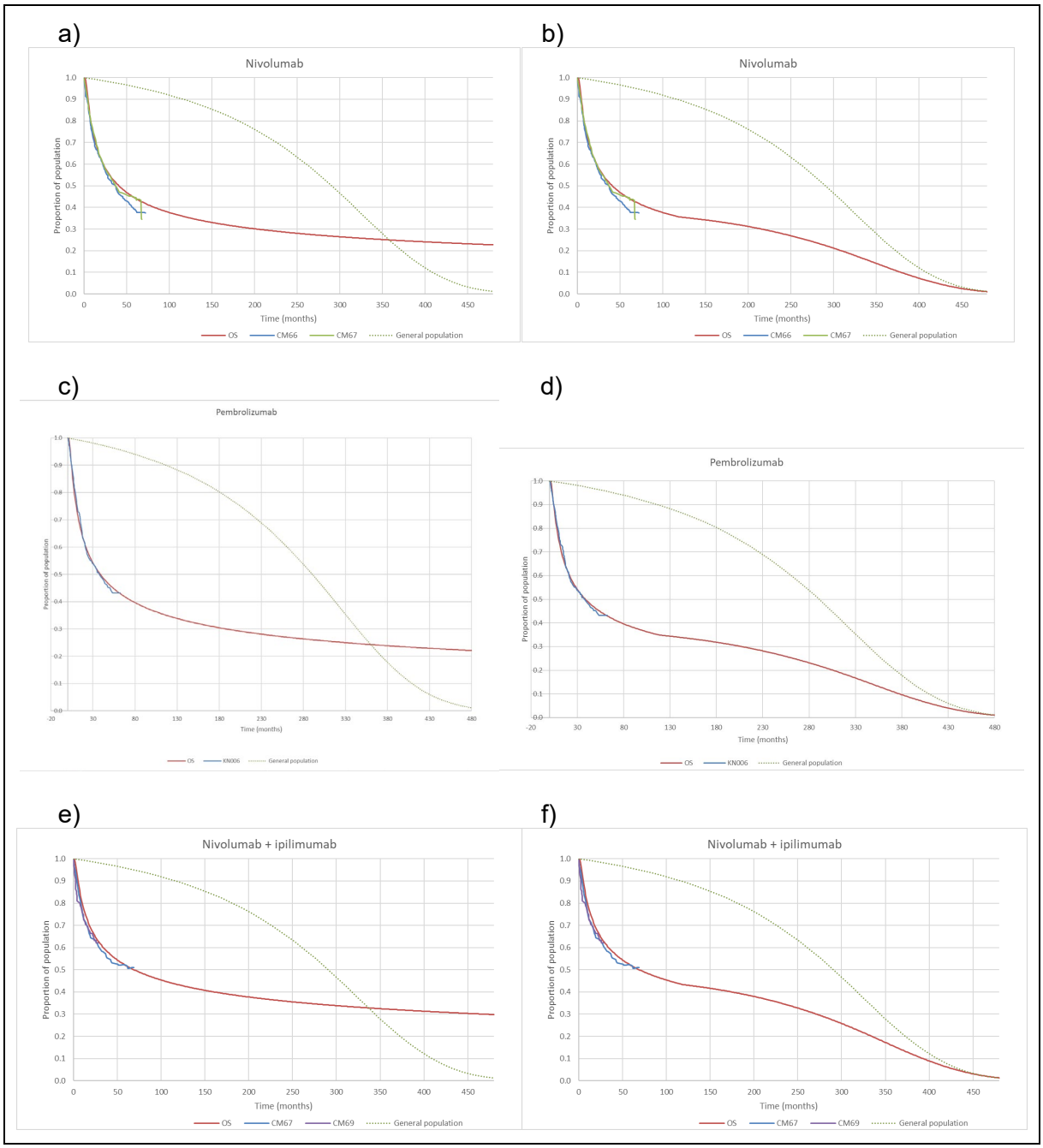

Figure HE006: Survival curves unadjusted (a, c, e) and adjusted (b, d, f) for general population mortality

HE1.4.3 Time on treatment

Time on treatment (ToT) was modelled using data from an analysis of the Systemic Anti-Cancer Therapy (SACT) database and from the respective pivotal trials for each treatment strategy. The sources of data used to model ToT in the base case and in scenario analyses are summarised in Table HE002.

Table HE002: Time on treatment data sources

Treatment	Source of data for ToT – Base case analysis	Source of data for ToT – Scenario analysis
Pembrolizumab	SACT database	KeyNote-006 (TA366)
Nivolumab	SACT database	CheckMate-066 (TA384)
Nivolumab and ipilimumab	CheckMate-067 (TA400)	SACT database
Trametinib and dabrafenib	BRF113220 (Long et al. 2018)	n/a
Encorafenib and binimetinib	Columbus (Gogas et al. 2019)	n/a

HE1.4.3.1 Treatment-specific duration of therapy

Pembrolizumab

ToT for pembrolizumab in the base case analysis was modelled using Kaplan-Meier data generated and analysed from the SACT database, which collects systemic anti-cancer therapy activity from all NHS England providers. Patients who had died or who not received treatment in the last three months, as per the follow-up in SACT, were assigned as having stopped treatment. All patients are then allocated an 'administration interval' which is a set number of days added to the end of their final treatment date to allow for the fact they are effectively still 'on treatment' until the next administration, unless a patient has died and then their date of death is used. The administrative interval for pembrolizumab was 20 days (i.e. one day less than the prescription cycle length).

The analysis for pembrolizumab was based on 1,174 patients. The median ToT was 6.18 months (95% CI 5.49 to 6.64 months), and approximately 20% of patients received treatment for at least two years.

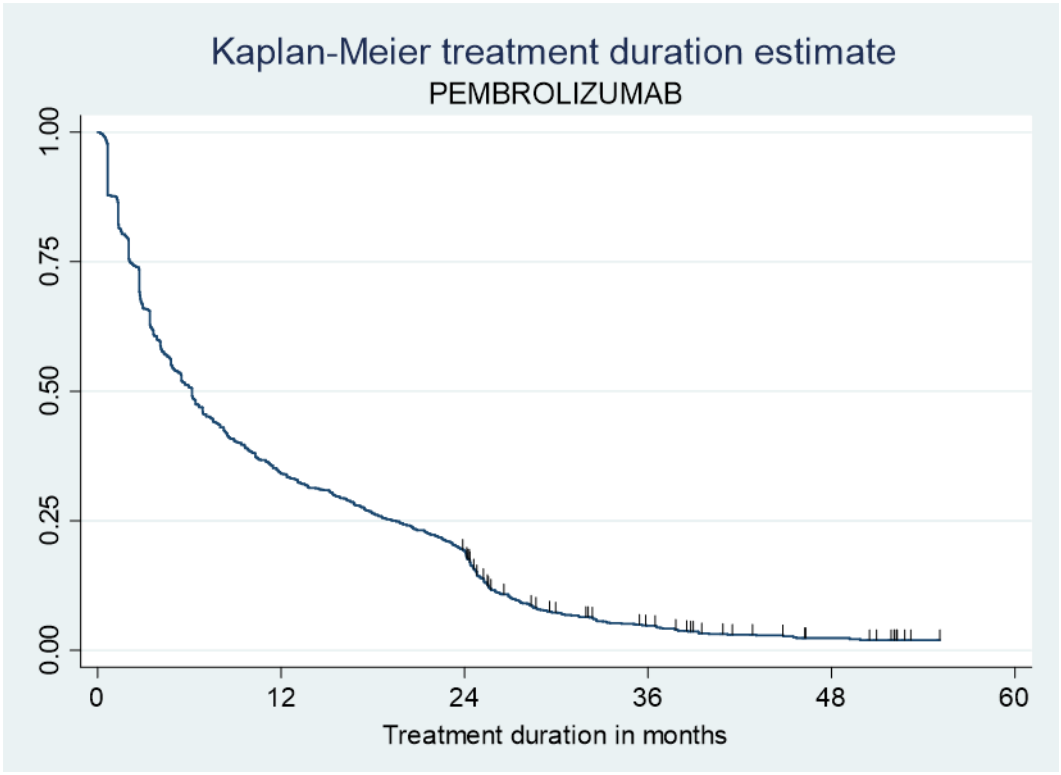

Figure HE007: Time on treatment – Pembrolizumab (SACT)

A scenario analysis explored the use of ToT data from the trial setting, although it was associated with a number of limitations. Kaplan-Meier data for ToT estimated from KeyNote-006, the pivotal trial for pembrolizumab, were not readily available, and published articles of the trial were limited to reporting the median ToT only and did not disaggregate between line of therapy. The technology appraisal of pembrolizumab for advanced melanoma (TA366) provided a Kaplan-Meier analysis of data for the Q3W arm (n=277) of KeyNote-006, alongside projected estimates of ToT using an exponential survival distribution fit to the data, pictured in Figure HE008. We digitised the ToT plot in TA366 and used this directly in the economic model in a scenario analysis.

However, the survival analysis in TA366 was based on a 1-year data cut from KeyNote-006, the most recent data available at the time of the appraisal. As a result of the immaturity of the data, there were concerns around the reliability of the extrapolation provided in TA366. No details were provided in regard to the validation of the survival model, including fit statistics of the survival model, details of other models explored or an assessment of clinical validity of projected estimates. In order to validate the extrapolation against long-term data from the trial, summary data from a published analysis of the 5-year data cut were compared to the ToT projections from the survival model. This stated that 19% of patients received treatment for two years, while the ToT extrapolation from TA366 puts the two-year treatment rate at approximately 5%. The extrapolation in Figure HE008 is also substantially lower than those estimated from SACT. As such, the ToT extrapolations from TA366 were considered to vastly underestimate the true ToT, which would then underestimate treatment costs and lead to a biased estimate of cost-effectiveness in favour of pembrolizumab in the scenario analysis that we conducted.

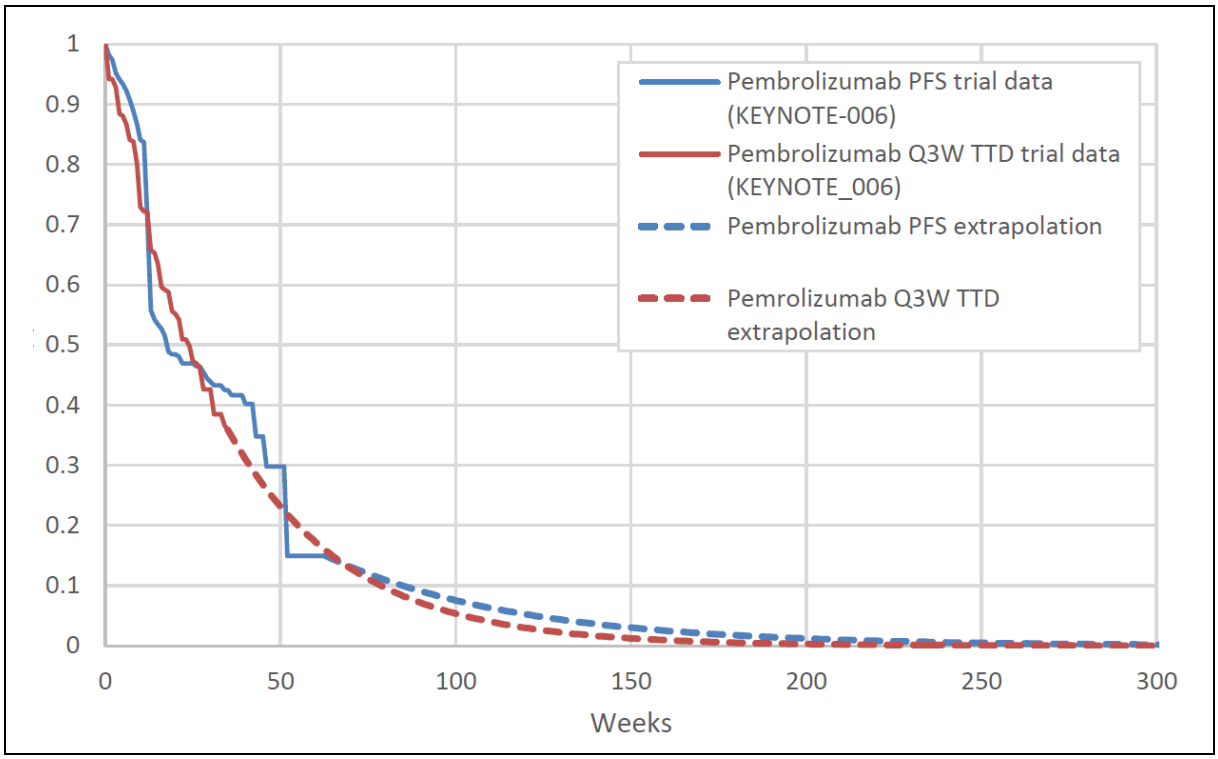

Figure HE008: Time on treatment – Pembrolizumab (TA366)

Nivolumab monotherapy

ToT for nivolumab in the base case analysis was modelled using Kaplan-Meier data generated and analysed from the SACT database, using a similar methodology as described above for pembrolizumab, although based on far fewer patients (n=52). The median ToT was 8.64 months (95% CI 3.98 to 16.07 months), and approximately 30% of patients received treatment for at least two years.

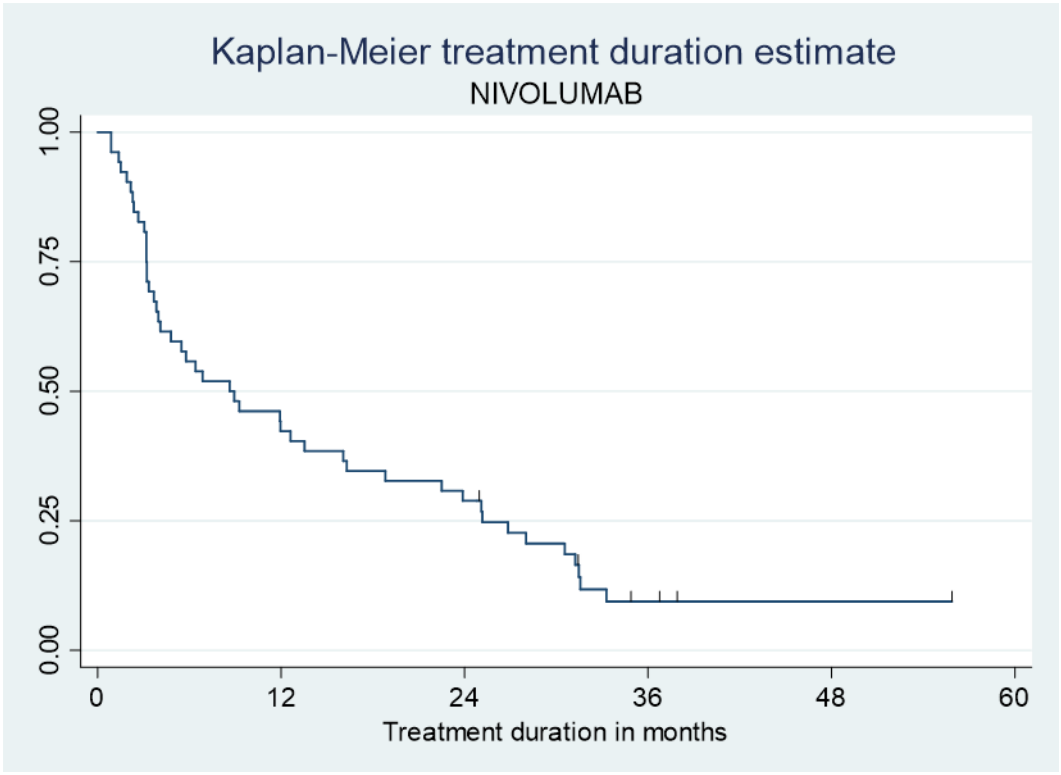

Figure HE009: Time on treatment – Nivolumab (SACT)

A scenario analysis explored the impact of incorporating trial data on ToT for nivolumab. Kaplan-Meier data for ToT estimated from the pivotal trials for nivolumab were also not readily available. The technology appraisal of nivolumab for advanced melanoma (TA384) provided a Kaplan-Meier analysis of data from CheckMate-066 for *BRAF* negative patients, alongside projected estimates of ToT using a covariate-adjusted log-logistic distribution fit to the data. ToT for people with *BRAF* mutant melanoma was inferred using patient characteristics from the vemurafenib arm of BRIM-3 in the covariate-adjusted log-logistic analysis of CheckMate-066 ToT, and was predicted to be very similar to the ToT for people with *BRAF* wild type melanoma. The survival analysis in TA384 was based on a 1-year data cut from CheckMate-066 of n=206 patients, with a large degree of censoring after 6 months, and so there were similar concerns around the maturity of the data and the robustness of the survival analysis. From a visual inspection of the KM and the extrapolation plots, the extrapolation appears to underestimate the KM.

In the analysis of the 4-year data-cut from CheckMate-067 which has a greater number of patients, both *BRAF* mutant and *BRAF* WT, the median number of doses of nivolumab monotherapy was 15 and the IQR was 6 to 54 doses. Based on the dosing schedule, 54 doses correspond to around 2 years on treatment (i.e. implying 25% on treatment at 2 years), and the extrapolation of ToT in Figure HE010 estimates around 20% on treatment at two years. Since the extrapolation appears to underestimate the ToT in CheckMate-067, SACT was the preferred source of data in the base case analysis for this parameter, although the small patient numbers is acknowledged as a limitation of this analysis.

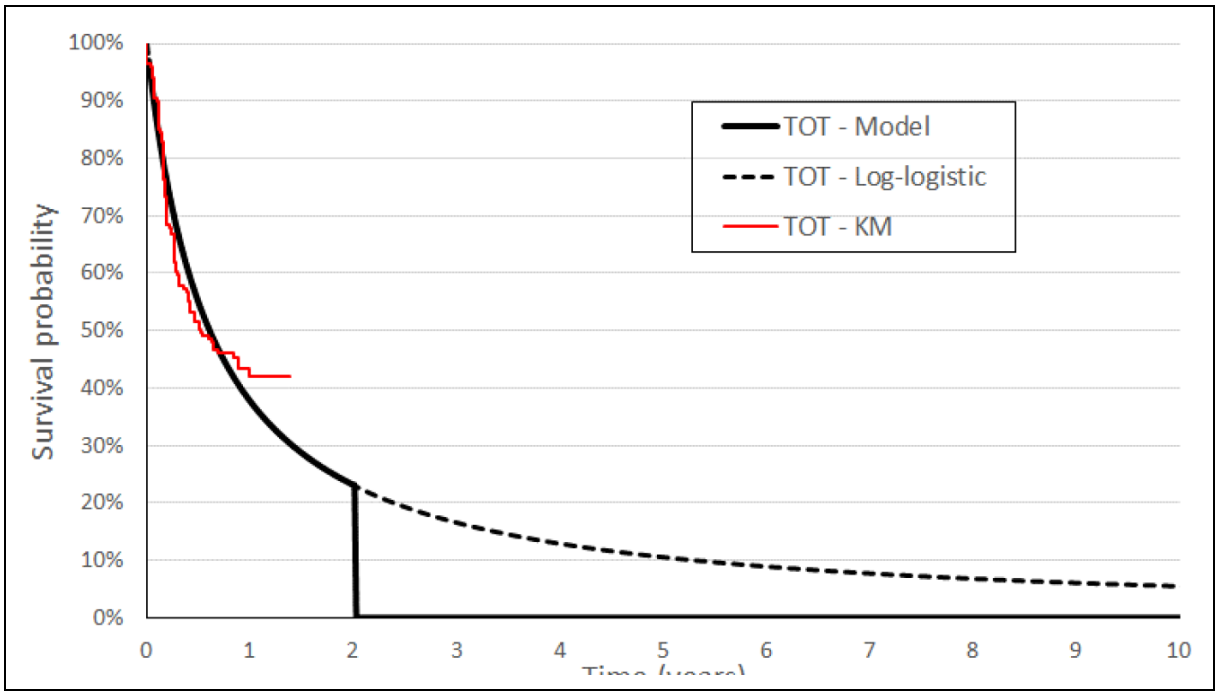

Figure HE010: Time on treatment – Nivolumab (TA384)

Nivolumab and ipilimumab

Kaplan-Meier data generated and analysed from the SACT database (n=372) was not used to model nivolumab and ipilimumab in the base case analysis due to concerns around data quality, although it was used in a scenario analysis. Although the median ToT of 2.04 months (95% CI 2.04 to 2.07 months) was very similar to that in CheckMate-067, the very low rate of patients on treatment after 6 months, alongside the stepwise discontinuation over the first three months that mirrors that of ipilimumab suggests that the maintenance phase of nivolumab was not captured appropriately and that the total treatment duration has been underestimated.

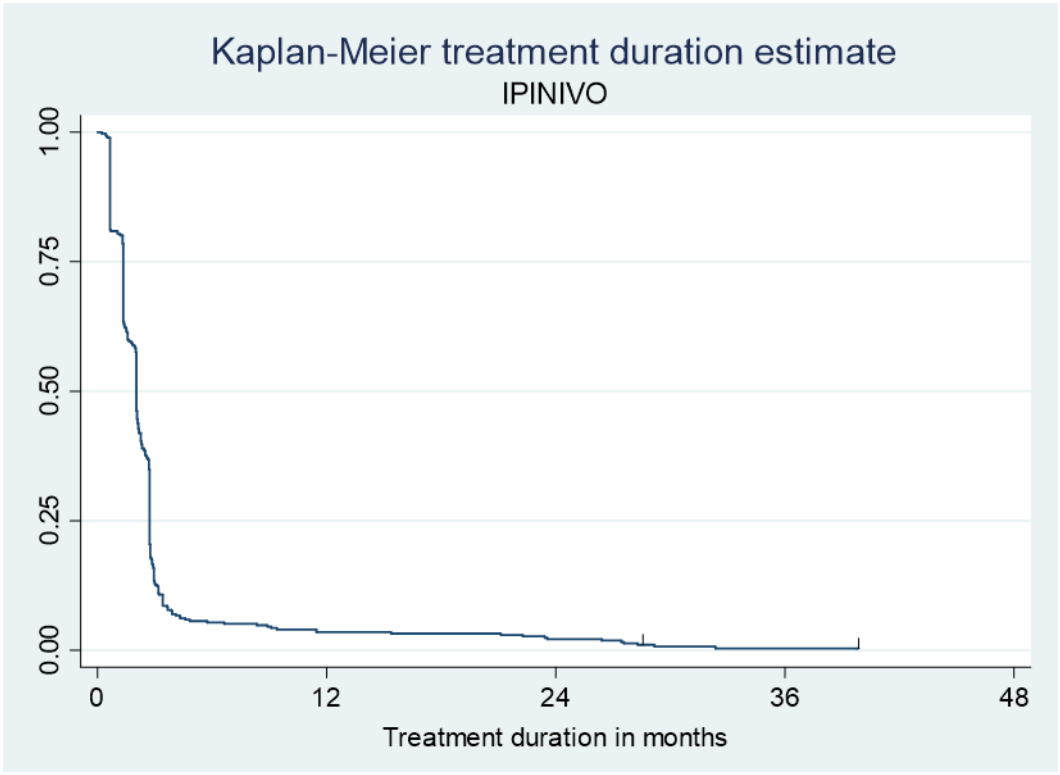

Figure HE011: Time on treatment – Nivolumab and ipilimumab (SACT)

The technology appraisal of nivolumab & ipilimumab for advanced melanoma (TA400) provided a Kaplan-Meier analysis of data from CheckMate-067 for people with *BRAF* wild type melanoma based on a one-year data cut, alongside projected estimates of ToT using a log-logistic distribution. The 4-year data cut of CheckMate-067 presented by Hodi (2018) reports a median of 4 doses and an interquartile range (IQR) of 2 to 32 doses received. Based on the dosing schedule, 32 doses correspond to around 15 months on treatment (i.e. implying 25% on treatment at 15 months) The TA400 extrapolation at 15 months gives an estimated 24% on treatment, which is not too dissimilar and lends support to the use of the projections in Figure HE012.

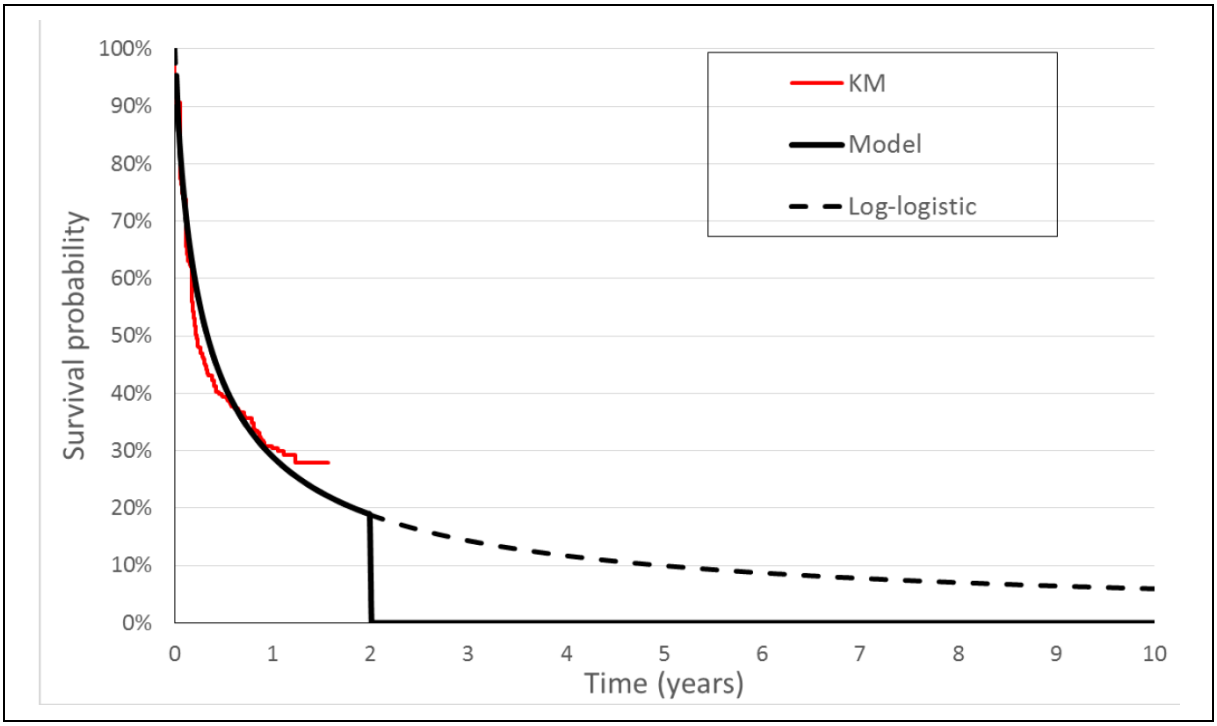

Figure HE012: Time on treatment – Nivolumab and ipilimumab (TA400)

While there are limitations with both approaches, the committee felt that the estimates from SACT were too low and preferred to use data from the technology appraisal in the base case analysis, with SACT data in scenario analyses.

In both scenarios duration of treatment with nivolumab was modelled using the approaches described above, while the duration of treatment with ipilimumab was modelled using the proportion of patients receiving each number of doses of ipilimumab in CheckMate-067 reported in Table HE003.

Table HE003: Number of doses of ipilimumab received in combination with nivolumab

Total number of doses	Proportion of patients
One dose	5.1%
Two doses	10.0%
Three doses	15.4%
Four doses	69.5%

Trametinib and dabrafenib

Data on ToT was more limited for the targeted treatments. We did not have access to SACT data for ToT for this treatment strategy, and KM data in the technology appraisal (TA396) was redacted. In this appraisal, PFS was used as a proxy for ToT; however, this was considered to be an inappropriate method for estimating treatment duration. ToT is often less than PFS due to patients stopping due to poor tolerability. Conversely, some trials permit patients to continue to receive treatment after progression. Overall, the relationship between ToT and PFS has not been demonstrated to be equivalent.

The median ToT for trametinib and dabrafenib was provided in the BRF113220 trial publication by Long et al. (2018). In this trial, the median ToT was 10.9 months (range 1.9 to 68.7 months). This was converted to a mean value for ToT assuming that it is exponentially

distributed, and was estimated to be 15.7 months. An exponential distribution was selected firstly for ease of computation: there was lack of data available to model the distribution of ToT, and the exponential distribution only has one parameter required. It is also consistent with the modelling of PFS (see HE1.4.2.1); while not appropriate to model one as a proxy of the other, it was thought not to be unreasonable to consider that the overall distribution would be similar between the two parameters. When modelling ToT over the course of the time horizon, the lambda parameter of the exponential model was set to be equal to 1/mean.

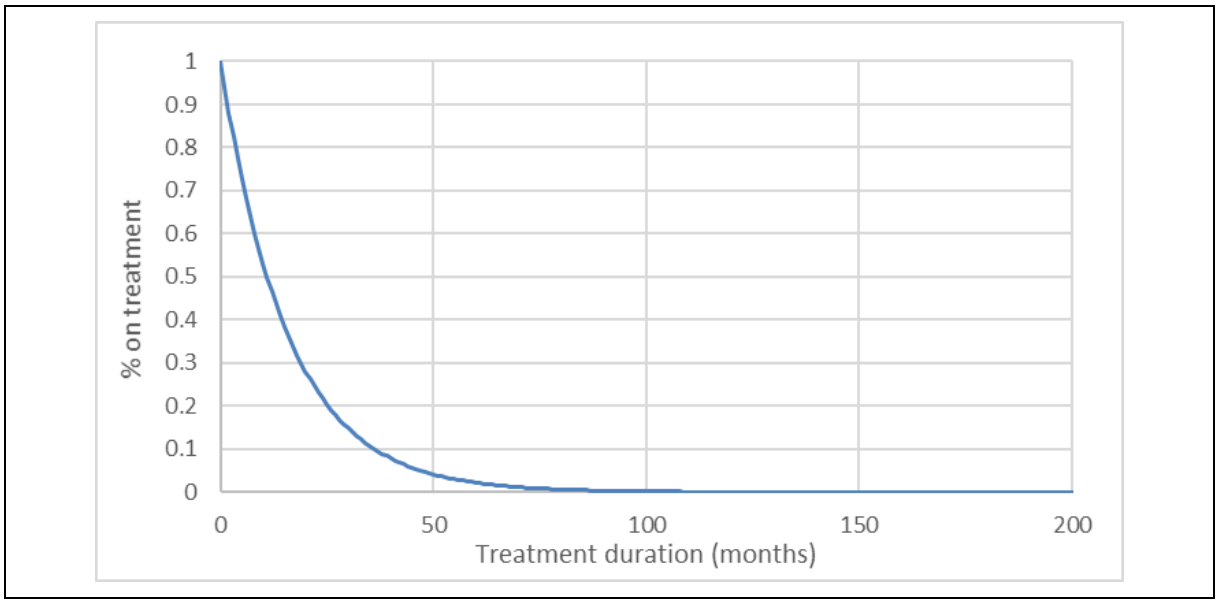

Figure HE013: Time on treatment – dabrafenib + trametinib

Encorafenib and binimetinib

We were not provided with SACT data for ToT for this treatment strategy, and KM data in the technology appraisal (TA562) was redacted. A similar approach to trametinib and dabrafenib for modelling ToT was taken.

The median ToT for encorafenib and binimetinib was provided in the Columbus trial. The median ToT was 51 weeks (IQR 27.1 to 139.1 weeks). This was converted into a mean ToT of 73.6 weeks (16.9 months) and assumed to follow an exponential distribution, where the lambda parameter of the equation is equal to 1/mean.

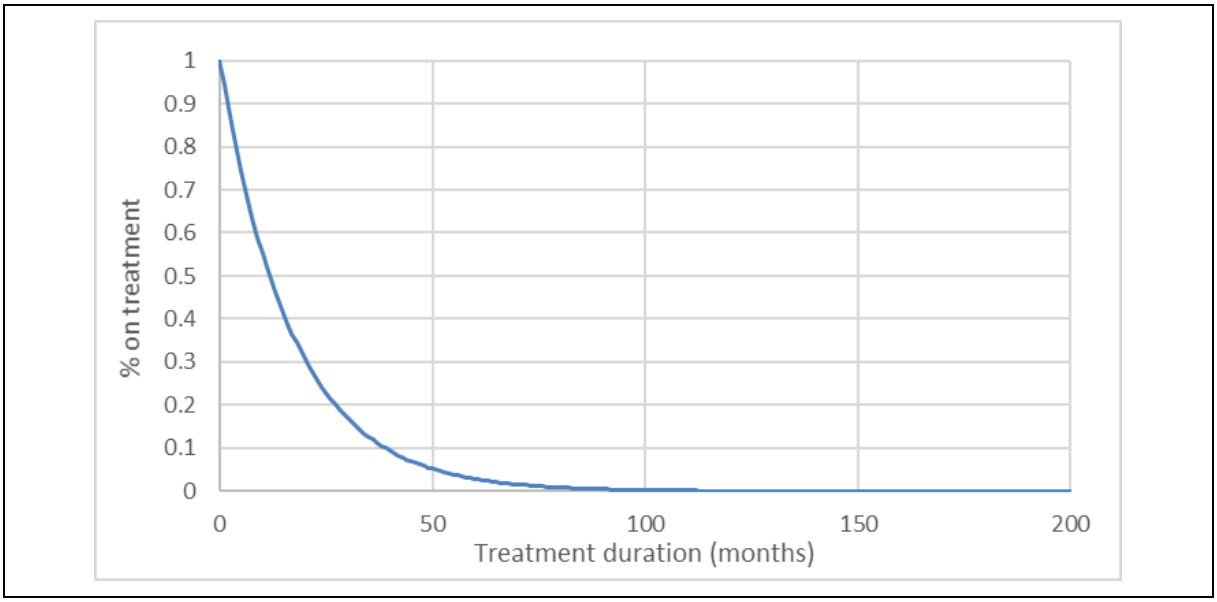

Figure HE014: Time on treatment – encorafenib + binimetinib

HE1.4.3.2 Stopping rules

In the cost-effectiveness analysis, we assumed that patients would not receive immunotherapy treatment (nivolumab, pembrolizumab, nivolumab and ipilimumab) for longer than two years. There was no time-related stopping rule applied for targeted treatment. More broadly, patients receive treatment for as long as clinical benefit is observed or until treatment is no longer tolerated; this is not modelled explicitly but is captured within the estimates of ToT presented in HE1.4.3.1. In KeyNote-006 patients were not permitted to receive pembrolizumab for longer than two years, although in other trials of immunotherapy patients were permitted to continue beyond this time. In clinical practice, the committee felt strongly that patients would not continue treatment beyond two years, based on their clinical experience. They acknowledged that a very small number of patients may have received treatment beyond two years, as reflected in the SACT data used to model ToT for pembrolizumab and nivolumab. This was the case at the time that these immunotherapies entered into practice; however, as clinician experience and confidence in treatment with these therapies has grown, they are happy to stop treatment at two years and can be sure of an ongoing immune response. As such, a scenario analysis explored the impact of dropping the stopping rule for these two therapies. In the case for nivolumab and ipilimumab, the committee felt that it was necessary to maintain the stopping rule in all scenarios and that modelling ToT as projected by Figure HE012 would overestimate the duration that patients spent on treatment.

HE1.4.4 Treatment sequencing

HE1.4.4.1 Proportion of patients receiving subsequent therapy

The proportion of patients that received subsequent therapy following discontinuation of their first-line treatment for advanced melanoma is presented in Table HE004. The proportion receiving second-line therapy was taken from the respective RCTs using the latest data available, and were reflective of the committee's experience of treating patients with advanced melanoma. The impact of using rates from a real-world cohort reported by Sacco et al. (2018) were explored in a scenario analysis.

Table HE004: Proportion of patients receiving subsequent therapy

Treatment	Patients receiving subsequent therapy – base case	Patients receiving subsequent therapy – scenario
Pembrolizumab	59% (CheckMate-067)	17% (Sacco et al.)
Nivolumab	59% (CheckMate-067)	17% (Sacco et al.)
Nivolumab and ipilimumab	46% (CheckMate-067)	41% (Sacco et al.)
Trametinib and dabrafenib	56% (Columbus)	40% (Sacco et al.)
Encorafenib and binimetinib	56% (Columbus)	40% (Sacco et al.)

The proportion of patients receiving subsequent therapy after pembrolizumab was assumed to be equivalent to those receiving subsequent therapy after nivolumab. In an analysis of the two-year datacut from KeyNote-006 presented by Schacter et al. (2017), 39% of patients on Q3W pembrolizumab started new oncologic therapy after discontinuation. The equivalent data were not reported for the analyses of more mature datacuts, and so there were concerns that this rate of subsequent therapy would be an underestimate, given that a large proportion of patients remained on treatment at their last follow-up visit. Further to this, KeyNote-006 enrolled patients who were either previously treated and treatment-naïve to systemic therapy for melanoma, and the rate of subsequent therapy was reported for the whole ITT population and not for each group of patients. It was thought that patients receiving pembrolizumab after already received systemic therapy would generally be less well than patients who were treatment naïve and were less likely to be eligible for subsequent therapy, and so the inclusion of these patients in the estimate for subsequent therapy rates would lead to it being underestimated. After discussion of these issues with the committee, they considered it most plausible that rates of subsequent therapy could be assumed equal to nivolumab given their similarities in efficacy, in the absence of more applicable evidence.

The committee also considered that the rates of subsequent therapy after encorafenib + binimetinib and after trametinib + dabrafenib would be equivalent to each other. The rate for encorafenib + binimetinib from the Columbus trial reported by Ascierto et al. (2019) was also applied for trametinib + dabrafenib. The rate in Columbus (56%) is very similar to the rate in the most mature analysis of the BRF113220 trial reported by Long et al. (2018) (54%). A lower estimate for trametinib + dabrafenib was provided by the COMBI-d study (33%), however this trial had a median follow-up of 20 months and many patients remained on study treatment at their last visit, and so this estimate was thought to be too low.

The committee noted a number of limitations with using rates of subsequent therapy from RCTs. Patients in trials are generally fitter than they are in clinical practice at the start of treatment and may be more likely to be fit enough to receive another active treatment, and so trials may overestimate the proportion of patients receiving subsequent therapy. Conversely, at the time that these trials were recruiting patients, there were fewer systemic therapy options available and so the trials may to some extent underestimate the number of patients receiving subsequent therapy due to there being less options to move onto.

To explore this uncertainty, rates from a real-world cohort reported by Sacco et al. (2018) were used in a scenario analysis. Rates of subsequent therapy were generally lower in Sacco et al. than in the RCTs. This study was a retrospective chart review (n=280) was conducted in 7 UK cancer centres, which included patients with advanced melanoma who started first line therapy. Patients received at least 1 dose between July 2016 and June 2017, and were followed for median 9 months (range <1 to 19 months).

While this dataset is more likely to be representative of advanced melanoma patients in the UK, the committee were concerned as to its validity as the rates of subsequent therapy after pembrolizumab were higher than in their experience. One possible reason was that, due to

the relatively short time horizon of the analysis, that patients remained on their first-line treatment. Secondly, patients receiving pembrolizumab are generally less well in clinical practice and therefore less likely to receive another line of systemic therapy, as those with more favourable performance status are generally given double agent nivolumab and ipilimumab. It was difficult to assess the reasons for this discrepancy in rates since the analysis was reported in abstract form and contained few details on the patient population. For this reason, the committee preferred to use the rates from the RCTs.

HE1.4.4.2 Distribution of subsequent therapies

The distribution of subsequent therapies received by those patients receiving second-line treatment is presented in Table HE005. In the base case analysis, the proportion of patients receiving each subsequent therapy was taken from the respective RCTs, adjusted to reflect treatment rules for advanced melanoma patients in England. The impact of using unadjusted rates from the trial and rates from a real-world cohort reported by Sacco et al. were explored in a scenario analysis.

Table HE005: Distribution of subsequent therapy

Treatment (first-line)	Second-line therapies	Proportion receiving 2L therapy (adjusted)	Proportion receiving 2L therapy (unadjusted)	Sacco (2018)
Pembrolizumab	Ipilimumab	60.0%	31.0%	57.0%
	Enco + bini	20.0%	11.5%	10.5%
	Dab + tram	20.0%	11.5%	10.5%
	Chemotherapy	0.0%	46.0%	22.0%
Nivolumab	Ipilimumab	60.0%	60.0%	57.0%
	Pembrolizumab	0.0%	32.0%	0.0%
	Enco + bini	20.0%	19.5%	10.5%
	Dab + tram	20.0%	19.5%	10.5%
	Chemotherapy	0.0%	43.0%	22.0%
Nivolumab and ipilimumab	Ipilimumab	0.0%	19.0%	0.0%
	Pembrolizumab	0.0%	36.0%	21.0%
	Enco + bini	19.5%	19.5%	31.5%
	Dab + tram	19.5%	19.5%	31.5%
	Chemotherapy	61.0%	47.0%	16.0%
Trametinib and dabrafenib	Ipilimumab + nivo	n/a	5.0%	71.0%
	Pembrolizumab		30.0%	29.0%
	Ipilimumab		35.0%	0.0%
	Enco + bini		20.0%	0.0%
	Chemotherapy		10.0%	0.0%
Encorafenib and binimetinib	Ipilimumab + nivo	n/a	5.0%	71.0%
	Pembrolizumab		30.0%	29.0%
	Ipilimumab		35.0%	0.0%
	Dab + tram		20.0%	0.0%
	Chemotherapy		10.0%	0.0%

The subsequent therapies used after discontinuation in each the RCTs were not reflective of clinical practice and their inclusion in the model without any adjustment would overestimate treatment costs. Funding arrangements in England, as set out in the Cancer Drugs Fund (CDF), currently allow patients to receive pembrolizumab, nivolumab or nivolumab and ipilimumab for previously untreated advanced resectable melanoma, and so patients are prohibited from receiving more than one of these immunotherapy strategies. However, the majority of patients in the RCTs used to inform subsequent therapy usage were enrolled in

non-UK centres, where no such restrictions exist, and so a large number of patients in the trials received more than immunotherapy strategy. For example, in CheckMate-067 a third of patients received second-line pembrolizumab after nivolumab and ipilimumab. An additional limitation of CheckMate-067 is that many nivolumab and ipilimumab patients received second-line ipilimumab, and the committee felt strongly that patients discontinue this regimen due to toxicity and are unlikely to receive ipilimumab second-line on this basis.

As such, to reflect clinical practice, we made adjustments to the proportions receiving each treatment second-line to reflect clinical practice. The committee considered that patients receiving nivolumab and ipilimumab first-line who are sufficiently fit to receive further systemic therapy would then either receive chemotherapy if they were *BRAF*-wild type, or a targeted treatment if they were *BRAF*-mutant. Patients receiving nivolumab or pembrolizumab would either receive ipilimumab if they were *BRAF*-wild type, or a targeted treatment if they were *BRAF*-mutant.

One of the limitations with using rates of subsequent therapy from RCTs was that there were fewer systemic therapy options available at the time that these trials were recruiting patients and so the trials may to some extent underestimate the number of patients receiving subsequent immunotherapy. For example, it is now more usual to use anti-PD1 treatment (such as nivolumab or pembrolizumab) after discontinuation on *BRAF*+MEK inhibitors rather than ipilimumab. This may mean that subsequent therapy costs are underestimated in the model for the targeted therapy arms.

Real world usage of subsequent therapy from an analysis by Sacco et al. were used in a scenario analysis. However, in addition to the limitations of this analysis described above, there were additional limitations related to generalisability with this analysis, where about a fifth of patients received pembrolizumab after nivolumab and ipilimumab, which would lead to an overestimation of costs in this arm.

In the *BRAF* wild type subgroup analysis the proportions of each subsequent therapy were altered to exclude the *BRAF*/MEK inhibitors, and instead allocate the remainder of the second line population to the other plausible therapies. In the base case this results in all pembrolizumab or nivolumab patients receiving ipilimumab second line, and all ipilimumab + nivolumab patients receiving chemotherapy second line.

HE1.4.5 Adverse events

A network meta-analysis was conducted for adverse events to inform rates of events used in the economic model using the code and methods detailed in the NICE Decision Support Unit Technical Support Document 2. Two generalised linear fixed effects models were considered for the adverse events analysis; one with a binomial likelihood and cloglog link, and one with a binomial likelihood and a logit link. Both models were checked for convergence using the history plots and the Brooks Gelman-Rubin diagnostics, and the DIC values were assessed and are presented in Table HE006. Since time is an important factor in the number of adverse events recorded and studies had different lengths of follow-up the logit model was considered less appropriate, so the cloglog model was used.

Table HE006: Adverse event models DIC

Model	DIC
Binomial likelihood, cloglog link	147.241
Binomial likelihood, logit link	147.361

The clinical trials and therapies included in the network are those listed in Table HE007, and the network is presented in Figure HE015. The outcome of interest was grade 3-5 adverse events.

Table HE007: Adverse event NMA data

Clinical trial	Study treatment	Events (n)
CHECKMATE 066	Nivolumab	33 (206)
CHECKMATE 066	Dacarbazine	36 (205)
KEYNOTE 006	Pembrolizumab 10mg/2wk	102 (555)
KEYNOTE 006	Pembrolizumab 10mg/3wk	-
KEYNOTE 006	Ipilimumab	54 (256)
CHECKMATE 067	Ipilimumab + nivolumab	186 (313)
CHECKMATE 067	Nivolumab	73 (313)
CHECKMATE 067	Ipilimumab	86 (311)
CHECKMATE 069	Ipilimumab + nivolumab	51 (94)
CHECKMATE 069	Ipilimumab	9 (46)
COLUMBUS	Encorafenib + binimetinib	131 (192)
COLUMBUS	Encorafenib	130 (192)
COLUMBUS	Vemurafenib	122 (186)
BRF113220	Dabrafenib + trametinib(1mg)	29 (54)
BRF113220	Dabrafenib + trametinib(2mg)	37 (55)
BRF113220	Dabrafenib	25 (53)
COMBI-V	Dabrafenib + trametinib	170 (350)
COMBI-V	Vemurafenib	203 (349)
COMBI-D	Dabrafenib + trametinib	67 (209)
COMBI-D	Dabrafenib	66 (211)
BRIM 3	Vemurafenib	252 (336)
BRIM 3	Dacarbazine	123 (287)

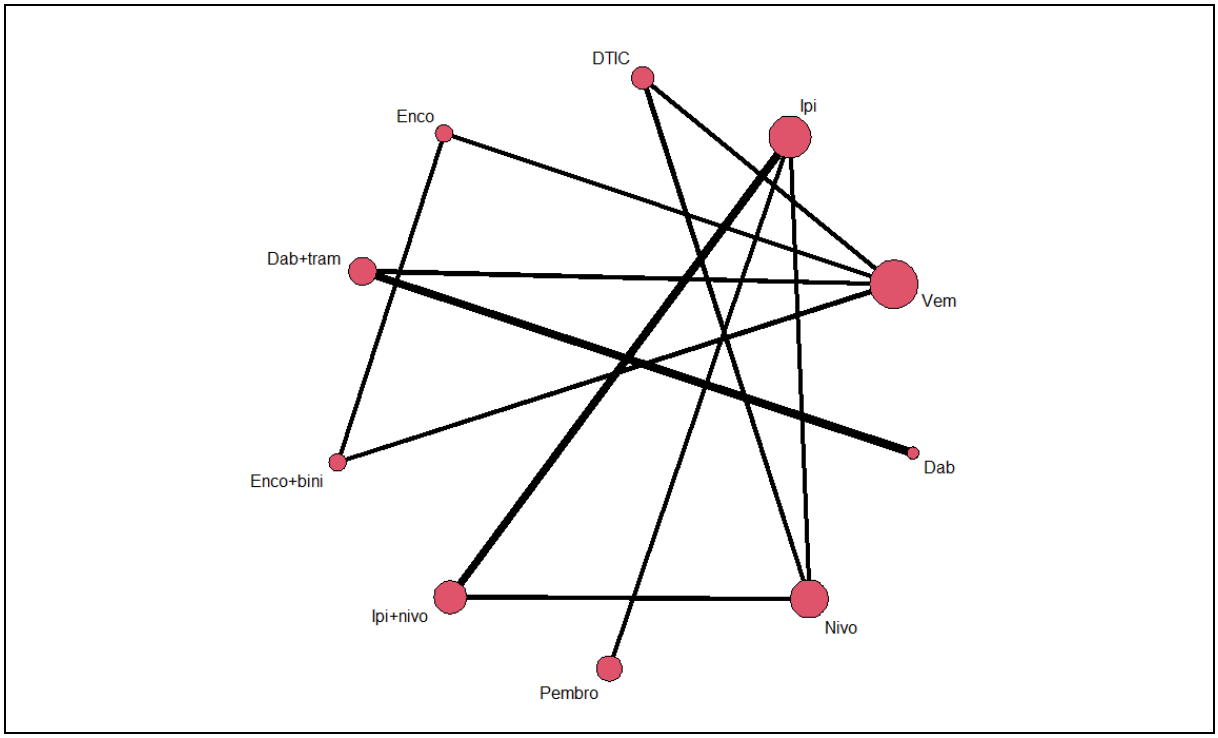

Figure HE015: Adverse event NMA network

The reference treatment was selected as nivolumab from the CheckMate-067 trial, and the treatment effects for the other modelled treatments were generated as hazard ratios relative to nivolumab.

Table HE008: Adverse event NMA results

Parameter	Value	95% CI
Nivolumab baseline hazard rate	0.044	0.035 – 0.055
Pembrolizumab hazard ratio	1.059	0.660 – 1.622
Ipilimumab + nivolumab hazard ratio	3.482	2.634 – 4.553
Encorafenib + binimetinib hazard ratio	3.053	1.641 – 5.181
Dabrafenib + trametinib hazard ratio	2.160	1.198 – 3.633
Ipilimumab hazard ratio	1.210	0.881 – 1.627
DTIC hazard ratio	1.132	0.689 – 1.756

HE1.4.6 Quality of life

HE1.4.6.1 Health state utility

To evaluate quality of life in the model, utility values are attached to each health state and are applied for the proportion of patients in a health state in each cycle for the duration of the cycle. The modelled values were taken from the technology appraisals in advanced melanoma for the therapies included in the model (see Appendix B), and in the base-case an average of all values for each health state were used. An unweighted average was considered appropriate here as all values in the TAs were derived from the relevant trials with none of them considered to be better or worse estimates. A scenario was considered in which the health state utility values for PFS and PPS were estimated separately for the two modes of treatment; immunotherapies and *BRAF*/MEK inhibitors. The *BRAF* wild type subgroup analysis used the immunotherapy-only utility values. The utility values used in the model base-case and scenarios are presented in Table HE009.

Table HE009: Health state utility values

Health state	Average of all Tx	Immunotherapies	*BRAF*/MEK inhibitors
PFS	0.7977	0.7785	0.8050
PPS	0.6885	0.7142	0.6823

HE1.4.6.2 Adverse events

The effects of adverse events on quality of life are included in the model as a one-off QALY decrement of -0.12 at the time the adverse event occurs. This value was taken from a cross-sectional study eliciting utilities for advanced melanoma health states (Beusterien et al. (2009)). The value used is an average of the UK elicited values for two events; a 1-day inpatient or outpatient stay for severe toxicity (grade III/IV), and a 2–5-day hospitalisation for severe toxicity (grade III/IV). This approach has been used in previous technology appraisals. The impact of this QALY decrement was tested in a scenario where it was excluded and the impact of adverse events was assumed to be implicitly captured in the health state utility values.

HE1.4.7 Cost and healthcare resource use identification, measurement and valuation

HE1.4.7.1 Direct costs of interventions

Drug costs were taken from the British National Formulary and are presented in Table HE010 alongside the dosing information and calculated cost per model cycle (one month). The modelled therapies all have confidential patient access schemes (PAS) which are not presented in this report but were used to generate model results for committee discussion during development of recommendations. All PAS were simple price discounts. Results using

the PAS prices were generated and presented to the committee for the base-case analysis and all sensitivity analyses. All analyses in this report are based on the list prices of the therapies, with the results of the PAS price analyses described qualitatively.

First line treatment costs for immunotherapies are applied in every cycle to the proportion of people still on treatment as per the ToT curves. For *BRAF*/MEK inhibitors the treatment costs are applied in every cycle to the proportion of people still on treatment using

Table HE010: Drug costs

Strategy	Pack size	Dosage	List price	Cost per month
Nivolumab	1x240mg	240mg every 2 weeks	£2,633.00	£5,704.83
Pembrolizumab	1x100mg	200mg every 3 weeks	£2,630.00	£7,597.78
Ipilimumab (with nivo)	1x50mg	3mg/kg every 3 weeks	£3,750.00	£27,083.33
Nivolumab (with ipi)	1x40mg	1mg/kg every 3 weeks	£439.00	£1,268.22
Encorafenib (with bini)	28x50mg	450mg per day	£622.22	£6,087.48
Binimetinib (with enco)	84x15mg	45mg twice a day	£2,240.00	£4,870.00
Dabrafenib (with tram)	28x50mg	300mg per day	£933.33	£6,087.48
Trametinib (with dab)	7x2mg	2mg per day	£1,120.00	£4,870.00
Ipilimumab	1x50mg	3mg/kg every 3 weeks	£3,750.00	£27,083.33
DTIC (dacarbazine)	1x1000mg	850mg/m² every 3 weeks	£70.00	£165.87

HE1.4.7.2 Administration costs

Administration costs for each strategy were informed by those used in the relevant technology appraisals and are detailed in Table HE011. For all of the immunotherapies the administration cost is applied for the number of doses per model cycle (one month), and for the *BRAF*/MEK inhibitors the administration cost is simply a prescription dispensing cost applied once per model cycle.

Table HE011: Administration costs

Strategy	Cost	Source
Ipilimumab, nivolumab	£306.90	TA400 and TA384, NHS Reference costs HRG code SB13Z
Pembrolizumab	£241.06	TA366, NHS Reference costs HRG code SB12Z
Encorafenib+binimetinib, dabrafenib+trametinib	£10.00	Cost of 12 minutes of hospital pharmacist time (hourly rate of a hospital pharmacist £50÷5=£10.00) PSSRU

HE1.4.7.3 Second line costs

Second line therapies following each first line therapy are defined in HE1.4.4. The per-cycle costs associated with second line therapies are the same as those listed in HE1.4.7.1 and HE1.4.7.2, but these costs are applied as a one-off at the time of starting second line therapy, multiplied by the mean ToT for these therapies. A potential limitation of this

approach is that the cost of second line therapy may be overestimated since people may be on treatment for a shorter time during second line therapy.

HE1.4.7.4 Costs associated with health states

Health state costs are attached to each health state and are applied for the proportion of patients in a health state in each cycle for the duration of the cycle. The modelled costs were taken from the technology appraisals in advanced melanoma (see Appendix B), and in the base-case an average of all values for each health state were used. Costs associated with palliative care and terminal care were also included in the model and were applied at the time of death. The health state costs used in the model are presented in Table HE012.

Table HE012: Health state costs

Health state	Average cost from all TAs
PFS	£323.69
PPS	£490.32
Palliative care for 3 months (applied at death)	£3,642.02
Terminal care (applied at death)	£6,369.82

HE1.4.7.5 Adverse events

Costs associated with adverse events were applied in the model as one-off costs when the event occurred. The cost of an average adverse event was calculated by taking the adverse events that were grade 3 or above and occurring in more than one person from the clinical trials, and assigning a cost of treating that event. The adverse events included are presented in Table HE013, and the calculated average cost of events (estimated as a simple average of costs) used in the model was £434.54. To test the impact of AE costs on the results, scenario analyses were conducted using the highest and lowest costs reported in Table HE013.

The data informing adverse events was taken from the clinical trials, however the committee noted that there are limitations with this data as it may not capture all of the long-term toxicity.

Table HE013: Adverse event costs

Adverse event	Cost	Cost reference
Nausea	£167.24	NHS National Cost Collection data [2018/19] – total outpatient attendances, general medicine
Diarrhoea	£167.24	NHS National Cost Collection data [2018/19] – total outpatient attendances, general medicine
Vomiting	£167.24	NHS National Cost Collection data [2018/19] – total outpatient attendances, general medicine
Fatigue	£167.24	NHS National Cost Collection data [2018/19] – total outpatient attendances, general medicine
Arthralgia	£157.20	NHS National Cost Collection data [2018/19] – total outpatient attendances, pain management, service code 191
Colitis	£140.89	NHS National Cost Collection data [2018/19] – total outpatient attendances, gastroenterology, service code 301
Pyrexia	£1,893.48	NHS National Cost Collection data [2018/19] – elective inpatient stay and excess bed days, weighted average of codes WJ07A-WJ07D, fever of unknown origin

Adverse event	Cost	Cost reference
Abdominal pain	£157.20	NHS National Cost Collection data [2018/19] – total outpatient attendances, pain management, service code 191
Rash	£112.88	NHS National Cost Collection data [2018/19] – total outpatient attendances, dermatology, service code 330
Hypertension	£598.58	NHS National Cost Collection data [2018/19] – total cases, code EB04Z, hypertension total cases
Back pain	£157.20	NHS National Cost Collection data [2018/19] – total outpatient attendances, pain management, service code 191
Peripheral edema	£575.99	NHS National Cost Collection data [2018/19] – weighted average of codes WH10A and WH10B, unspecified oedema
Pain in extremity	£157.20	NHS National Cost Collection data [2018/19] – total outpatient attendances, pain management, service code 191
Increased aspartate aminotransferase	£195.63	NHS National Cost Collection data [2018/19] – total outpatient attendances, hepatology, service code 306
Hepatitis	£1,702.94	NHS National Cost Collection data [2018/19] – weighted average of codes GC17A-GC17K, Non-Malignant Hepatobiliary or Pancreatic Disorders
Average	**£434.54**	-

Adverse event costs were also estimated separately for the two modes of treatment; immunotherapies and *BRAF*/MEK inhibitors and the *BRAF* wild type subgroup analysis used the immunotherapy only adverse event costs. Adverse events were included in the immunotherapy costing if they had been included in trials for at least two of the four immunotherapies. The modelled adverse event cost for immunotherapies only is £347.86.

HE1.4.8 Summary

All parameters used in the model are summarised in Table HE014, including details of the distributions and parameters used in probabilistic analysis.

Table HE014: All parameters in original cost–utility model

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Model settings				
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	12	N/A	N/A	N/A
Cycle length (months)	1	N/A	N/A	N/A
Time horizon as a maximum age (years of age)	101	N/A	N/A	N/A, assumed lifetime
Baseline				
Starting age	59	N/A	N/A	Average from clinical trials in treatments for advanced melanoma
Sex (% male)	60.9%	N/A	N/A	Average from clinical trials in treatments for advanced melanoma

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Weight (kg)	80	N/A	N/A	Break-3 clinical trial
Body surface area (m²)	1.93	N/A	N/A	Break-3 clinical trial
BRAF status (% *BRAF* mutant)	31.6%	N/A	N/A	TA400
Second line therapy				
Patients going on to 2L therapy after nivo (%)	59.00%	Beta	α=1.603 β=1.114	CheckMate067 clinical trial
Patients going on to 2L therapy after pembro (%)	59.00%	Beta	α=1.035 β=1.620	Assumed the same as for nivo
Patients going on to 2L therapy after ipi+nivo (%)	46.00%	Beta	α=1.296 β=1.521	CheckMate067 clinical trial
Patients going on to 2L therapy after enco+bini (%)	56.00%	Beta	α=1.560 β=1.226	COLUMBUS clinical trial
Patients going on to 2L therapy after dab+tram (%)	56.00%	Beta	α=1.560 β=1.226	COLUMBUS clinical trial
Patients receiving 2L ipi after 1L nivo (%)	60.00%	Beta	α=1.613 β=1.075	Clinical trials adjusted to fit CDF rules
Patients receiving 2L pembro after 1L nivo (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L enco+bini after 1L nivo (%)	20.00%	N/A	1 minus probabilistic value for 2L ipi, halved	Clinical trials adjusted to fit CDF rules
Patients receiving 2L dab+tram after 1L nivo (%)	20.00%	N/A	1 minus probabilistic value for 2L ipi, halved	Clinical trials adjusted to fit CDF rules
Patients receiving 2L chemo after 1L nivo (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi after 1L pembro (%)	60.00%	Beta	α=1.613 β=1.075	Clinical trials adjusted to fit CDF rules
Patients receiving 2L enco+bini after 1L Pembro (%)	20.00%	N/A	1 minus probabilistic value for 2L ipi, halved	Clinical trials adjusted to fit CDF rules
Patients receiving 2L dab+tram after 1L pembro (%)	20.00%	N/A	1 minus probabilistic value for 2L ipi, halved	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi after 1L pembro (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi after 1L ipi+nivo (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L pembro after 1L ipi+nivo (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L enco+bini after 1L ipi+nivo (%)	19.50%	N/A	1 minus probabilistic value for 2L chemo, halved	Clinical trials adjusted to fit CDF rules

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Patients receiving 2L dab+tram after 1L ipi+nivo (%)	19.500%	N/A	1 minus probabilistic value for 2L chemo, halved	Clinical trials adjusted to fit CDF rules
Patients receiving 2L chemo after 1L ipi+nivo (%)	61.00%	Beta	α=1.620 β=1.036	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi+nivo after 1L enco+bini (%)	71.00%	Beta	α=1.536 β=0.628	Clinical trials adjusted to fit CDF rules
Patients receiving 2L pembro after 1L enco+bini (%)	29.00%	N/A	1 minus probabilistic value for 2L ipi+nivo	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi after 1L enco+bini (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L enco+bini after 1L enco+bini (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L dab+tram after 1L enco+bini (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L chemo after 1L enco+bini (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi+nivo after 1L dab+tram (%)	71.00%	Beta	α=1.536 β=0.628	Clinical trials adjusted to fit CDF rules
Patients receiving 2L pembro after 1L dab+tram (%)	29.00%	N/A	1 minus probabilistic value for 2L ipi+nivo	Clinical trials adjusted to fit CDF rules
Patients receiving 2L ipi after 1L dab+tram (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L enco+bini after 1L dab+tram (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L dab+tram after 1L dab+tram (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
Patients receiving 2L chemo after 1L dab+tram (%)	0.00%	N/A	N/A	Clinical trials adjusted to fit CDF rules
General population mortality (time of switch)				
Nivolumab (years)	10	N/A	N/A	Committee consensus
Pembrolizumab (years)	10	N/A	N/A	Committee consensus
Ipilimumab + nivolumab (years)	10	N/A	N/A	Committee consensus
Encorafenib + binimetinib (years)	10	N/A	N/A	Committee consensus
Dabrafenib + trametinib (years)	10	N/A	N/A	Committee consensus
Treatment effect (TE)				
Duration of TE - Nivolumab (months)	All time	N/A	N/A	Committee consensus

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Duration of TE - Pembrolizumab (months)	All time	N/A	N/A	Committee consensus
Duration of TE - Ipilimumab + nivolumab (months)	All time	N/A	N/A	Committee consensus
Duration of TE - Encorafenib + binimetinib (months)	36	N/A	N/A	Committee consensus
Duration of TE - Dabrafenib + trametinib (months)	24	N/A	N/A	Committee consensus
TE adjustment factor - Nivolumab (months)	12	N/A	N/A	Committee consensus
TE adjustment factor - Pembrolizumab (months)	12	N/A	N/A	Committee consensus
TE adjustment factor - Ipilimumab + nivolumab (months)	12	N/A	N/A	Committee consensus
TE adjustment factor - Encorafenib + binimetinib (months)	12	N/A	N/A	Committee consensus
TE adjustment factor - Dabrafenib + trametinib (months)	12	N/A	N/A	Committee consensus
Natural history (nivolumab)				
Generalised gamma, overall survival, mu	2.35277	Multivariate normal	Covariance matrix Table HE026	CheckMate067 clinical trial digitised survival curves
Generalised gamma, overall survival, sigma	1.51144	Multivariate normal	Covariance matrix Table HE026	CheckMate067 clinical trial digitised survival curves
Generalised gamma, overall survival, Q	-2.04634	Multivariate normal	Covariance matrix Table HE026	CheckMate067 clinical trial digitised survival curves
Piecewise exponential, progression-free survival, months 0-12	0.08048	NMA CODA simulations	N/A	CheckMate067 clinical trial digitised survival curves
Piecewise exponential, progression-free survival, months 13-18	0.01254	NMA CODA simulations	N/A	CheckMate067 clinical trial digitised survival curves
Piecewise exponential, progression-free survival, months 19+	0.00827	NMA CODA simulations	N/A	CheckMate067 clinical trial digitised survival curves
Treatment efficacy parameters				
Generalised gamma, overall survival, pembrolizumab mu	-0.03646	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, ipilimumab+nivolumab mu	0.25940	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, encorafenib+binimetinib mu	-0.03601	NMA CODA simulations	N/A	Network meta-analysis

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Generalised gamma, overall survival, dabrafenib+trametinib mu	-0.15620	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, ipilimumab mu	-0.58630	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, pembrolizumab sigma	-0.01878	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, ipilimumab+nivolumab sigma	0.29490	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, encorafenib+binimetinib sigma	-0.55070	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, dabrafenib+trametinib sigma	-0.68480	NMA CODA simulations	N/A	Network meta-analysis
Generalised gamma, overall survival, ipilimumab sigma	-0.19050	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, pembrolizumab 0-12 months	0.89299	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, ipilimumab+nivolumab 0-12 months	0.76205	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, encorafenib+binimetinib 0-12 months	0.67252	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, dabrafenib+trametinib 0-12 months	0.76346	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, ipilimumab 0-12 months	1.97340	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, pembrolizumab 13-18 months	3.38885	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, ipilimumab+nivolumab 13-18 months	1.02253	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, encorafenib+binimetinib 13-18 months	5.25605	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, dabrafenib+trametinib 13-18 months	6.63109	NMA CODA simulations	N/A	Network meta-analysis

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Piecewise exponential, progression-free survival, ipilimumab 13-18 months	3.31662	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, pembrolizumab 19+ months	1.81419	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, ipilimumab+nivolumab 19+ months	0.68407	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, encorafenib+binimetinib 19+ months	0.63531	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, dabrafenib+trametinib 19+ months	0.40593	NMA CODA simulations	N/A	Network meta-analysis
Piecewise exponential, progression-free survival, ipilimumab 19+ months	1.71763	NMA CODA simulations	N/A	Network meta-analysis
Adverse event (AE) rate, nivolumab	0.044	NMA CODA simulations	N/A	Network meta-analysis
Pembrolizumab AE hazard ratio vs nivolumab	1.059	NMA CODA simulations	N/A	Network meta-analysis
Ipilimumab + nivolumab AE hazard ratio vs nivolumab	3.482	NMA CODA simulations	N/A	Network meta-analysis
Encorafenib + binimetinib AE hazard ratio vs nivolumab	3.053	NMA CODA simulations	N/A	Network meta-analysis
Dabrafenib + trametinib AE hazard ratio vs nivolumab	2.160	NMA CODA simulations	N/A	Network meta-analysis
Ipilimumab AE hazard ratio vs nivolumab	1.210	NMA CODA simulations	N/A	Network meta-analysis
DTIC AE hazard ratio vs nivolumab	1.132	NMA CODA simulations	N/A	Network meta-analysis
Time on treatment (ToT)				
2L after nivolumab ToT (months)	7.77	Gamma	N/A – uses average of probabilistic values of mean ToT	Calculated: mean ToT from clinical trials, % of patients on that therapy as 2L
2L after pembrolizumab ToT (months)	7.77	Gamma	N/A – uses average of probabilistic values of mean ToT	Calculated: mean ToT from clinical trials, % of patients on that therapy as 2L
2L after ipilimumab+nivolumab ToT (months)	8.81	Gamma	N/A – uses average of probabilistic values of mean ToT	Calculated: mean ToT from clinical trials, % of patients on that therapy as 2L

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
2L after encorafenib+binimetinib ToT (months)	13.97	Gamma	N/A – uses average of probabilistic values of mean ToT	Calculated: mean ToT from clinical trials, % of patients on that therapy as 2L
2L after dabrafenib+trametinib ToT (months)	13.97	Gamma	N/A – uses average of probabilistic values of mean ToT	Calculated: mean ToT from clinical trials, % of patients on that therapy as 2L
Costs				
Nivolumab (1x240mg)	£2,633.00	N/A	N/A	British National Formulary
Pembrolizumab (1x100mg)	£2,630.00	N/A	N/A	British National Formulary
Ipilimumab [with nivo] (1x50mg)	£3,750.00	N/A	N/A	British National Formulary
Nivolumab [with ipi] (1x40mg)	£439.00	N/A	N/A	British National Formulary
Encorafenib [with bini] (28x50mg)	£622.22	N/A	N/A	British National Formulary
Binimetinib [with enco] (84x15mg)	£2,240.00	N/A	N/A	British National Formulary
Dabrafenib [with tram] (28x50mg)	£933.33	N/A	N/A	British National Formulary
Trametinib [with dab] (7x2mg)	£1,120.00	N/A	N/A	British National Formulary
DTIC [dacarbazine] (1x1000mg)	£70.00	N/A	N/A	British National Formulary
Administration cost: ipilimumab, nivolumab	£306.90	N/A	N/A	NHS Reference costs HRG code SB13Z
Administration cost: pembrolizumab	£241.06	N/A	N/A	NHS Reference costs HRG code SB12Z
Administration cost: encorafenib+binimetinib, dabrafenib+trametinib	£10.00	N/A	N/A	Cost of 12 minutes of hospital pharmacist time
Progression-free survival health state cost per month	£323.69	Lognormal	μ=5.780 σ=0.287	Average of PFS state costs from advanced melanoma TAs
Progressed disease health state cost per month	£490.32	Lognormal	μ=6.195 σ=0.190	Average of PPS state costs from advanced melanoma TAs
Palliative care cost (applied at death)	£3,642.02	Lognormal	μ=8.200 σ=0.189	Average of palliative care costs from advanced melanoma TAs
Terminal care cost (applied at death)	£6,369.82	Lognormal	μ=8.759 σ=0.412	Average of terminal care costs from advanced melanoma TAs
AE average cost	£434.54	Lognormal	μ=6.074 σ=0.719	Calculated in HE1.4.7.5

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Utilities				
Progression-free survival health state utility value	0.7977	Beta	α=209.429 β=53.112	Average of PFS utility values from advanced melanoma TAs
Progressed disease health state utility value	0.6885	Beta	α=295.662 β=133.767	Average of PPS utility values from advanced melanoma TAs
AE disutility (one-off decrement at time of event)	-0.12	Beta	α=31.560 β=231.440	Beusterien 2009

HE1.5 Sensitivity analyses

HE1.5.1 Deterministic sensitivity analyses

We conducted deterministic sensitivity analyses in the form of scenario analyses to identify which model parameters had a substantial impact on the overall results. The scenarios included in the analysis were chosen based on which parameters the committee felt less certain of.

Table HE015: Scenarios considered in the analysis

Section	Base-case	Scenarios
General population mortality	• Switch to general population mortality at 10 years	• Switch at 5 years • Switch at 15 years • General population mortality not applied
Treatment effect duration	• 36 months for enco + bini, 24 months for dab + tram	• 24 months for enco + bini, 12 months for dab + tram • 36 months for both enco + bini and dab + tram • No end to treatment effect
Treatment effect adjustment factor	• 12-month adjustment period	• 0-month adjustment period • 36-month adjustment period
Pembrolizumab PFS extrapolation adjustment	• No adjustment	• Hazard set equal to that of nivolumab from 24 months
Model starting age	• 59 years	• 50 years • 70 years
Data source for 2L treatment distribution	• Trial data modified to align with the CDF rules	• Unmodified trial data • Data from Sacco et al.
Data source for ToT	• SACT data for nivo and pembro. Trial data for ipi + nivo. 2 year stopping rule for all	• SACT data for all • Trial data for all • 5 year stopping rule for nivo, pembro
AEs	• AE disutility included, 2L AEs included, average AE cost used	• AE disutility excluded • 2L AEs excluded • Lowest AE cost used • Highest AE cost used

Section	Base-case	Scenarios
Utility values	• Health state utility values the same across all treatments	• Health state utility values split by treatment class

HE1.5.2 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We specified probability distributions for all input variables with the exception of drug acquisition and administration costs, baseline patient characteristics, time of switch to general population mortality, and parameters describing the adjustments to the survival curves for the targeted therapies. This was due to a lack of data on the uncertainty around the parameters and that adding an arbitrary standard deviation would increase uncertainty rather than reduce it. Instead, these parameters were examined in scenario analyses to determine their impact on the results.

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 and we use gamma distributions for cost parameters that cannot be negative). 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. For treatment effects, the mean effect was estimated from the NMA and we randomly sampled from the CODA output from WinBUGS for the probabilistic analysis.

There are three sources of costs for the model, from NHS reference costs, from the Personal Social Services Research Unit (PSSRU, Curtis 2019) and the NHS drug tariff. 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.

For all the parameters not included in the probabilistic sensitivity analysis it was felt that not including them was unlikely to be a major limitation and scenario analysis was sufficient to investigate the uncertainty of those parameters.

HE2 Results

HE2.1 Base-case cost–utility results

The results of the base-case analysis based on list prices for drugs are presented in Table HE016. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each treatment. The list price-based results show that nivolumab plus ipilimumab is the most cost-effective strategy in the base-case analysis, with an ICER of £5,148 compared with nivolumab. Pembrolizumab, dabrafenib plus trametinib, and encorafenib plus binimetinib are dominated (i.e. more costly and less effective) by nivolumab plus ipilimumab. These results are visualised in the cost utility plane in Figure HE016.

The between-treatment differences in total QALYs are fairly large, however this was not considered an issue by the committee as they agreed that the data from the NMA showed that there were significant differences in survival between the treatments and that longer progression-free and overall survival would result in more QALYs.

The committee was presented with the results of the base case and scenario analyses when the confidential PAS discounts were applied and used these results as the basis for their recommendations. These results cannot be presented here due to their commercially sensitive nature. When these discounts are applied, nivolumab plus ipilimumab is still the most cost-effective therapy with an ICER below £20,000. Nivolumab is extendedly dominated by nivolumab plus ipilimumab, and pembrolizumab and nivolumab have similar estimates of net monetary benefit. Additionally, when the confidential PAS discounts are applied, encorafenib plus binimetinib is dominant over dabrafenib plus trametinib.

Table HE016: Base-case deterministic results (list price analysis)

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
Nivo	£179,323	4.320			
Nivo+ipi	£183,360	5.104	£4,038	0.784	£5,148
Pembro	£187,466	4.152	£4,106	-0.952	dominated
Dab+tram	£244,872	3.091	£61,512	-2.013	dominated
Enco+bini	£259,792	3.431	£76,432	-1.673	dominated

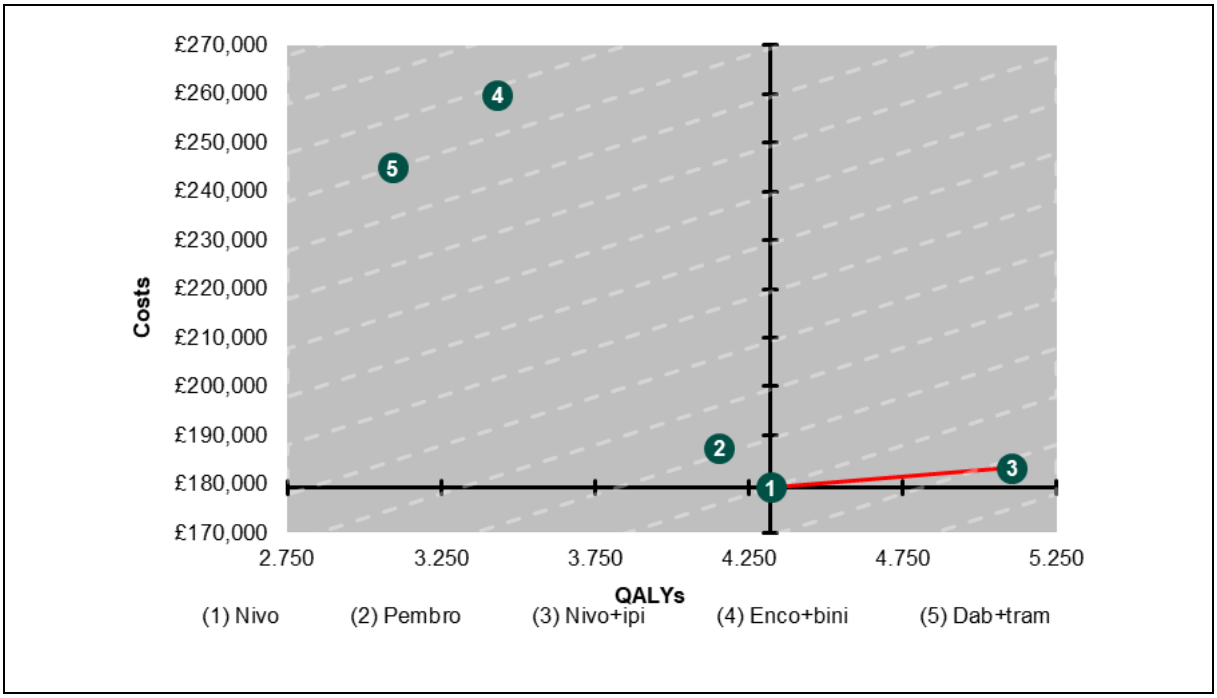

Figure HE016: Base-case deterministic results – cost–utility plane

HE2.2 *BRAF* wild type subgroup cost–utility results

The results of the *BRAF* wild type subgroup analysis indicate that with nivolumab plus ipilimumab is still the most cost-effective of the available strategies in that population, with an ICER of less than £20,000 per QALY when all confidential discounts are applied. All strategies in the subgroup analysis were associated with lower costs and QALYs than in the total population.

Table HE017: *BRAF* wild type subgroup deterministic results (list price analysis)

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Pembro	£98,697	3.715			
Nivo	£109,675	4.101	£10,978	0.386	ext. dom.
Nivo+ipi	£110,049	4.472	£11,352	0.758	£14,982

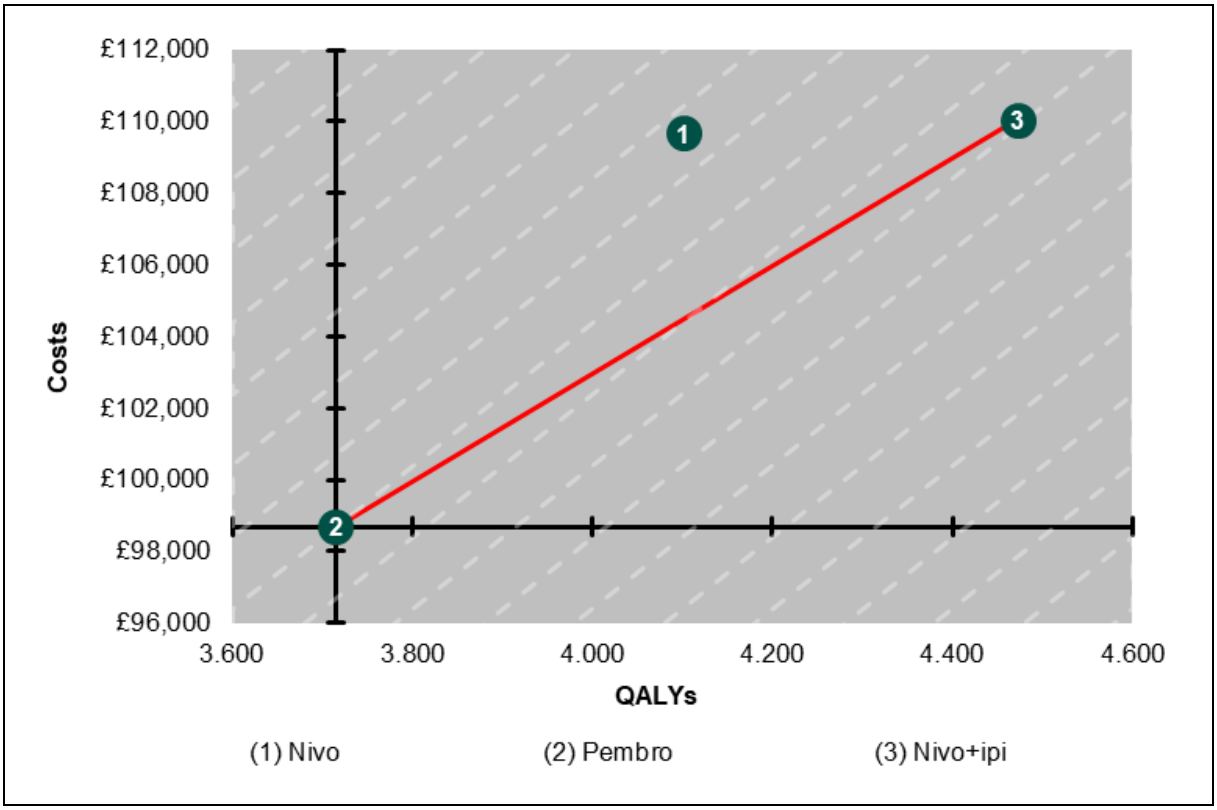

Figure HE017: BRAF wild type subgroup deterministic results – cost–utility plane

HE2.3 Sensitivity analysis

HE2.3.1 Deterministic sensitivity analysis

The results of the scenario analyses are presented in Table HE018 and reflect an analysis when the list price of each drug was used. The majority of the scenarios investigated had a minimal impact on the results, with the order of therapies remaining the same in terms of their ranked cost-effectiveness, and the ICER for ipilimumab and nivolumab remaining between £4,000 and £6,000 per QALY. Scenarios around the data used for second line treatment distribution and around ToT were the only scenarios that substantially changed the results in both the list and PAS price analyses.

When the second-line treatment distribution is informed by the trial data unadjusted for CDF rules, in both the list and PAS analyses pembrolizumab becomes the most cost-effective, with ipilimumab and nivolumab having an ICER substantially higher than the £20,000 per QALY threshold. When the second-line treatment distribution is informed by the data from Sacco, in the list and PAS price analyses nivolumab is the most cost-effective, with ipilimumab and nivolumab having an ICER much higher than the £20,000 per QALY threshold and the targeted therapies dominated.

The results of scenarios where second-line treatment distributions are informed by modified trial data and by the data from Sacco et al. are not considered to be representative due to the limitations of those data sources described in HE1.4.4.2.

The scenarios around ToT data sources, although having fairly similar conclusions based on the scenario results, are not considered the most representative due to the reasons explored in HE1.4.3.1. The options selected for the base-case (SACT data for pembrolizumab and nivolumab, and trial data for ipilimumab+nivolumab) were considered by the committee to be the most representative of what is seen in clinical practice.

Table HE018: Scenario analysis results (list price analysis)

Scenario	Nivo	Pembro	Ipi+nivo	Enco+bini	Dab+tram
Base-case	Reference	Dominated	£5,148	Dominated	Dominated
5-year switch to general population mortality	Reference	Dominated	£5,017	Dominated	Dominated
15-year switch to general population mortality	Reference	Dominated	£5,391	Dominated	Dominated
General population mortality not applied	Reference	Dominated	£6,100	Dominated	Dominated
TE duration: enco+bini 24 mos, dab+tram 12 mos	Reference	Dominated	£5,148	Dominated	Dominated
TE duration: enco+bini and dab+tram both 36 mos	Reference	Dominated	£5,148	Dominated	Dominated
TE duration: no end to TE	Reference	Dominated	£5,148	Dominated	Dominated
TE adjustment factor: 0 months	Reference	Dominated	£5,148	Dominated	Dominated
TE adjustment factor: 36 months	Reference	Dominated	£5,148	Dominated	Dominated
Pembro PFS hazard set equal to nivo from 24 months	Reference	Dominated	£5,148	Dominated	Dominated
Starting age: 50 years	Reference	Dominated	£4,897	Dominated	Dominated
Starting age: 70 years	Reference	Dominated	£5,558	Dominated	Dominated
2L Tx: trial data with no modification	**Ext. dominated**	**Reference**	**£46,183**	**Dominated**	**Dominated**
2L Tx: Sacco data	**Reference**	**Dominated**	**£69,710**	**Dominated**	**Dominated**
ToT: trial data for all	**Ext. dominated**	**Reference**	**£13,606**	**Dominated**	**Dominated**
ToT: SACT data for immunoTx	**Dominated**	**Dominated**	**Reference**	**Dominated**	**Dominated**
AE disutility excluded	Reference	Dominated	£5,102	Dominated	Dominated
2L AEs excluded	Reference	Dominated	£5,148	Dominated	Dominated
Lowest AE cost used	Reference	Dominated	£5,198	Dominated	Dominated
Highest AE cost used	Reference	Dominated	£4,921	Dominated	Dominated
HSUV by type of treatment	Reference	Dominated	£5,370	Dominated	Dominated

HE2.3.2 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis based on list price are presented in Table HE019. In this analysis, ipilimumab in combination with nivolumab is still the most cost-effective strategy, although the probabilistic ICER is higher than the deterministic ICER. The order of the other treatments also remains stable in the probabilistic analysis.

The results of the probabilistic sensitivity analysis based on the PAS prices cannot be presented here due to their commercially sensitive nature. When these discounts are applied in the probabilistic analysis, ipilimumab in combination with nivolumab is still the most cost-effective with an ICER below £20,000 compared with pembrolizumab, and nivolumab is extendedly dominated.

Table HE019: Base case probabilistic results (list price analysis)

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
Nivo	£179,882	4.318			
Nivo+ipi	£185,407	5.093	£5,525	0.775	£7,132

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Pembro	£187,601	4.148	£2,194	-0.945	dominated
Dab+tram	£231,702	3.143	£46,295	-1.949	dominated
Enco+bini	£247,378	3.420	£61,971	-1.672	dominated

A cost-utility plane was generated for the 10,000-simulation probabilistic sensitivity analysis, presented in Figure HE018. The graph shows that in most simulations, ipilimumab in combination with nivolumab had the highest number of QALYs, and the *BRAF*/MEK inhibitors generally have higher costs and fewer QALYs than the immunotherapies.

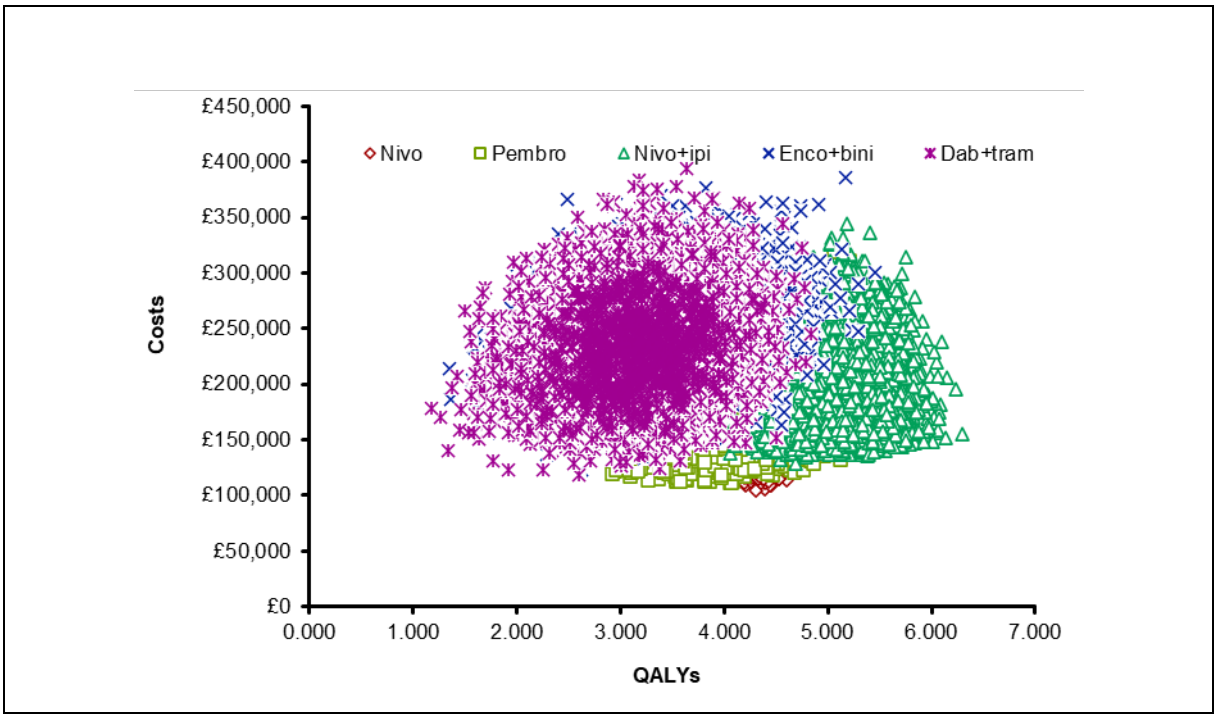

Figure HE018: Base-case probabilistic results (list price) – cost–utility plane

A cost-effectiveness acceptability curve was generated from the probabilistic analysis and is presented in Figure HE019. The graph shows that if the willingness to pay threshold is below approximately £2,500 then nivolumab is the most likely strategy to be cost-effective, and at thresholds above this the strategy most likely to be cost-effective is ipilimumab + nivolumab. The *BRAF*/MEK inhibitor combinations are never the most likely to be cost-effective at list price. Under PAS prices, pembrolizumab is the most likely strategy to be cost-effective at lower willingness to pay thresholds, and ipilimumab in combination with nivolumab is the most likely to be cost-effective at higher willingness to pay thresholds, with the result switching at a threshold below £20,000.

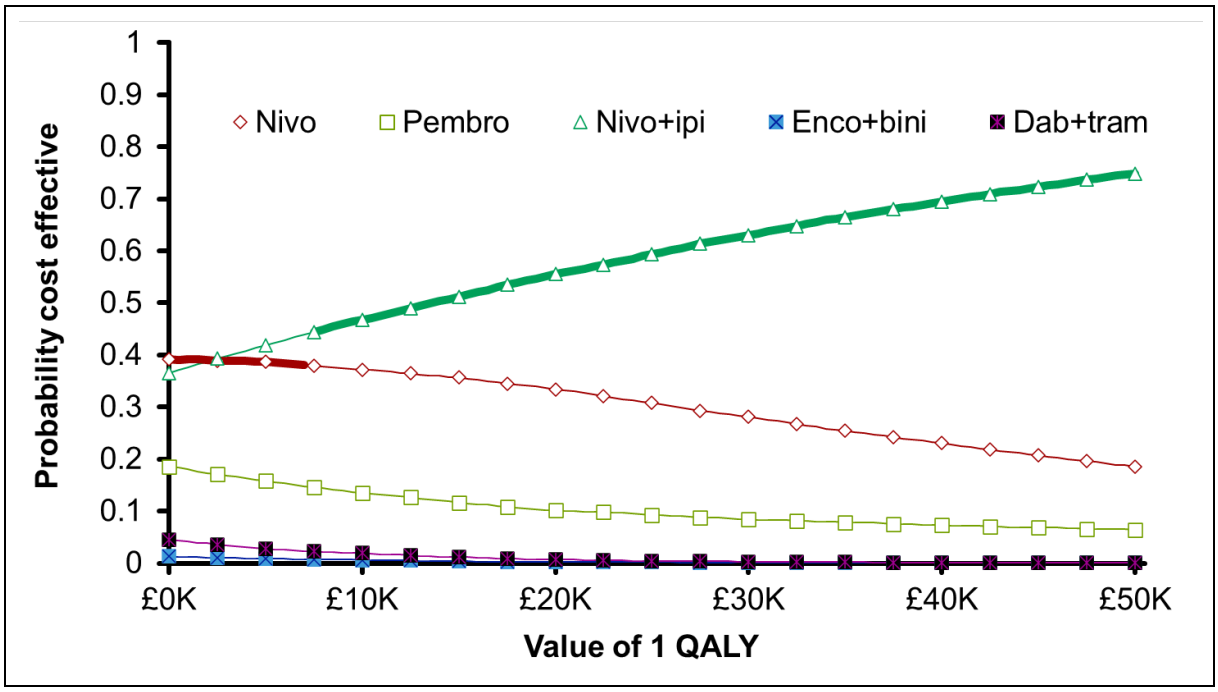

Figure HE019: Base-case probabilistic results (list price) – cost–effectiveness acceptability curve

HE2.4 Discussion

HE2.4.1 Principal findings

The principal finding of the model was that ipilimumab in combination with nivolumab is the most cost-effective strategy for first line treatment of advanced melanoma when compared with the other licensed immunotherapies and *BRAF*/MEK inhibitors. Both combination *BRAF*/MEK inhibitor strategies were more costly and less effective than the immunotherapies in the base-case and all scenario analyses.

Although *BRAF*/MEK inhibitors are not as cost-effective as the immunotherapies, there are factors that mean that patients may prefer them that we were not able to model, for example where the clinician has judged the patient to be at risk of rapid progression, or preference due to concerns around side effects of immunotherapies.

The most influential parameters driving the model results, as identified in sensitivity analysis, are the parameters around second line therapies and time on treatment.

HE2.4.2 Strengths of the analysis

The analysis included all relevant licensed strategies for treatment of advanced melanoma, allowing for a fully incremental comparison of all strategies rather than pairwise comparisons only.

The model results are robust to the majority of parameters explored in sensitivity analysis, with ipilimumab in combination with nivolumab being most cost-effective in almost all scenarios. The scenarios where the order of results dramatically changed were those where the distribution of second line treatment was based on alternative data, however these alternative sources were not considered to be as applicable to current practice and the committee felt more confident in the base-case distributions.

HE2.4.3 Weaknesses of the analysis

Due to a lack of data, the economic analysis only considered first line therapies, and did not compare the cost-effectiveness of sequences of therapies in advanced melanoma. A simplification was made in the model to include second line therapies only in terms of treatment costs and adverse event costs and outcomes.

The costs associated with second line treatment may be overestimated since the data for time on treatment for second line therapies was not available and people may receive treatments for a shorter duration in second line.

There may be limitations with the data informing the adverse event analysis, as it was noted that clinical trials cannot always capture the long-term effects and toxicity. The committee advised that some of these long-term side effects and conditions are asymptomatic and therefore would not fall into the category of Grade 3-4 adverse event. Therefore, this is not expected to have an impact on the conclusions of the analysis.

There is uncertainty around the assumptions used to model the two targeted treatment strategies and the economic model did not demonstrate clear differences in cost-effectiveness between the two strategies.

The main analysis conducted grouped all people with advanced melanoma regardless of *BRAF* status, as there was a lack of data specific to each of the subgroups and the committee agreed that there was a general consensus that treatment effect is largely driven by factors other than *BRAF* status. A subgroup analysis for the *BRAF* wild-type population was conducted to evaluate this uncertainty (see section HE1.4.2.1) and the results of this analysis were relatively congruent with those of the base-case analysis, indicating that *BRAF* status has a relatively small impact on the model results.

HE2.4.4 Comparison with other CUAs

Published studies

Of the studies identified in the systematic review, only Houten et al. (2020) was directly applicable to the review question. The modelled results align with the results presented by Houten et al. when the confidential PAS prices are used, but not when the list prices are used. The Houten et al. analysis used the confidential PAS for encorafenib plus binimetinib and the publicly available prices for dabrafenib + trametinib.

The remaining studies had some applicability issues. Pike et al. (2017) compared 11 strategies including all of the strategies modelled for this question except encorafenib plus binimetinib. The modelled results contradict the results reported by Pike et al. however the study was in a different country (Norway) and had some differences in assumptions, the main difference being that the analysis did not capture any costs or events for second line treatments. This is likely to have had an impact on the analysis as it was identified as a key driver of results in the economic model.

Quon et al. (2019) was a Canadian study comparing single agent immunotherapies and combination ipilimumab + nivolumab. The model results are not consistent with those reported by Quon et al. however, the Quon analysis had some significant differences and limitations in terms of applicability, for example being conducted from a Canadian healthcare perspective, having a 20-year time horizon rather than lifetime, and using a 5% discount rate for costs and outcomes. Quon et al. did not include subsequent therapies in their base-case analysis, however when second line costs were included in a scenario the results were closer to those found in the *de novo* model.

Both studies by Tarhini et al. (2018, 2018) compared sequential treatment in either *BRAF*-mutant or *BRAF*-wild type advanced melanoma, from a US third party payer perspective. A significant difference between the *de novo* model and the Tarhini et al. studies is that the *de novo* model only compared first line therapies and included costs of second line therapies rather than modelling sequences. Therefore, the results cannot confidently be compared.

NICE technology appraisals

All treatments included in the model are NICE approved and therefore have technology appraisals, relevant appraisals being TA366, TA384, TA400, TA396, and TA562. Some key details of these appraisals are provided in Table HE020.

All TAs were single technology appraisals, and all but TA562 used comparators that are no longer considered current practice, as single agent ipilimumab and single agent BRAF inhibitors are not frequently used in first line. All appraisals were in the appropriate populations in terms of BRAF status, which was implementable since the companies likely had the patient-level data split by BRAF status. The *de novo* model however could not be informed by this data as it was unavailable, and not all Kaplan Meier data was reported by BRAF status.

Total costs of each intervention were redacted in the majority of TAs, and the comparisons are not equivalent to those in the *de novo* model so we cannot compare the incremental results. However, the absolute QALYs reported in each of the appraisals are fairly congruent with those estimated in our model. The largest difference between our results and those in the TA was for those estimated in the technology appraisal for pembrolizumab (TA366): this is likely due to different long-term survival predictions between the two analyses. However, due to the use of more mature trial data for extrapolation, we are confident that our analysis provides more accurate predictions of survival and therefore for total QALYs.

Table HE020: Summary of relevant technology appraisals

Model	Guideline model	TA366	TA384	TA396	TA400	TA562
BRAF population	Mixed	Both	Both	BRAF mutant	Both	BRAF mutant
Intervention	-	Pembro	Nivo	Dab+tram	Ipi+nivo	Enco+bini
Comparators	Ipi+nivo, nivo, pembro, enco+bini, dab+tram	Ipi Ipi, vem, dab	Ipi, DTIC Ipi, vem, dab	Dab, tram	Ipi Ipi, dab, vem	Dab+tram
Model structure	Partitioned survival model	Partitioned survival model	Semi-Markov	Partitioned survival model	Semi-Markov	Partitioned survival model
Efficacy data source	NMA	Trial data	Covariate-adjusted indirect comparison	Pooled trial data	Mixed treatment comparison	NMA
Absolute costs - intervention	-	£76,689	NR	NR	NR	NR (£353,603 dab+tram)
Absolute QALYs - intervention	-	3.14	4.31 (WT) 4.27 (M)	3.443	5.09 (WT) 4.85 (M)	4.223 (3.770 dab+tram)

HE2.5 Conclusions

Nivolumab plus ipilimumab is the most cost-effective strategy to use for first line treatment of advanced melanoma and overall, immunotherapies are more cost-effective to use first line than *BRAF*/MEK inhibitors. These results are largely robust to probabilistic sensitivity analysis and scenario analysis, with a key driving factor in the model being the distribution of second line therapies and the costs associated with those therapies.

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Appendices

Appendix A Clinical trial reports

The published studies of clinical trials of the treatments included in the model were used to inform the population demographics and characteristics and are listed in Table HE021.

Table HE021: Included studies

Author	Trial	Title
Robert 2020	CheckMate 066	Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma.
Larkin 2019	CheckMate 067	Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma
Larkin 2018	CheckMate 037	Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial.
Lebbe 2019	CheckMate 511	Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial.
Ascierto 2020	COLUMBUS	Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma.
Robert 2015	Combi-V	Improved overall survival in melanoma with combined dabrafenib and trametinib.
Long 2015	Combi-D	Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial
Long 2017	BRF113220	Long-Term Outcomes in Patients With BRAF V600-Mutant Metastatic Melanoma Who Received Dabrafenib Combined With Trametinib

Appendix B Technology appraisals

To inform costs, quality of life, and resource use, published technology appraisals in advanced melanoma were searched. The following appraisals evaluated the relevant strategies included in the economic model and were used to find relevant parameters.

Table HE022: Included technology appraisals

TA number	Year	Title
562	2019	Encorafenib with binimetinib for unresectable or metastatic *BRAF* V600 mutation-positive melanoma
400	2016	Nivolumab in combination with ipilimumab for treating advanced melanoma
396	2016	Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma
384	2016	Nivolumab for treating advanced (unresectable or metastatic) melanoma
366	2015	Pembrolizumab for advanced melanoma not previously treated with ipilimumab
357	2015	Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab

Appendix C NMA model results

The following tables contain the model parameters for the OS and PFS curves generated by the NMA.

Table HE023: Overall survival model parameters

	Reference	Treatment effect			
	Nivolumab	Pembro	Ipi+nivo	Enco+bini	Dab+tram
Mu	2.3528	-0.0365	0.2594	-0.0360	-0.1562
Sigma	1.5114	-0.0188	0.2949	-0.5507	-0.6848
Q	-2.0463	-	-	-	-

Table HE024: Progression-free survival model parameters

	Reference	Treatment effect			
	Nivolumab	Pembro	Ipi+nivo	Enco+bini	Dab+tram
Lamda_1	0.0805	0.8917	0.7616	0.6732	0.7636
Lamda_2	0.0125	3.4124	1.0221	5.5740	6.9383
Lamda_3	0.0083	1.8278	0.6855	0.5747	0.3742

Table HE025: *BRAF* wild type subgroup overall survival model parameters

	Reference	Treatment effect		
	Nivolumab	Pembro	Ipi+nivo	Ipi
Mu	3.2	-0.07504	0.16750	-0.59680
Sigma	2.16	-0.2842	0.1015	-0.3412
Q	-0.637	-	-	-

Table HE026: Overall survival model – nivolumab covariance matrix

	Mu	Sigma	Q
Mu	0.026786897	0.003612453	0.029064539
Sigma	0.003612453	0.003524344	0.003207396
Q	0.029064539	0.003207396	0.048114853

Appendix D WinBugs NMA code

```
# Binomial likelihood, cloglog link
# Fixed effects model for multi-arm trials
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
    for (k in 1:na[i]) {            # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
        cloglog(p[i,k]) <- log(time[i]) + mu[i] + d[t[i,k]] - d[t[i,1]]
        rhat[i,k] <- p[i,k] * n[i,k]         # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))         }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA
#A ~ dnorm(-1.546,29.678)
#for (k in 1:nt) { cloglog(T[k]) <- log(6.25) + A + d[k]  }

#Ranking and prob{treatment k is best}
for (k in 1:nt){
      rk[k]<-rank(d[],k)
                                        best[k]<-equals(rank(d[],k),1)
                                                    }
```

```
#Pairwise HRs
for (c in 1:(nt-1)){
                        for (k in (c+1):nt){
                                                                    lhr[c,k]<-d[k]-d[c]
                                    log(hr[c,k])<-lhr[c,k]
                                    }
                              }
}                                   # *** PROGRAM ENDS
```