Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Ipilimumab for previously untreated advanced malignant melanoma [ID74]

Prepared by:

Bristol-Myers Squibb Pharmaceuticals Limited

18th March 2014

REDACTED VERSION

Response to the Appraisal Consultation Document: Ipilimumab for previously untreated advanced malignant melanoma [ID74]	
Confidential information is highlighted and underlined, e.g. [redacted]	
Approved Name of Medicinal Product:	ipilimumab
Brand Name:	Yervoy
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd
Submitted by:	[redacted]
Position:	[redacted]
Date:	18th March 2014

Dear Dr Adam,

Bristol-Myers Squibb (BMS) welcome the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma [ID74]. The ACD recommends ipilimumab for this indication *"only in the context of research as part of a clinical study".*

We are disappointed with the Committee's decision which will restrict NHS patients' access to a breakthrough treatment in a life-limiting, incurable condition.

We acknowledge that the Appraisal Committee (AC) understood the European Medicines Agency's (EMA) considerations when extending the marketing authorisation for 3mg/kg ipilimumab to first-line, and that the AC concluded that there is an unmet need for effective therapies in this patient population. The AC also recognised that ipilimumab would be valuable as a first-line treatment option for patients. Given the high unmet medical need in this patient group we feel it is important that a pragmatic approach is taken regarding the uncertainty around the cost-effectiveness results.

You may be aware that, in January 2014, the National Cancer Drugs Fund (NCDF) panel *"concluded that the best option for patients, NHSE and the CDF would be to seek baseline commissioning for 1st line ipilimumab in advanced melanoma as the funding was already in place [for second-line] and the impact [of extending the treatment recommendation to first-line patients] was considered to be cost neutral."* [14]

Upon review of the ACD, BMS does not believe that all the relevant evidence has been taken into account by the ERG and then by the AC:

- We have presented clinical evidence for 3mg/kg ipilimumab monotherapy from two robust observational studies in previously untreated patients and from a pooled analysis of chemo-therapy-naïve patients which compared favourably to dacarbazine (DTIC) in first-line – despite inclusion of patients with poor prognostic factors (e.g. brain metastases) in both observational studies.
    - We emphasised the importance of the above data sets for the licence extension by the EMA - which testifies to the increasing acceptance of the value of real-world data in the scientific community. However, disappointingly, the NICE Economic Review Group (ERG) ruled *"it was not as robust as the RCT evidence and the results were similar, therefore, we [the ERG] did not consider that these studies provided additional relevant data."* [1]

- We feel that because of this ERG judgment, the evidence may not have been considered adequately, in particular:
  - the robustness of long-term data in these studies;
  - the importance of long-term survival as a benefit to patients with advanced melanoma (given the often terminal nature of this disease);
  - the existence of historical data from numerous sources which provide evidence to support the long-term benefits of ipilimumab;
  - the scientific basis on which to extrapolate benefits in previously treated patients (second-line) to those patients with untreated advanced melanoma (first-line).

- We asked the Committee to consider the similarity between first- and second-line melanoma patients. For second-line treatment of advanced melanoma, ipilimumab was previously deemed cost-effective by NICE and approved. Given the similarity clinically of first- and second-line patients (separated from each other often by only a few weeks of DTIC chemotherapy, which is generally accepted as being ineffective) we once again ask the Committee to take the relevant evidence from the second-line appraisal (TA268) into consideration for this appraisal.
- There is no rationale as to why the efficacy (measured as overall survival) of 3mg/kg ipilimumab in the first-line setting would be inferior to 3mg/kg ipilimumab in the second-line setting (This was confirmed in the EMA's European Public Assessment Report (EPAR): *"From a pharmacological or biological point of view it is not rational to suspect a different activity for ipilimumab treatment in the first or the next line setting, because the mechanism of action of ipilimumab is general stimulation of the immune-system, which is rather aspecific."* [2]).
- The clinical evidence given to the Committee was very clear in its belief that the two patient populations (first- and second-line) are essentially the same. Furthermore, the earlier the patients initiate treatment with ipilimumab within the path of their disease progression, the more likely it is they will be able to benefit from the entire course of ipilimumab (4 doses) which, in turn, can improve their survival prospects. So the longer the patients are delayed from accessing ipilimumab, whilst using DTIC, where it is known that there is no overall survival (OS) benefit, the more their chance of successful treatment diminishes. This is surely an illogical and undesirable outcome.
- We have submitted comparative efficacy data of ipilimumab in previously untreated patients, which proved a significant difference in OS over DTIC. In the EPAR it is acknowledged that *"the median OS observed with ipilimumab is consistently at least >2 months longer [vs. DTIC] regardless of the line of therapy used as shown by the results from the pivotal and the supportive studies."* [2]
- We presented trial data for ipilimumab 3mg/kg showing that more than one in five (20%) of melanoma patients survive long-term (>2 years).

Despite the wealth of clinical evidence presented, the Committee concluded that *"although it was possible that the ICERs may be in a range considered to be cost effective [...] it was not possible to come to a conclusion without further evidence on the clinical effectiveness of ipilimumab 3mg/kg alone in the first-line setting."*

- A Phase 3 trial to provide "exact" comparative clinical efficacy results for ipilimumab 3mg/kg in previously untreated patients is lacking. However, based on the arguments above, the most, and indeed a highly plausible position is that 3mg/kg ipilimumab is a cost-effective treatment in first-line.
- As stated in the EPAR, *"OS analyses from 3 mg/kg ipilimumab monotherapy (pooled) in previously untreated advanced melanoma demonstrate that 3 mg/kg ipilimumab monotherapy has at least similar OS (median, 1 year and 2 year) to the ipilimumab treated patients in the two randomized Phase 3 studies. Furthermore, in previously untreated patients, the median and*

long-term OS from 3 mg/kg ipilimumab monotherapy and 10 mg/kg ipilimumab + DTIC are similar and both are numerically higher than DTIC alone (median OS = 9.07 months; 1 yr: 36%, 2 yr: 18%).” [2]

- We therefore believe that the Committee’s summaries of clinical- and cost-effectiveness do not represent a reasonable and logical interpretation of the evidence.

In order to provide the Committee with increased certainty in the incremental cost-effectiveness ratios (ICERs), additional cost-effectiveness analyses have been conducted for this response, using extrapolated data from previously treated patients with the 3mg/kg dose.

Since new evidence, relevant to the decision problem and addressing areas of uncertainty, has become available since date of submission (October 2013), these additional data have been provided within this response, with the pre-approval of NICE. In particular, this refers to an update of the follow-up data from the vemurafenib trial (BRIM-3) and independent publications relating to treatment sequencing of ipilimumab and vemurafenib.

Our response to the ACD is split into 5 sections:

- **Section 1** presents the additional cost-effectiveness analyses conducted to address the key areas of uncertainty highlighted by the Committee.
  - Chief amongst these is the utilisation of second-line evidence for ipilimumab 3mg/kg in a first-line setting – acknowledging the similarity between previously treated and previously untreated patients in UK clinical practice.
    - The initial analysis incorporates adjusted second-line OS data to predict outcomes for the 3mg/kg dose in first-line, based on the prognostic characteristics of an untreated patient population.
    - We then present two further analyses in which we adjust for: (a) the effect of using second-line ipilimumab in the vemurafenib trial; and (b) the differences in prognostic patient characteristics seen in the vemurafenib trial compared with the ipilimumab first-line trial.
  - These steps are subsequently presented in a combined scenario, with resulting cost-effective ICERs below the relevant willingness-to-pay thresholds (£48k per QALY gained vs. DTIC [with end of life allowances] and £29k vs. vemurafenib). The ICERs were produced with a conventional 3-state model (as preferred by the ERG).
  - In the first-line submission, where a sequential model was used, the ICERs amounted to £32k per QALY gained vs. DTIC and ipilimumab was dominant vs. vemurafenib. A scenario analysis, using a conventional 3-state model, resulted in higher yet cost-effective ICERs of £42k vs. DTIC and £29k vs. vemurafenib.
  - We also present additional scenario analyses in section 1: The scenario adopting the sequential modelling approach yields an ICER of £41k for ipilimumab vs. DTIC. The scenario which included the latest data cut from the vemurafenib trial and assumes that the proportion of patients alive is equal to DTIC at and after 30 months, yields a highly cost-effective ICER of £13k for ipilimumab vs. vemurafenib.
  - Section 1 concludes that results for ipilimumab are similar across the multiple sources of evidence used and that ipilimumab is a cost-effective treatment option for all patients when previously validated data for the 3mg/kg dose at second-line is incorporated into the model. Results of one-way and probabilistic sensitivity analyses as well as further scenario analyses demonstrate the robustness of the model for the conservative base case result.

- **Section 2** clarifies the assumption made regarding the relative efficacy of 3mg/kg ipilimumab and 10mg/kg ipilimumab + DTIC.
  - While BMS does not argue that the two doses are clinically equivalent, the evidence for the 10mg/kg ipilimumab + DTIC regimen was considered to support the recommendation of 3mg/kg ipilimumab at first-line, as acknowledged in the EPAR.
  - This section also clarifies that the ongoing CA184-169 trial will only address whether or not 10mg/kg is the optimal dose of ipilimumab. Treatment with ipilimumab 3mg/kg is approved as effective with similar OS benefit in both first- and second-line by the EMA, as stated in the EPAR. The evidence from CA184-169 will not provide further support for the licensed 3mg/kg dose.
- **Section 3** presents newly available evidence substantiating the treatment sequencing assumptions for ipilimumab and vemurafenib.
  - From the publications we conclude that ipilimumab is a suitable choice of first-line treatment for a subgroup of BRAF mutation-positive patients, and that clinicians should have the option of choosing the most appropriate treatment, based on prognostic characteristics, in order to achieve improved survival for patients.
  - It further clarifies that results from ongoing trials, whilst they will provide additional guidance to clinicians regarding the optimal treatment of patients, will only be of limited value for the present decision problem.
- **Section 4** provides additional clarification on the effect of DTIC when administered in combination with ipilimumab.
  - BMS maintain that DTIC has not enhanced the efficacy of the ipilimumab regimen used in the first-line trial, and that this is supported by the available evidence and by the Clinical Experts present at the first AC meeting.
  - In addition, the effect of concomitant DTIC on clinical efficacy of ipilimumab is considered less relevant given that concomitant DTIC has not been and will not be used with ipilimumab 3mg/kg (the only licensed dose of ipilimumab) and therefore its impact should not be regarded as critical.
- **Section 5** provides a table of factual inaccuracies identified by BMS in the ACD.

In light of the additional analyses and evidence provided here, we ask that the Committee reconsiders its initial conclusions and grants NHS patients access to a breakthrough treatment in a life-limiting, incurable condition.

We look forward to the ensuing discussions at the next Committee meeting on 23rd April 2014.

Yours sincerely

[redacted]

Bristol-Myers Squibb

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Section 1: Additional cost-effectiveness analyses conducted to address uncertainties highlighted by the AC

Summary:

- Committee members raised two main concerns with the body of evidence used to model the cost-effectiveness of ipilimumab: (a) the use of data for the 10mg/kg ipilimumab + DTIC regimen as a proxy for the licensed 3mg/kg regimen, and (b) differences in the CA184-024 and BRIM-3 trial populations not being considered in the comparison to vemurafenib. Regarding the comparability of the BRIM-3 trial data the Committee was concerned that, within BRIM-3, there was a considerable uptake of ipilimumab as follow-on treatment and patients had worse prognostic characteristics (compared with the CA184-024 trial).
- BMS has therefore conducted additional analyses aiming to resolve the uncertainty surrounding the decision problem that stems from the above issues.
- There were three components to the additional analyses performed:
  - The MDX010-20 trial reported efficacy data for the 3mg/kg dose of ipilimumab, and was the primary data source for the appraisal of ipilimumab at second-line (TA268). This data was incorporated into the economic model to provide an alternative estimate of the cost-effectiveness of ipilimumab in previously untreated patients, based on data for the 3mg/kg dose. Given patients in the MDX010-20 trial had worse prognostic characteristics at baseline than is typical of patients treated at first-line, a Cox proportional hazards model was used to adjust the OS from this trial to predict outcomes for the 3mg/kg dose in first-line, based on the prognostic characteristics of an untreated patient population (as in CA184-024).
  - More than 20% of patients enrolled in both arms of the BRIM-3 trial received follow-on treatment with ipilimumab, artificially inflating the long-term survival in both arms. The OS curve for vemurafenib was adjusted in an attempt to correct for the treatment effect of ipilimumab in the BRIM-3 trial data.
  - There are differences in the patient populations in the CA184-024 and BRIM-3 trials. The OS and PFS for vemurafenib have been adjusted to account for these, by means of a previously presented model (Korn model) constructed to predict the differences in outcomes for DTIC-treated patients between the two trials, based on patient baseline characteristics.
- The updated base case analysis, using a 3-state model, produces cost-effective ICERs of £48k per QALY gained compared with DTIC and £29k compared with vemurafenib.
- We also present three additional scenario analyses:
  - When a sequential modelling approach is followed, the ICER for ipilimumab compared to DTIC amounts to £41k per QLAY gained. Quantitative assessment of the sequencing of ipilimumab and vemurafenib is not considered due to the lack of data in the BRAF mutation-positive subgroup of patients in whom ipilimumab is likely be used first-line.
  - Using an alternative adjustment approach for the MDX010-20 trial data, i.e. applying a hazard ratio, produces ICERs of £38k and £16k vs. DTIC and vemurafenib, respectively, in the 3-state model.
  - The latest data cut from the BRIM-3 trial presents OS curves that converge before 30 months. The ICER for ipilimumab vs. vemurafenib reduces significantly to £13k when the proportion of patients alive with vemurafenib is assumed to be equal to the proportion of patients alive with DTIC at and after 30 months.
- BMS conclude that ipilimumab is a cost-effective treatment option for all patients when previously validated data for the 3mg/kg dose at second-line is incorporated into the model. One-way and probabilistic sensitivity analyses confirm the robustness of the modelled result.

Context:

The Appraisal Committee stated that, although it was possible that the ICERs may be in a range considered to be cost effective, the ERG's exploratory analyses indicated that the results were very sensitive to the assumptions in the model. In particular, the Committee raised concerns about the clinical effectiveness of ipilimumab 3mg/kg monotherapy first-line.

Randomised, controlled Phase 3 trial evidence assessing the clinical effectiveness of ipilimumab 3mg/kg monotherapy first-line is lacking. However the similarity between first-line (untreated) and second-line (previously treated) patients is recognised by the EMA:

The Committee for Medicinal Products for Human Use (CHMP) concluded that "*the efficacy of 3mg/kg ipilimumab monotherapy has been established in previously treated melanoma patients; the baseline characteristics of the patients included in the pivotal studies in previously treated and previously untreated subpopulations were similar; the similar patient characteristics of the two trials [MDX010-20 and CA184-024] support the relevance of the results observed in a previously treated population to the first-line setting.*" [2]

As stated by the Clinical Experts who gave evidence to the AC, and acknowledged by the Committee, there is no biological reason why the efficacy of ipilimumab should be different between the first- and second-line settings in UK clinical practice, especially given the short duration of the DTIC "hurdle" patients must pass to be eligible for second-line ipilimumab.

Committee members raised two main concerns with the body of evidence used to model the cost-effectiveness of ipilimumab: (a) the use of data for the 10mg/kg ipilimumab + DTIC regimen as a proxy for the licensed 3mg/kg regimen, and (b) differences in the CA184-024 and BRIM-3 trial populations not being considered in the comparison to vemurafenib. Regarding the comparability of the BRIM-3 trial data the Committee was concerned as in BRIM-3 there was (a) a considerable uptake of ipilimumab as follow-on treatment and (b) patients had worse prognostic characteristics (compared with the CA184-024 trial).

Aim and summary of the additional cost-effectiveness analyses:

Given the similarity between previously treated and previously untreated patients in UK clinical practice, the evidence available for ipilimumab 3mg/kg in second-line should be considered relevant to this decision problem and extends the evidence base for ipilimumab 3mg/kg monotherapy.

BMS has therefore conducted additional analyses aiming to resolve the uncertainty surrounding the decision problem that stems from the above issues. The additional cost-effectiveness analyses utilise the available evidence for second-line patients (MDX010-20; appraised in TA268) in a first-line setting.

In order to produce a sensible base case, adjusted analyses of data from both MDX010-20 and BRIM-3 were performed and are broken down into the following new components:

A. Adjustment of the OS curve for 3mg/kg ipilimumab second-line (MDX010-20) to predict outcomes for the 3mg/kg dose in first-line, based on the prognostic characteristics of an untreated patient population (as in CA184-024);
B. Adjustment of the BRIM-3 vemurafenib OS curve to account for the effect of second-line ipilimumab;
C. Adjustment of BRIM-3 vemurafenib and DTIC OS curves to account for differences in patient baseline characteristics (between BRIM-3 and CA184-024).

The analyses have been combined to produce a new estimate of the ICERs vs. DTIC and vemurafenib. The combined impact of new analyses is referred to as "Section 1 base case".

In the first-line submission we adopted a sequential modelling approach and presented results which included data from CA184-024 for ipilimumab and yielded an ICER of £32k per QALY gained vs. DTIC and ipilimumab dominated vemurafenib. The second set of results in the submission, i.e. when using data for 3mg/kg in a chemotherapy-naïve population, produced similar (slightly more favourable) results. We believe that a sequential model is not only clinically plausible but also better reflects current patterns of clinical practice in the NHS. The structure is largely consistent with previous models used to represent the treatment of advanced melanoma (TA268, TA269).

The ERG however expressed a strong preference for a conventional 3-state model based on pre-progression, post-progression, and death, with BSC being the only second-line treatment considered (ERG report, p. 18). Ignoring the impact of active second-line treatments, i.e. when the sequencing is "switched off" (presented as scenario analysis in the submission), increased the ICERs to £42k vs. DTIC and to £29k vs. vemurafenib.

When using a 3-state model, outcomes are considered to reflect an overly conservative estimate of the cost-effectiveness associated with 3mg/kg ipilimumab. However, as described in the following paragraphs in detail, even when using a conventional 3-state model, the results prove ipilimumab to be cost-effective: In the "Section 1 base case", the ICERs amount to £48k vs. DTIC and £29k vs. vemurafenib (Table 7).

These results are similar to the scenario analysis in the submission and hence provide further reassurance that the ICERs vs. DTIC and vemurafenib can be accepted to be cost-effective.

Results from both one-way and probabilistic sensitivity analyses, performed for the "Section 1 base case", demonstrate that the conclusion of the cost-effectiveness analysis is insensitive to most changes in parameter values and assumptions.

The methods of the analyses and the results are described in detail below.

Methodology:

Component A: Adjustment of the OS curve for 3mg/kg ipilimumab second-line (MDX010-20) to predict outcomes for the 3mg/kg dose in first-line, based on the prognostic characteristics of an untreated patient population (as in CA184-024)

Cost-effectiveness results for ipilimumab second-line (MDX010-20) in TA268

To recapitulate, MDX010-20 assessed ipilimumab in the licensed dose of 3mg/kg versus best supportive care (simulated using gp100) in previously treated patients with metastatic melanoma. The trial demonstrated that ipilimumab significantly improved survival. MDX010-20 was the pivotal trial for the previous appraisal TA268 and is described there in detail.[3] In previously treated patients, ipilimumab was deemed cost-effective versus best supportive care, i.e. received a positive NICE recommendation (results are presented in Table 1 and include the PAS).[3]

Table 1: Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma - Final base case results (incl. PAS) from TA268

Technology	Total			Incremental			ICER incremental (costs per QALY gained)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£[redacted]	1.07	0.82				
Ipilimumab	£[redacted]	2.71	2.02	£[redacted]	1.64	1.20	£46,739

In order to be able to use ipilimumab 3mg/kg second-line evidence as an approximation for the efficacy of 3mg/kg in first-line, adjustments had to be made to the data which are described in the subsequent paragraphs.

Interim results for the adjustments, demonstrating the impact on the outcomes, are presented in Appendix 1.

The strengths and weaknesses of the clinical trial data available in relation to the decision problem are summarised in Table 2.

Table 2: Strengths and weaknesses of available RCT evidence from CA184-024, MDX010-20 and BRIM-3 in terms of applicability to the current submission

Trial	Strengths	Weaknesses
CA184-024	• Conducted in the relevant patient population: all first-line advanced melanoma patients • Contains relevant comparator, i.e. DTIC • No confounding via crossover or follow-on to other active treatments	• Conducted at an unlicensed dose of ipilimumab (10mg/kg) used in conjunction with DTIC • The combined use of a higher dose of ipilimumab and DTIC resulted in substantial toxicity which limited the ability of patients to receive all 4 doses of ipilimumab (and therefore the efficacy of ipilimumab) • BRAF status not collected making comparison with BRIM-3 more difficult
BRIM-3	• Conducted in the relevant patient population: first-line advanced melanoma patients • Contains relevant comparator, i.e. DTIC	• Trial confounded by second-line use of ipilimumab in both arms meaning a true treatment effect of vemurafenib alone is difficult to establish • Efficacy of DTIC also confounded by crossover to vemurafenib at later data cuts • Results not presented for the subgroups – i.e. low tumour burden (as defined by LDH level and tumour stage) where ipilimumab would most likely be used or by whether or not patients received ipilimumab at second-line
MDX010-20	• Conducted at the licensed dose of ipilimumab (3mg/kg) • No confounding via crossover or follow-on to other active treatments • Considered to provide a lower-bound for the efficacy of ipilimumab at first-line at the licensed dose	• Conducted in the second-line setting at a time when no treatments proven to prolong OS were available and therefore contained a much higher proportion of patients with more severe prognostic characteristics than it would be expected in current clinical practice • Comparator not used in clinical practice (gp100) • BRAF status not collected making comparison with BRIM-3 more difficult

As a first step, OS and PFS data for patients receiving 3mg/kg ipilimumab in second-line (MDX010-20) were implemented into the model. Methodologically, the OS and PFS curve fits used in TA268 have been examined and accepted by the Committee and ERG in the appraisal process for ipilimumab in previously treated patients.[3] The base case OS and PFS curves were taken directly from the cost-effectiveness model submitted as part of TA268.

The comparator arm in MDX010-20 used a vaccine (gp100) whereas the comparator in the CA184-024 trial and the health economic model is DTIC. OS and PFS outcomes for the DTIC arm were therefore obtained from the CA184-024 trial (as in the original manufacturer submission). OS and PFS outcomes for vemurafenib were taken from the BRIM-3 trial (as in the original manufacturer submission).

OS of patients receiving ipilimumab second-line (MDX010-20) compared with first-line (CA184-024)

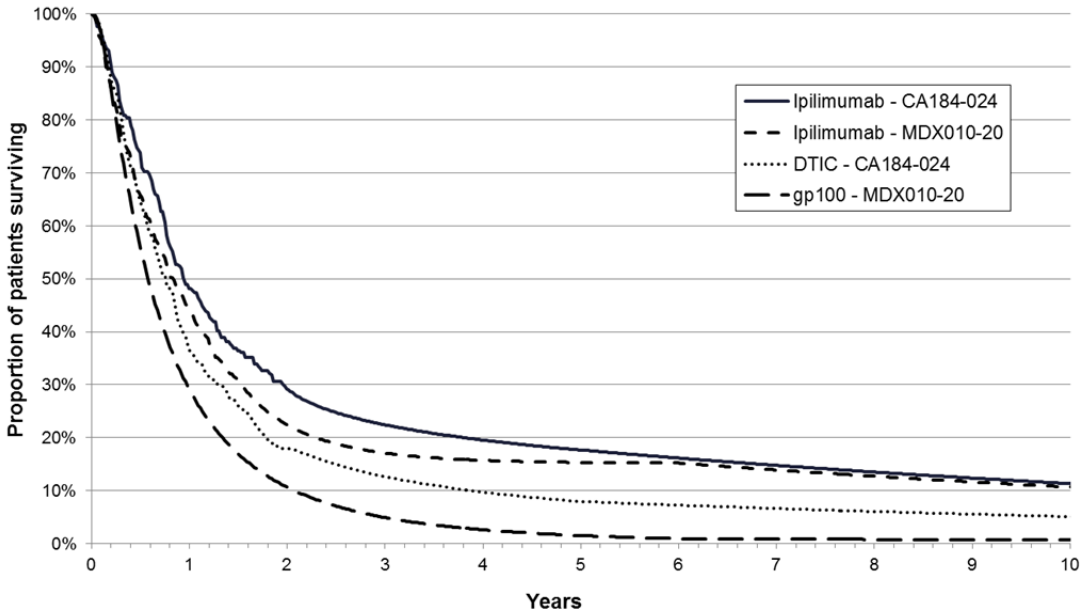
The three-part curve constructed to model OS based on data from the MDX010-20 trial is summarised in Table 3 below. In TA268, the parametric curve piece continued until 6 years, the last point at which data are available from the trial. At this point the curve switched to registry data. The separation point at which the curve switched from Kaplan-Meier data to the parametric curve was 18 months. These separation points have also been used when incorporating the MDX010-20 data into the first-line model.

Table 3: Summary of the modelled OS curve based on data from MDX010-20

Trial	Curve Part	Duration	Curve fit and parameters	Source
MDX010-20 OS	Kaplan Meier data	Cycles 0-78	Not applicable (as KM data were used)	MDX010-20 clinical trial
	Parametric curve	Cycles 79-313	Gompertz alpha: -6.0807 beta: -0.0032	Curve fitted to survival of patients alive at 18 months
	Registry data hazards	Cycles 314+	Weibull Stage IIIC: Constant -2.5134 ln(p) -0.2139 Stage IV: Constant -2.3854 ln(p) -0.0118	Balch et al. (2001)

Figure 1 presents a comparison of OS curves from both the MDX010-20 trial and the CA184-024 trial, which was the pivotal trial in the first-line submission.

Figure 1: Comparison of three-part OS curves from CA184-024 and MDX010-20



PFS of patients receiving ipilimumab second-line (MDX010-20) compared with first-line (CA184-024)

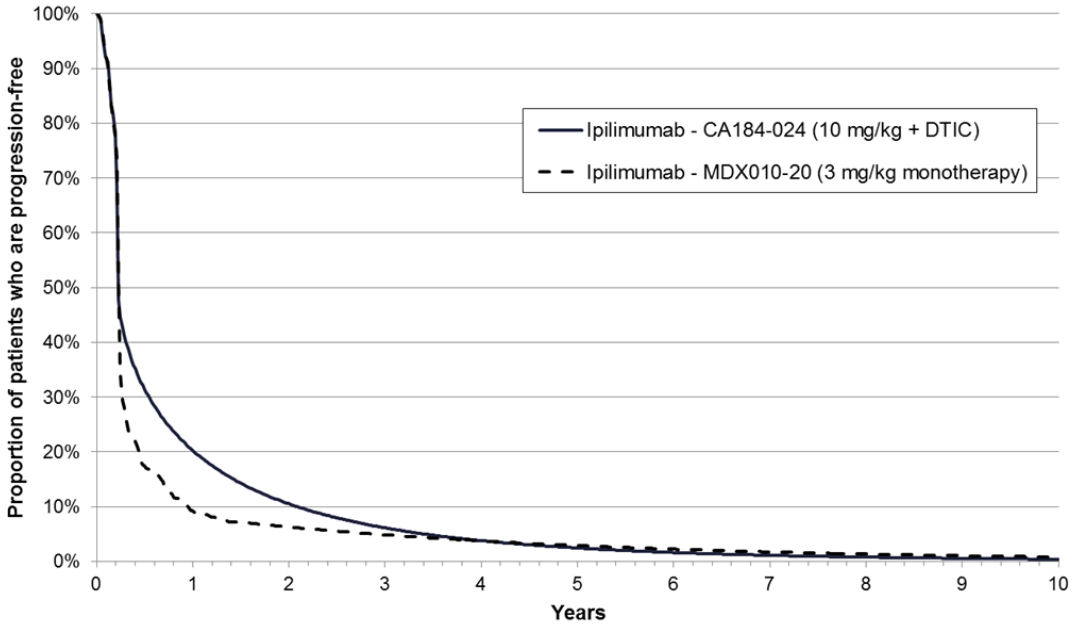
The modelled two-part PFS curve for ipilimumab in TA268 comprised of the parts shown in Table 4. The curve switched from KM data to the exponential parametric curve fit at 18 months. This 18 month point was chosen based on examination of Nelson Aalen plots to determine the point at which the hazards change. Nelson Aalen plots were also used to determine the separation point in the first-line submission.

Table 4: Summary of the modelled PFS curve based on data from MDX010-20

Trial	Curve Part	Duration	Curve fit and parameters	Source
MDX010-20 PFS	Kaplan Meier data	Cycles 0-78	Not applicable (as KM data were used)	MDX010-20 clinical trial
	Parametric curve	Cycles 79+	Exponential alpha: -6.0807	Curve fitted to PFS of patients who were progression free at 12 weeks

Figure 2 shows the PFS curves of the ipilimumab arms from both the MDX010-20 trial and the CA184-024 trial.

Figure 2: Comparison of two-part PFS curves from CA184-024 and MDX010-20



Adjustment of 3mg/kg ipilimumab OS data from second-line (MDX010-20) for use in a first-line setting

Although the baseline characteristics were generally similar between MDX010-20 and CA184-024, the patients included in the MDX010-20 trial had generally more severe disease than patients in both the CA184-024 and BRIM-3 trials (see comparison of the trial population characteristics in Table 5). In order to present a reasonable base case analysis, the worse prognosis of patients in second-line (MDX010-20) was adjusted to the baseline characteristics patients had in the first-line trial (CA184-024).

Table 5: Comparison of baseline patient characteristics from CA184-024, MDX010-20 and BRIM-3

Patient characteristic	CA184-024 first-line ipilimumab trial [4] (n=502)	BRIM-3 vemurafenib trial[5] (n=675)	MDX010-20 second-line ipilimumab trial[6] (n=676)
Age	mean: 56.9	medians: vemurafenib = 56 DTIC = 52	mean: 56.2
Mean time since diagnosis of metastatic melanoma	38.5 months[a]	NR	60.6 months[a]
Male sex (%)	60.0	56.4	59.3

Patient characteristic	CA184-024 first-line ipilimumab trial [4] (n=502)	BRIM-3 vemurafenib trial[5] (n=675)	MDX010-20 second-line ipilimumab trial[6] (n=676)
ECOG performance status (%)			
0	70.9	68.0	55.3
1	29.1	32.0	43.0
2	0.0	0.0	1.3
3	0.0	0.0	0.1
Unknown	0.0	0.0	0.1
M stage (%)			
M0	2.8	4.9	1.5
M1a	15.9	11.0	9.2
M1b	25.1	18.8	17.9
M1c	56.2	65.3	71.4
Brain metastases (%)	0.4[b]	0.0	12.1
Lactate dehydrogenase (%)			
≤Upper limit of the normal range	59.2	42.1	61.7
>Upper limit of the normal range	40.4	57.9	37.6
Unknown	0.0	0.0	0.7

[a] Duration of metastatic melanoma was taken from the clinical study report for the CA184-024 and MDX010-20 trials.
[b] 2 patients in the CA184-024 trial had CNS lesions at baseline.
NR, not reported; DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group

The adjustment for the differences in patient baseline characteristics between the CA184-024 and MDX010-20 trials was achieved by means of a Cox proportional hazards model which was implemented by BMS to fit the data from study MDX010-20 among all ipilimumab treated subjects (i.e. 3mg/kg ipilimumab only and 3mg/kg ipilimumab + gp100, as per TA268) with the following five baseline prognostic factors:

- Gender (Female vs. Male)
- ECOG PS (0 vs. >0)
- Visceral disease status (No vs. Yes)
- Brain metastases (No vs. Yes)
- LDH (Normal vs. Elevated[a])

A total of six variables were included in the model initially. One variable that could be disregarded in the model was 'baseline disease stage'. The variable 'gender' also did not appear to be a strong covariate in this modelling. However it was kept in this model since it was found to be an important covariate in previous modelling (i.e. the Korn model analysis which is used later in this section).

A predicted survival curve was obtained for each of the 32 combinations from these five prognostic variables. An averaged survival curve was computed by weighing these 32 predicted survival curves with corresponding proportions of patients in these categories from study CA184-024. The resulting OS curve represents the adjusted MDX010-20 OS curve expected for the 3mg/kg ipilimumab dose in the first line setting with similar compositions of the CA184-024 population.

The following equation shows the survival probability as a function of the HR and a reference survival:

Figure 3: Survival probability equation

$$S_j(t) = S_{i=1}(t)^{HR}$$

where $j = 1, \ldots, 32$ represented 32 predicted survival groups with various combinations of five prognostic factors and $S_{i=1}(t)$ represented the reference survival curve of the worst prognostic group of subjects, i.e., male subjects with ECOG>0, visceral disease, brain metastases and elevated LDH level.

[a] Elevated LDH was defined as >1 x upper limit normal (ULN).

The equation with estimated parameters for the five prognostic covariates (by means of which the hazard ratio for each combination of characteristics were derived) was defined as follows:

Figure 4: Cox proportional hazards model equation (rounded to 3 decimal places)

$$\log(\widehat{HR}) = -0.154\, X_{\text{Gender=Female}} - 0.400\, X_{\text{ECOG=0}} - 0.285\, X_{\text{Viscera=NO}} - 0.306\, X_{\text{Brain=NO}} - 0.782\, X_{\text{LDH=NORMAL}}$$

Table 6 presents the characteristics included in the model and the coefficients used in the equation.

Table 6: Prognostic characteristics included in Cox proportional hazards model to adjust MDX010-20 data

Prognostic Variables	Estimate	Standard Error	P-value
Gender	**-0.15379**	0.10252	0.1336
ECOG	**-0.39958**	0.10141	<0.0001
Visceral Disease Status	**-0.28468**	0.12610	0.0240
Brain Metastasis	**-0.30605**	0.14782	0.0384
LDH	**-0.78166**	0.10864	<0.0001

The adjusted OS was estimated the following equation:

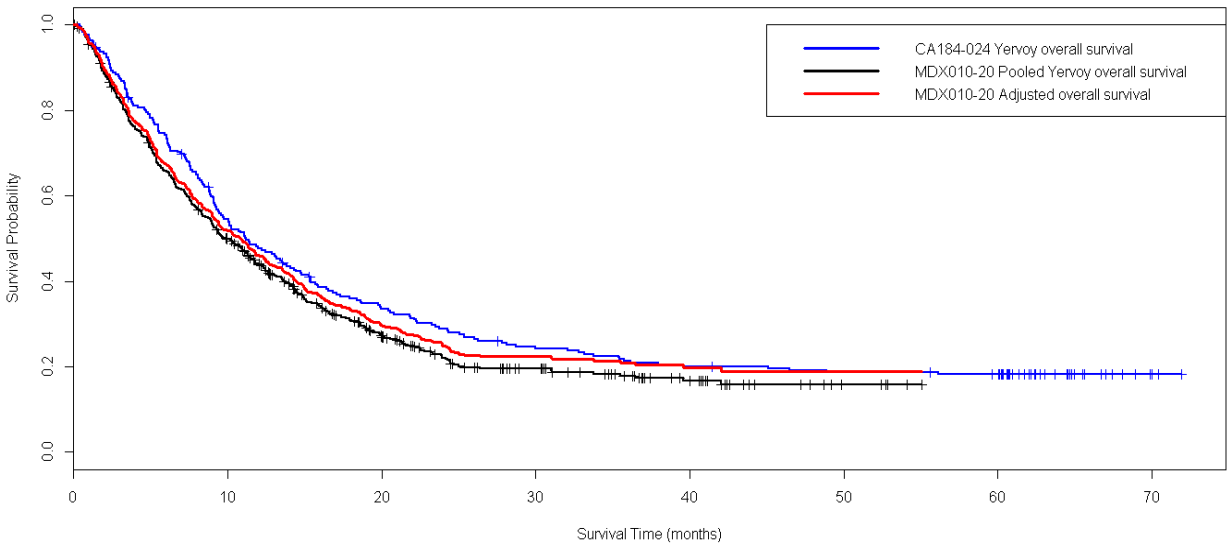
Figure 5: Equation used to estimate adjusted OS

$$\ddot{S}_{adj} = \ddot{P}_j \ddot{S}_j(t)$$

where $\ddot{P}_j$ represented the proportion of subjects in the jth subset from study CA184-024.

Figure 6 compares the unadjusted and adjusted (Cox model) MDX010-20 KM data, and the KM data from the CA184-024 trial.

Figure 6: Unadjusted and adjusted Kaplan-Meier curves for OS from MDX010-20, compared with Kaplan-Meier curve for OS from CA184-024



There are two methods to incorporate this new OS data into the model: (a) Application of the new (adjusted) KM data directly into the model and extrapolation of the curve based on available evidence from CA184-024; or (b) simulation of the new OS curve by applying a hazard ratio comparing the adjusted to the unadjusted KM data from MDX010-20.

For the base case analysis, the first method has been selected because the second approach, a continued application of a hazard ratio, would have resulted in long-term survival estimates above those from the CA184-024 modelled curve. The latter was tested in an additional scenario analysis in

which the adjustment is applied as a hazard ratio to the entirety of the modelled curve from the second-line economic model (ICERs = £38k vs. DTIC; £16k vs. vemurafenib; presented from p. 23). In the base case however, the adjusted KM data were used for the first 4.5 years, at which point the KM OS curve switched to the CA184-024 OS curve. Given that the proportion alive at 4.5 years is equal for the adjusted KM data and the CA184-024 modelled curve this approach was considered appropriate.

The adjustment for patients' baseline characteristics was performed for the OS curve only. It was assumed that no adjustment was required for the PFS curve from the MDX010-20, meaning, the modelled curve was input directly from TA268. As the PFS of the ipilimumab arms from both the MDX010-20 and the CA184-024 trials is similar (Figure 2), the impact on results of introducing some adjustment is expected to be small.

Number of ipilimumab doses received in MDX010-20 (compared with CA184-024)

As discussed at the first AC meeting, patients received more doses of ipilimumab in MDX010-20 than in CA184-024 (i.e. mean doses during induction were 3.4 in MDX010-20 vs. 2.9 in CA184-024). For the "Section 1 base case", the higher number of doses from the MDX010-20 trial is applied to patients receiving ipilimumab at first-line.

Component B: Adjustment of BRIM-3 vemurafenib OS curve to account for the effect of second-line ipilimumab

Although the Committee acknowledged that a mixed treatment comparison (MTC) was inappropriate to compare the survival of patients treated with ipilimumab and vemurafenib, members of the Committee expressed concerns regarding the submitted comparison of the unadjusted trial data between ipilimumab (CA184-024) and vemurafenib (BRIM-3). In the submission, BMS reasoned that the unadjusted comparison was appropriate despite differences in patient characteristics as the OS for patients in the DTIC control arms was similar. This finding was based on a visual comparison of the 9-month Kaplan-Meier data for OS of patients treated with DTIC in the BRIM-3 trial and in the CA184-024 trial (MS, Figure 35, p 129).

However, the latest data cut from the BRIM-3 trial (presented in this section as new evidence on page 25) shows differences in the DTIC OS curves between BRIM-3 and CA184-024 (Figure 9). This may reflect the increased availability of subsequent therapies for patients treated in the more recent BRIM-3 trial and/or different baseline prognostic factors in the populations included in the two studies.

Given those recent findings, there are two key issues with the unadjusted comparison of BRIM-3 to CA814-024:

- Bias in OS outcomes of vemurafenib due to administration of ipilimumab second-line to more than 20% of patients in both arms of the BRIM-3 trial (addressed under 'component B'); and
- differences in patients' baseline characteristics (addressed under 'component C').

To address these key issues and enhance the robustness of the comparison to vemurafenib, we updated the cost-effectiveness model with an adjusted comparison vs. vemurafenib.

Published data cuts from the BRIM-3 trial show that a substantial proportion of patients (>20%) received ipilimumab after both vemurafenib and DTIC, as this was allowed in the trial protocol. It is expected that this use of ipilimumab second-line has positively impacted the survival of some patients. Therefore the OS of vemurafenib shown within the Kaplan Meier curves (and within the original manufacturer modelling which mirrors those Kaplan Meier curves) in fact presents a

combined effect of vemurafenib followed by ipilimumab and therefore overestimates the survival of patients receiving only vemurafenib. As a result within the analyses presented below, the vemurafenib OS curve from the BRIM-3 trial has been adjusted to remove the effect of patients receiving ipilimumab as second-line treatment. The adjustment was executed in four steps:

1. The number of patients in BRIM-3 who received second-line treatment with ipilimumab per model cycle was estimated.
2. The patients' expected risk of death per cycle, dependent on the time of initiation of second-line treatment, was calculated.
3. The OS curve for vemurafenib was "recalculated", excluding the patients who received ipilimumab second-line.
4. The resulting OS curve was compared with the original vemurafenib KM OS curve from the BRIM-3 trial in order to compute a hazard ratio which was applied to adjust the long-term tail of the curve.

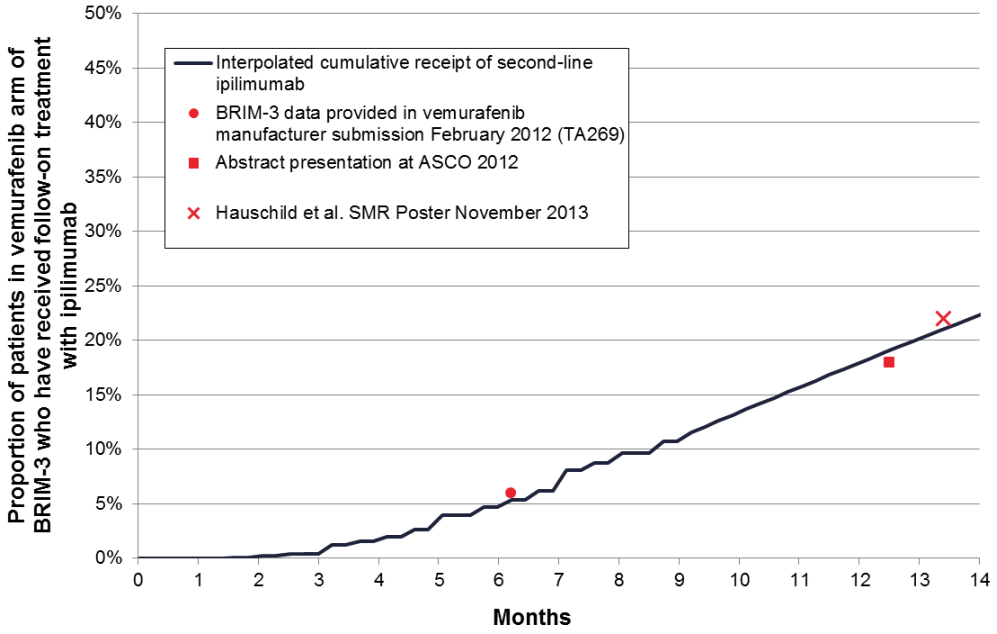
These steps are described in more detail below.

It should be noted that no adjustment is required to the results of the CA184-024 or MDX010-20 trials as no patients received vemurafenib after ipilimumab or DTIC within these trials, and crossover was not allowed from DTIC to ipilimumab.

1. *Estimation of the number of patients in the vemurafenib arm of the BRIM-3 trial that received ipilimumab second-line*

The proportion of patients who had received follow-on treatment with ipilimumab was sourced from published data cuts of the BRIM-3 trial (as shown in Figure 7).

Figure 7: Predicted cumulative receipt of second-line ipilimumab after vemurafenib in BRIM-3 trial patients[5, 7, 8]



Note: Curve shown is applied only to the 14 months of OS KM data available for vemurafenib.
ASCO, American Society of Clinical Oncology; SMR, Society of Melanoma Research

The information reported at the three cut-off points was used to estimate a cumulative curve of the total number of patients who had received second-line ipilimumab over the 14 months for which KM data for vemurafenib are available. This was expressed as the proportion of patients receiving second-line ipilimumab, who would have been eligible to receive a second-line treatment (i.e.

patients who either progressed or eventually died). The modelled PFS curve for vemurafenib (from TA269[5]) ensured the proportion of patients receiving ipilimumab second-line never exceeded the rate at which they progressed from first-line vemurafenib. This method manifests as “prongs” in the curve up to month 9 (Figure 7). As no KM data were available beyond month 9, the curve transitions to a smooth parametric piece at this point. Calibrating this curve to the observed data points allowed the estimation of the number of patients for each model cycle who would be expected to initiate treatment with ipilimumab following disease progression on vemurafenib.

2. *Prediction of patient death events during or after of second-line ipilimumab treatment in the BRIM-3 trial*

The survival of patients who received ipilimumab second-line was obtained from the OS curve presented in TA268. As second-line treatment in BRIM-3 started at different times (depending on individual patient progression), mortality hazards, derived from the second-line ipilimumab OS curve in TA268, were applied to the patients in the cycle in which their second-line treatment was initiated. This effectively models a set of “tunnel states” to track patient survival during follow-up treatment, depending on when their ipilimumab treatment was initiated after vemurafenib treatment.

The result is the prediction of the time-dependent mortality of patients who have received second-line ipilimumab. This allowed the total number of patients per weekly cycle who would be expected to die during or after second-line ipilimumab therapy to be calculated. This approach assumes that the efficacy of ipilimumab is specifically independent of prior therapy with vemurafenib, as supported by the conclusions of the EMA, and more generally that the efficacy of ipilimumab is not affected by any prior therapy. The available information on sequential use of treatments (Section 3) suggests that, due to their different modes of action, vemurafenib and ipilimumab are not expected to interact.

3. *Generation of the OS curve for patients treated with vemurafenib only*

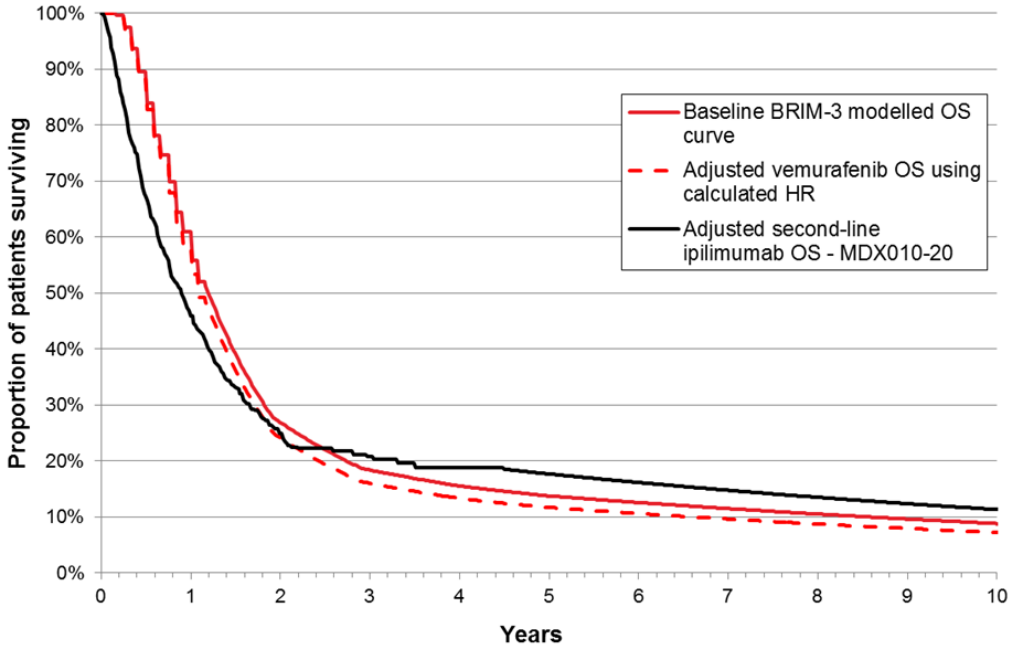
The 14 months of OS KM data available from the BRIM-3 trial was adjusted to recalculate the mortality hazards based on those patients who had only received first-line vemurafenib by removing the patients who died during or after second-line ipilimumab. This was done by calculating the risks of death for patients receiving vemurafenib only, from the risks of death per cycle for patients who had received follow-on treatment with ipilimumab, and the risks of death for the cohort as a whole. This produced an OS curve for patients who were treated with vemurafenib first-line, but did not receive follow-on treatment with ipilimumab.

4. *Adjustment of BRIM-3 vemurafenib OS curve to account for long-term treatment effect of follow-on treatment with ipilimumab*

The resulting curve from step 3 was compared with the original vemurafenib KM OS curve from the BRIM-3 trial in order to compute a hazard ratio (HR=0.92) which allowed equal adjustment of the extrapolated tail of the vemurafenib OS curve, i.e. beyond available KM data.

The adjusted vemurafenib OS curve is presented in Figure 8 alongside the curve for vemurafenib from TA269 and the adjusted MDX010-20 ipilimumab OS curve (as described in ‘component B’). The adjustment results in a slight reduction of OS for vemurafenib. Given the high proportion of patient who received follow-on treatment with ipilimumab, the true OS of patients who only received vemurafenib may be lower still. However, as no detailed information is publically available on how this has affected patient survival, we expect this to be a reasonably conservative estimate.

Figure 8: Comparison of adjusted ipilimumab OS curve, BRIM-3 vemurafenib OS curve and modelled vemurafenib OS curve adjusted for the effect of follow-on treatment with ipilimumab



OS, overall survival.

Component C: Adjustment of BRIM-3 vemurafenib and DTIC OS curves to account for differences in patient baseline characteristics (between BRIM-3 and CA184-024)

As noted earlier, the ERG stated that it did not consider that using data directly (i.e. unadjusted) from the BRIM-3 trial within the model was appropriate because of concerns about the exchangeability of populations across the BRIM-3 and CA184-024 trials. Based on this, the ERG concluded that there was no reliable clinical-effectiveness evidence for a comparison of ipilimumab with vemurafenib.

In component B, we adjusted for the effect of second-line ipilimumab on the survival of patients receiving vemurafenib - removing one of the key differences between the two trials which is likely to influence survival. In order to further enhance the robustness of the indirect comparison to vemurafenib, the vemurafenib OS curve was further adjusted to account for the different patient baseline characteristics.

More patients in the BRIM-3 trial had severe disease in terms of tumour stage and LDH levels compared with CA184-024. This is consistent with the clinical literature which indicates that BRAF V600 mutation-positive patients may have less favourable prognostic characteristics (tumour stage and LDH) reflecting a more aggressive disease, and due to these characteristics rather than mutation status alone, a worse prognosis.[9] Adjusting for the imbalances in these prognostic characteristics should therefore be equivalent to adjustment for BRAF V600 mutation status.[9]

Although, as recognised by the Committee and the ERG, a formal MTC cannot be used to indirectly compare the efficacy outcomes for ipilimumab and vemurafenib, this adjustment for baseline characteristics is expected to adequately account for the differences in patient outcomes between the two trial cohorts.

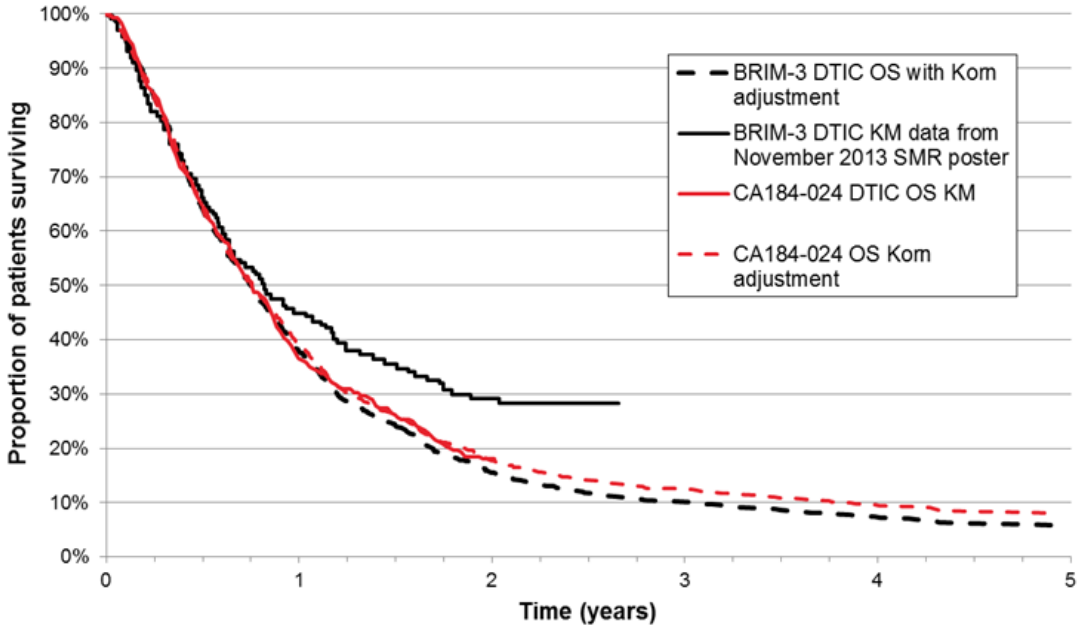
Patient-level data for the BRIM-3 study are not publicly available. The vemurafenib OS curve was therefore adjusted to match the CA184-024 patient baseline characteristics by means of the Korn model.[10] The model reported by Korn et al. allows the prediction of OS for metastatic melanoma patients based on four prognostic characteristics: Gender; ECOG performance status; tumour stage;

and presence of brain metastases. The model was based on evaluation of individual-level data for 2,100 patients enrolled onto 42 Phase 2 trials between 1977 and 2005.

The vemurafenib OS curve was adjusted in a four-step process:

1. The DTIC arm of the BRIM-3 trial was reproduced with the Korn model, based upon the patient characteristics of the BRIM-3 trial. This allowed a prediction of the survival of patients receiving DTIC only (i.e. not followed by ipilimumab or vemurafenib). As <2% of patients in either BRIM-3 or CA184-024 had brain metastases at baseline, this parameter was not included in the analysis.
2. The DTIC arm of the CA184-024 trial was also reproduced using the Korn model based upon the patient characteristics of the CA184-024. This analysis has been presented before (MS, Figure 21, p 90) and shows that the observed OS coincided with or fell below the model predicted OS, confirming the validity of the Korn model to serve as a predicted control for the current patient population of previously untreated, advanced melanoma patients.
3. To quantify the true effect of the different baseline characteristics between BRIM-3 and CA184-024, a hazard ratio was calculated (HR = 0.96) by comparing the Korn model simulated OS curves for DTIC in BRIM-3 and the CA184-024 trial (Figure 9).
4. To adjust the vemurafenib OS curve for the true effect of differences in patient baseline characteristics between BRIM-3 and CA184-024, the hazard ratio of 0.96 was subsequently applied to the vemurafenib arm of the BRIM-3 trial.

Figure 9: Comparison of Kaplan-Meier curves for OS with DTIC from CA184-024 and BRIM-3, and simulated OS with DTIC using the Korn model



Note: Presented KM data for DTIC from the BRIM-3 trial includes censoring at crossover to vemurafenib. Presented KM data for DTIC from the BRIM-3 trial however includes patients who received second-line ipilimumab. Patients in the DTIC arm of the BRIM-3 trial had longer survival times than the Korn model predicts because 24% of DTIC patients received ipilimumab after DTIC and many patients also received vemurafenib after DTIC. A similar proportion (22%) received second-line ipilimumab in the vemurafenib arm. This has been accounted for in the analysis described in the previous section, which removed the treatment effect of follow-on treatment with ipilimumab in the BRIM-3 trial.

ASCO, American Society of Clinical Oncology; DTIC, dacarbazine; KM, Kaplan–Meier; OS, overall survival.

This method assumes there is no differential efficacy of vemurafenib compared with DTIC (according to the prognostic characteristics for which the model is adjusted). The forest plots presented for the BRIM-3 trial indicate no significant difference in effect according to gender, ECOG status or tumour stage.

The limitations of the Korn model are that it does not correct for potential differences in unmeasured prognostic factors. As LDH data were only available for a very small subset of patients (6%), LDH was discarded when the Korn model was being developed. The Korn algorithm also requires the use of a suboptimal parametric distribution (i.e. Weibull distribution) to describe survival over time. However, as BRAF status was not measured in CA184-024 or MDX010-20 (preventing a comparison of ipilimumab and vemurafenib in the same population), this method pragmatically addresses the issue of differences in baseline characteristics between trials. As presented in the submission, based on the data available from other studies, and based on mechanism of action, ipilimumab's efficacy is expected to be independent of BRAF status.

Final results - combined impact of new analyses ("Section 1 base case")

The analyses described previously are combined in the following set of results. This also includes the results when using the sequential model approach.

Results for the 3-state model

The analyses have been combined to produce a new estimate of the ICERs versus DTIC and vemurafenib. Table 7 presents the "Section 1 base case" results for a 3-state model – the approach preferred by the ERG.

These results comprise the main set of results in support of ipilimumab 3mg/kg first-line: i.e. ipilimumab is cost-effective compared with both DTIC and vemurafenib. These results for ipilimumab are further similar to the results observed across the multiple sources of evidence used in the submission.

Table 7: Final results (3-state model) – combined impact of new analyses ("Section 1 base case")

Comparison vs. ipilimumab – 3-state model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	Net benefit*
Ipilimumab	£[redacted]	3.2326	2.2566					
DTIC	£[redacted]	2.0018	1.4611	£[redacted]	1.2309	0.7955	£47,899	£[redacted]
Vemurafenib	£[redacted]	2.8401	2.0550	£[redacted]	0.3925	0.2016	£28,642	£[redacted]

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £50,000 versus DTIC (end of life), £30,000 versus vemurafenib

It has to be noted that the ICER presented vs. vemurafenib (£28,642 per QALY gained) presents a conservative estimate for two reasons:

- The modelled benefit of vemurafenib over DTIC looks unrealistically high based upon the latest data cut of the BRIM-3 trial where the curve for vemurafenib converges with the DTIC curve even after crossover patients are censored out, indicating that the benefits of vemurafenib over DTIC are not sustained in the long-term (also see Figure 11);
- It is expected that clinicians will only select BRAF mutation-positive patients with favourable prognostic characteristics for ipilimumab treatment (i.e. to improve their survival prospects) while the ICER in Table 7 includes all BRAF mutation-positive patients.

The first issue is addressed via a scenario analysis (Table 12, p 25): The ICER for ipilimumab compared with vemurafenib significantly reduces to £12,967 per QALY gained when the proportion of patients alive with vemurafenib is assumed to be equal to DTIC at and after 30 months. The second issue is addressed qualitatively below as data are not available from the BRIM-3 trial in the subgroup of patients in whom ipilimumab is likely be used.

It is expected that clinicians would use ipilimumab first-line in BRAF mutation-positive patients with a favourable prognosis, i.e. in whom the likelihood of completing the ipilimumab induction therapy is

high. As a consequence, BRAF mutation-positive patients with a rapid disease progression would be unlikely to receive ipilimumab.

Although an algorithm for sequencing ipilimumab and vemurafenib in clinical practice has not yet been agreed recently published papers (see Figure 10, Section 3) suggest that for BRAF mutation-positive patients with non-bulky, asymptomatic disease and a normal serum LDH concentration, immunotherapy with ipilimumab would be considered as a first-line treatment. A BRAF inhibitor would be clinically more appropriate for first-line use in patients with symptomatic, bulky, rapidly growing disease, or with high serum LDH concentrations. This thinking is reflected in the trial evidence available for the two therapies which, although no significant difference is shown, suggests a trend towards increased ipilimumab efficacy in patients with normal LDH concentration and IIIc to M1b disease and reduced vemurafenib efficacy in these patients (Table 8). In practice, clinicians will assess each patient individually in order to determine the most appropriate sequence of treatments.

Table 8: Hazard ratios for mortality based on prognostic characteristics

Hazard Ratio	Vemurafenib vs. DTIC[5]	Ipilimumab from MDX010-20[6]	Ipilimumab from CA184-024
Disease stage			
IIIc, M1a or M1b	0.64 (0.29-1.38)	0.47 (0.27–0.82)	NR
M1c	0.32 (0.21-0.50)	0.72 (0.53–0.97)	0.67 (0.52,0.86)
LDH			
Normal	0.37 (0.19-0.69)	0.56 (0.39–0.81)	0.75 (0.58-0.98)
Elevated	0.36 (0.22-0.57)	0.76 (0.51–1.13)	0.87 (0.65-1.15)

Results for the sequential model

Two modifications were implemented to enhance the validity of the sequential model, following feedback from the ERG and Committee:

- The mortality hazard for third-line treatment was assumed to be the same as for second-line ipilimumab after patients progressed onto BSC.
- The use of a hazard ratio to estimate efficacy of second-line ipilimumab was replaced with survival curves directly from MDX010-20.

In this response to the ACD the results, using the sequential model, are presented in Table 9 for the comparison of ipilimumab followed by BSC and DTIC followed by ipilimumab. In contrast to the simple 3-state model, following the sequential approach reduces the ICER vs. DTIC from £47,899 to £41,016 per QALY gained.

Table 9: Final results (sequential model) – combined impact of new analyses

Comparison vs. ipilimumab – sequential model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£)	Net benefit*
Ipilimumab → BSC	£[redacted]	3.2326	2.2566					
DTIC → ipilimumab	£[redacted]	2.8516	1.9959	£[redacted]	0.3810	0.2607	£41,016	£[redacted]

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £50,000 versus DTIC (end of life)

Regarding the comparison of ipilimumab and vemurafenib used in sequence, recent evidence (as presented in Section 3) indicates that increased survival can be achieved when clinicians appropriately select patients to receive ipilimumab first-line (rather than vemurafenib). Available observational data also suggest no impact of prior ipilimumab use on the efficacy of vemurafenib.

This evidence is, however, gleaned from observational studies: no randomised data exists that assess the efficacy of vemurafenib second-line, or assess sequential use. Therefore we have

attempted to address the Committee's concerns regarding the use of assumptions when modelling ipilimumab and vemurafenib sequentially. Due to the lack of data in the BRAF mutation-positive subgroup of patients in whom ipilimumab is likely be used first-line, a sequential comparison versus vemurafenib is not presented in this response. Instead, the ICER produced versus vemurafenib (£28,642 [Table 7]) comes from the ERG's preferred 3-state model, and suggests that ipilimumab is a cost-effective treatment vs. vemurafenib.

Calculation of upper bound ICERs by implementing unadjusted second-line (MDX010-20) ipilimumab data for use in a first-line setting ("worst case")

In order to provide the Committee with increased certainty around the upper bounds of the ICERs, unadjusted second-line (MDX010-20) ipilimumab data were included in the model. The application of the MDX010-20 data provides a "worst case" estimate of the efficacy of ipilimumab 3mg/kg monotherapy in previously untreated patients as the patients included in the MDX010-20 trial had generally more severe disease than patients in both the CA184-024 and BRIM-3 trials (Table 5). For this reason, it should not be considered as an appropriate comparison.

BMS encourages the Committee to consider the survival analyses presented in the context of the different baseline characteristics of the trial cohorts; in particular that, in current clinical reality, the absolute outcomes for the patients in the MDX010-20 trial are worse than would be expected from patients treated with second-line ipilimumab. This is because effective first-line treatments were not available at the time of the trial, and patients eligible for second-line treatment had substantially less favourable characteristics as a result.

For the upper bound ICER calculation, the base case OS and PFS curves were taken directly from the second-line cost-effectiveness model submitted as part of TA268.[3]

Efficacy outcomes for DTIC were obtained from the CA184-024 trial (as in the original manufacturer submission) and vemurafenib outcomes are taken from BRIM-3 (as in the original manufacturer submission). This is likely to overestimate the efficacy of DTIC and vemurafenib compared to ipilimumab, as the worse prognostic characteristics of the MDX010-20 trial population are not accounted for.

The meta-analysis originally provided in TA268 showed that there is no significant difference in survival between gp100 and DTIC.[11-13] This is supported by the evidence given to the Committee by clinicians both in this submission and for TA268:

"*The Committee then discussed the plausibility of the assumption that ipilimumab given in combination with dacarbazine would have the same therapeutic effect as ipilimumab alone. The Committee heard from the clinical specialists that this was a possibility because dacarbazine is associated with minimal response.*" – ACD, Paragraph 4.5

"*The Committee agreed with the clinical specialists that gp100 was likely to be an acceptable proxy for best supportive care in the model.*" – TA268 ACD, Paragraph 4.6

In Table 10 the "worst case" results are presented for the conventional 3-state cancer model. While the implementation of unadjusted MDX010-20 second-line data seemingly provides a "worst case" to determine the upper bound for the cost-effectiveness of the 3mg/kg ipilimumab dose at first-line, it cannot be considered a relevant. Furthermore, the results do not to present a fair comparison given the differences in the patient populations included in the three trials (Table 5).

Table 10: Upper bound ICER when implementing unadjusted MDX010-20 ipilimumab data for use in a first-line setting ("worst case")

Comparison vs. ipilimumab – 3-state model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	Net benefit*
Ipilimumab	£[redacted]	3.0025	2.0907					
DTIC	£[redacted]	2.0018	1.4611	£[redacted]	1.0007	0.6296	£58,593	£[redacted]
Vemurafenib	£[redacted]	3.0125	2.1658	£[redacted]	-0.0100	-0.0752	Dominated	£[redacted]

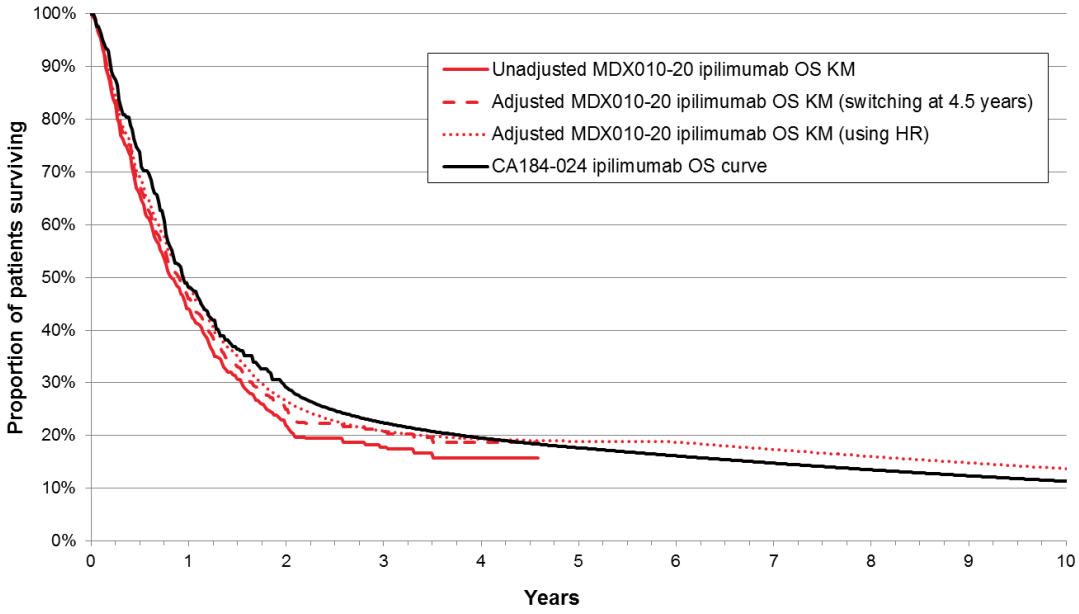
Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £50,000 versus DTIC (end of life), £30,000 versus vemurafenib

Additional scenario analysis applying adjustment of MDX010-20 OS data as a hazard ratio

In the "Section 1 base case", the Cox proportional hazards model was used to produce an adjusted OS KM curve based on data from the MDX010-20 trial, and switched to the OS curve from the CA184-024 at 4.5 years (the point at which survival was equal to DTIC). This scenario applies the adjustment instead as a constant hazard ratio, applied to the entirety of the modelled curve obtained from the MDX010-20 data. Based on the average results of the Cox model, a mortality hazard ratio of 0.88 was used.

The OS curve produced is shown in Figure 10, compared to the unadjusted OS curve from MDX010-20 KM, the adjusted OS curve used in the new base case, and the OS curve modelled on the CA184-024 trial data.

Figure 10: Comparison of adjustments made to the MDX010-20 ipilimumab OS curves



KM, Kaplan–Meier; OS, overall survival

The application of this adjusted curve is expected to be an optimistic estimate of survival, as it estimates a higher proportion of patients alive at the end of the parametric curve piece (6 years), than the curve based on the CA184-024 trial data. This may be a result of the concomitant DTIC used in the first-line trial negatively impacting long-term survival, in which case this scenario may provide an accurate estimate of the efficacy of the 3mg/kg dose as monotherapy at first-line.

As expected, the scenario of using this adjusted curve results in lower ICERs of £38k vs. DTIC and £16k vs. vemurafenib (Table 11).

Table 11: Model results (3-state model) – scenario analysis with alternative adjustment of MDX010-20 data

Comparison vs. ipilimumab – 3-state model

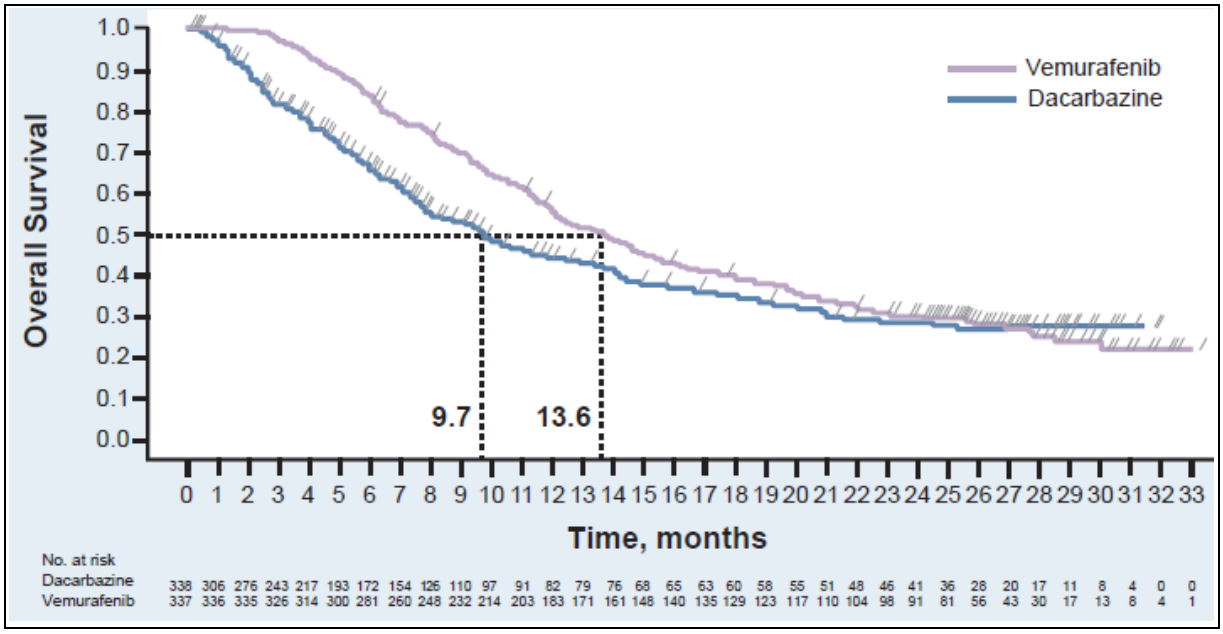
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	Net benefit*
Ipilimumab	£[redacted]	3.6713	2.5105					
DTIC	£[redacted]	2.0018	1.4611	£[redacted]	1.6695	1.0494	£37,575	£[redacted]
Vemurafenib	£[redacted]	2.8401	2.0550	£[redacted]	0.8312	0.4556	£15,592	£[redacted]

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £50,000 versus DTIC (end of life), £30,000 versus vemurafenib

Additional scenario analysis utilising new evidence available for vemurafenib

In addition to the new ICER estimates, we also present an additional scenario, in which the proportion of patients alive with vemurafenib was assumed to be equal to the proportion of patients alive with DTIC at and after 30 months. This is in line with the latest data cut from the BRIM-3 trial where the Kaplan-Meier curves cross between 25 and 30 months, indicating that there is no OS benefit of vemurafenib over DTIC in the long-term (Figure 11).

Figure 11: Updated Kaplan-Meier curves for OS in BRIM-3 with censoring at crossover on the DTIC arm[7]



In this scenario, the mortality hazards for vemurafenib between the end of the KM data (at 14 months) and the end of the newly available KM data (30 months) are increased such that the proportion of patients alive at 30 months is equal to that in the DTIC OS curve. After 30 months, vemurafenib survival is assumed to be equal to DTIC. The other changes adopted in the "Section 1 base case" are kept in this analysis (i.e. the adjustments for patient characteristics and second-line ipilimumab in the BRIM-3 trial are applied).

Results (Table 12) indicate that ipilimumab is a highly cost-effective treatment versus vemurafenib in this scenario.

Table 12: Model results (3-state model) - Scenario analysis limiting vemurafenib long-term benefits of DTIC to those observed in the latest trial data cut

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	Net benefit*
Ipilimumab	£[redacted]	3.2326	2.2566					
Vemurafenib	£[redacted]	2.2641	1.6747	£[redacted]	0.9685	0.5819	£12,967	£[redacted]

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £30,000 versus vemurafenib

Additional sensitivity and scenario analyses around the "Section 1 base case"

To assess the model sensitivities in the "Section 1 base case" (which includes all of the analyses presented in this section), one-way and probabilistic sensitivity analyses as well as several further scenario analyses were conducted and are presented in Appendix 1.

The most influential parameters in the deterministic sensitivity analysis were those used to estimate the OS of DTIC and vemurafenib.

The probabilistic sensitivity analysis shows that the ICER is distributed closely around the respective willingness-to-pay thresholds for the comparators: £50,000 per QALY vs. DTIC as end-of-life criteria apply and £30,000 vs. vemurafenib. The mean results show that ipilimumab is cost-effective compared with both DTIC and vemurafenib.

A concise table of the different scenario analyses performed (presented in Appendix 1) also includes the ERG preferred base case from the first Committee meeting (i.e. a 3-state model). The least favourable ICERs are produced by the shortening of the model time horizon. Again, the results are generally close to the maximum acceptable ICER thresholds.

In general, the sensitivity and scenario analyses show that the cost-effectiveness results are relatively insensitive to changes in most parameter values and assumptions, and demonstrate the robustness of the model for the conservative "Section 1 base case".

Section 2: Clarification of assumption made regarding the relative efficacy of 3mg/kg ipilimumab and 10mg/kg ipilimumab + DTIC

Summary:

- In the ACD the Committee noted that there were uncertainties generated by the evidence, i.e. that the manufacturer went beyond the conclusions of the regulator in making the assumption that 3mg/kg and 10mg/kg ipilimumab have equivalent effectiveness.
- The Committee concluded that further evidence from ongoing trials would reduce the uncertainty and allow the Committee to make an informed judgement on the likely relative clinical effectiveness of ipilimumab 3mg/kg alone compared with dacarbazine alone or vemurafenib alone. The Committee strongly encouraged recruitment and patient follow-up in these studies.
- This section is designed to make clear that the assumption on which BMS has been relying throughout this appraisal is: "**Clinical efficacy of 10mg/kg ipilimumab + DTIC is similar to 3mg/kg ipilimumab monotherapy**"; not "clinical efficacy of ipilimumab 10mg/kg and 3mg/kg is equivalent".
- The key data to support the licensed dose of 3mg/kg ipilimumab as first-line treatment come from multiple data sets including patients actually treated with 3mg/kg in this setting, showing overall survival which compares favourably to the DTIC arm in CA184-024. The randomised Phase 3 data from CA184-024 was considered to support for the recommendation of 3mg/kg ipilimumab at first-line and is acknowledged in the EPAR.
- The EPAR further confirms that previous Phase 3 RCT data have shown that ipilimumab's OS benefit at a dose of 3mg/kg is consistent between previously treated and untreated populations and was observed regardless of the number of or type of prior treatment.
- This section also clarifies that the ongoing CA184-169 trial will only address whether or not 10mg/kg is the optimal dose of ipilimumab.
    - Treatment with ipilimumab 3mg/kg is approved as effective with similar OS benefit in both first- and second-line by the EMA, as stated in the EPAR.
    - The evidence from CA184-169 will not provide further support for the licensed 3mg/kg dose. CA184-169 will also not provide additional information on the efficacy or safety of ipilimumab 10mg/kg in combination with DTIC.

Context:

In the ACD the Committee noted that there were uncertainties generated by the evidence, i.e. that BMS went beyond the conclusions of the regulator in making the assumption that 3mg/kg and 10mg/kg ipilimumab have equivalent effectiveness. The Committee heard from the Clinical Experts that there was no biological reason for the efficacy to be different for the 2 doses [3mg/kg and 10mg/kg]. However, the Committee noted that there was currently no robust evidence to support this view although there is an ongoing trial (CA184-169) that is directly comparing the 3mg/kg and 10mg/kg doses. The Committee concluded that further evidence from ongoing trials would reduce the uncertainty and allow the Committee to make an informed judgement on the likely relative clinical effectiveness of ipilimumab 3mg/kg alone compared with dacarbazine alone or vemurafenib alone.

Clarifying that assumption made was "clinical efficacy of 10mg/kg ipilimumab + DTIC is similar to 3mg/kg ipilimumab monotherapy":

We would like to clarify that the actual assumption BMS made for the economic model was "**clinical efficacy of 10mg/kg ipilimumab + DTIC is similar to 3mg/kg ipilimumab monotherapy**"; not "clinical efficacy of ipilimumab 10mg/kg and 3mg/kg is equivalent" (This has been clarified before in BMS's Pro-forma Response to the ERG report from 9th January 2014).

We believe this is a crucial distinction as the similarity between the overall survival outcomes associated with 3mg/kg ipilimumab monotherapy and 10mg/kg ipilimumab in combination with DTIC was accepted by the EMA and is hence thought to be appropriate. It is important to emphasise that whilst DTIC did not contribute to ipilimumab's efficacy, the combination with DTIC led to considerably

increased toxicity. This again resulted in patients receiving fewer doses of ipilimumab which has in all likelihood decreased the potential efficacy of the ipilimumab treatment (this issue is explained in detail on p 28).

As noted in the EMA's EPAR, *"in the MDX010-20, OS benefit was observed regardless of the number of or type of prior anti-cancer systemic treatment. Specifically, OS benefit was observed for patients who did or did not have prior DTIC or non-DTIC chemotherapy or prior immunotherapy and for patients who had 1 or ≥2 prior line of therapy. The treatment effect in favor of the 3mg/kg ipilimumab group was observed across all prior therapy subgroups: in all cases, the 95% CI of HR estimates in all subgroups included in the HR estimate for the overall (intent-to-treat [ITT]) population (HR=0.66; 95% CI: 0.51-0.87). These results demonstrate that the performance of ipilimumab within these subgroups is favorable and thus consistent with the survival advantage demonstrated for the overall study population."* [2]

The key data to support the licensed dose of 3mg/kg ipilimumab as first-line treatment come from multiple data sets including patients treated with 3mg/kg in this setting, showing overall survival which compares favourably to the DTIC arm in CA184-024.

The CHMP stated that *"The results of this study [CA184-024] were considered to support the efficacy of ipilimumab in previously untreated patients. Furthermore, exploratory analyses of the role of prior treatment did not reveal any important interaction. Clinical pharmacology data supported similar pharmacokinetics for previously treated and previously untreated patients, and was unaffected by dacarbazine. Thus, the efficacy of the ipilimumab 3 mg/kg monotherapy regimen in previously untreated patients was considered established."* [2]

The CHMP verified that the two randomised Phase 3 trials of ipilimumab [MDX010-20 and CA184-024] *"have demonstrated long-term OS benefit, confirming that ipilimumab is efficacious in previously untreated and previously treated advanced melanoma. In both studies, the 2 year OS rates were similar despite different eligibility (treatment naïve or pre-treated) and different regimens (3mg/kg ipilimumab or 10mg/kg ipilimumab + DTIC)". "OS analyses from 3mg/kg ipilimumab monotherapy (pooled) in previously untreated advanced melanoma demonstrate that 3mg/kg ipilimumab monotherapy has at least similar OS (median, 1 year and 2 year) to the ipilimumab treated patients in the two randomized Phase 3 studies. Furthermore, in previously untreated patients,* ***the median and long-term OS from 3mg/kg ipilimumab monotherapy and 10mg/kg ipilimumab + DTIC are similar*** *and both are numerically higher than DTIC alone (median OS = 9.07 months; 1 yr: 36%, 2 yr: 18%)"* [2] (see Table 13).

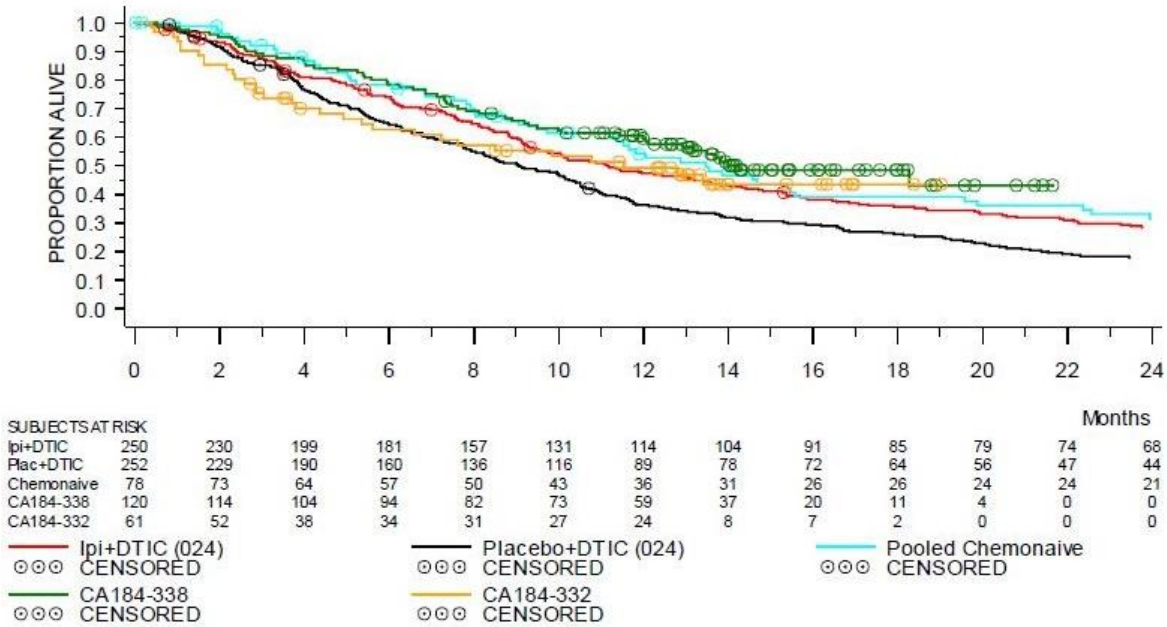
Table 13: Comparison of 3mg/kg ipilimumab in untreated and previously treated patients and 10mg/kg ipilimumab + DTIC in untreated patients (consolidated from tables 12 and 17 in EPAR)

	3mg/kg Previously treated Stage 3 (unresectable) or Stage 4 melanoma **MDX010-20**	**3mg/kg** Untreated Stage 3 (unresectable) or Stage 4 melanoma **Pooled monotherapy†**	**10mg/kg + DTIC** Untreated Stage 3 (unresectable) or Stage 4 melanoma **CA184-024**	**DTIC** Untreated Stage 3 (unresectable) or Stage 4 melanoma **CA184-024**
Primary endpoint (OS)				
Hazard Ratio (95% CI)	0.66 (0.51, 0.87)	NA	0.72 (0.59, 0.87)	
Log-rank p value	0.0026	NA	0.0009	
Efficacy				
Median OS, months (95% CI)	10.1 (8.0, 13.8)	13.5 (8.8, 15.5)	11.2 (9.4, 13.6)	9.1 (7.8, 10.5)
1 year OS, % (95% CI)	45.6 (37.0, 54.1)	51.5 (34.4, 68.6)	47.3 (41.0, 53.5)	36.3 (30.4, 42.4)
2 year OS, % (95% CI)	23.5 (16.0, 31.5)	24.2 (9.7, 39.4)	28.5 (22.9, 34.2)	17.9 (13.3, 22.8)
3 year OS, % (95% CI)	20.1 (13.2, 28.1)	23.7 (14.3, 34.4)	20.8 (15.7, 26.1)	12.2 (8.2, 16.6)

† Pooled OS analysis for 3mg/kg ipilimumab monotherapy: OS analysis of data from the ipilimumab monotherapy arms of MDX010-20, the pooled data of CA184004/022, and all pooled data provided an overall survival of about 9 months after initiation of the studies, providing a consistent result regarding OS after 3mg/kg ipilimumab monotherapy in patients with advanced melanoma (data not shown). Please also see table 14 in the EPAR.
CI = confidence interval; DTIC = dacarbazine; NA = not applicable ; OS = overall survival

In addition, the NCDF panel acknowledged the similarity (Figure 12) between the outcomes of 3mg/kg ipilimumab (in CA184-338) and 10mg/kg ipilimumab + DTIC (CA184-024) in its recent decision.[14]

Figure 12: Kaplan–Meier curves for OS of untreated patients in CA184-024 (10mg/kg + DTIC), CA184-332 (3mg/kg), CA184-338 (3mg/kg) and chemotherapy-naïve patients (3mg/kg)



Pooled Chemonaïve arm includes studies CA184-004/CA184-022, MDX010-08 and MDX010-20.

General note: In the above figure, survival profiles of ipilimumab 3mg/kg monotherapy from CA184-332, CA184-338 and pooled chemotherapy- naïve patients are compared with the DTIC arm from CA184-024. It is important to note that patient populations were comparable though patients treated in clinical practice (CA184-332 and CA184-338) showed worse prognostic features including greater ECOG performance status and a higher proportion of patients presenting with associated brain metastases, compared with patients enrolled in CA184-024 (see section 6.8.1 in submission).

Note on CA184-332 curve: The Kaplan-Meier OS curve for patients enrolled in CA184-332 is initially below that for patients treated with DTIC monotherapy in CA184-024, but crosses at approximately 8 months before joining the other ipilimumab treatment arm curves. This observation is likely explained by the high proportion (32.8%) of patients presenting with brain metastases in this trial. This hypothesis is supported with subset analyses of patients enrolled in CA184-332 that shows a median OS of 4.2 months in patients with brain metastases at baseline with ~45% dead at three months compared with a median OS of 13.4 months in patients without brain metastases (see section 6.8.1 in submission).

As described in detail in the EPAR, we believe that the survival outcomes in the CA184-024 study are similar to the outcomes observed with 3mg/kg monotherapy in patient populations with less favourable prognostic characteristics (Figure 12) due to the following reasons:

- Whilst DTIC did not contribute to ipilimumab's efficacy (see Section 7), the combination with DTIC led to considerably increased toxicity: The high percentage (46.2%) of AEs leading to drug discontinuation is indicative for severe toxicity of 10mg/kg ipilimumab + DTIC treatment and the poor tolerance of patients regarding this treatment regimen. A substantial proportion (31.2%) of the patients in the 10mg/kg ipilimumab + DTIC arm did not receive more than two doses of ipilimumab (mean number of doses were 2.9 out of the planned 4 doses in the CA184-024 study).
- The positive association between the number of ipilimumab doses and OS has been presented before (HR 1.874 for 1-2 vs. 4 doses, p value = 0.022 and HR 1.593 for 3 vs. 4 doses, p value = 0.0114)[10] as well as in a recent publication, meaning the lower number of doses received in CA184-024 has likely decreased the potential efficacy of the ipilimumab treatment.

Use of CA184-024 data in the health economic model:

Given the lack of randomised controlled Phase 3 studies comparing the efficacy of 3mg/kg ipilimumab monotherapy with (at least) DTIC in previously untreated patients with advanced melanoma, data from trial CA184-024 were used in the health economic model to estimate the cost-effectiveness of 3mg/kg ipilimumab. This was a pragmatic approach given trial CA184-024 is the only source of Phase 3 comparative (vs. DTIC) efficacy data in previously untreated patients. The use of CA184-024 data however presents a conservative estimate of the clinical and cost-effectiveness of the 3mg/kg dose, based on the rationales described before.

The CHMP concluded that *"the efficacy of 3mg/kg ipilimumab monotherapy has been established in previously treated melanoma patients; the baseline characteristics of the patients included in the pivotal studies in previously treated and previously untreated subpopulations were similar; the similar patient characteristics of the two trials [MDX010-20 and CA184-024] support the relevance of the results observed in a previously treated population to the first-line setting."* [2]

In conjunction with the new analysis presented in Section 1, using ipilimumab 3mg/kg evidence from MDX010-20, the additional explanations should provide the Committee with further reassurance that the in the submission presented ICERs versus DTIC and vemurafenib are plausible.

Clarifying what data will become available from the ongoing trial CA184-169:

The Committee noted that there is an ongoing trial (CA184-169) that is directly comparing ipilimumab at a 3mg/kg and 10mg/kg dose. We would like to specify that this trial, which we expect to report in approximately 15 months, investigates if the dose of 10mg/kg ipilimumab is superior, in terms of overall survival, compared with the 3mg/kg dose (i.e. the trial is not designed to show equivalence of 3mg/kg and 10mg/kg ipilimumab). This means that the trial will only address whether or not 10mg/kg ipilimumab is the optimal dose.

Treatment with ipilimumab 3mg/kg is approved as effective with similar OS benefit in both first- and second-line by the EMA, as stated in the EPAR. The evidence from CA184-169 will not provide further support for the licensed 3mg/kg dose.

The trial will not provide additional information regarding the efficacy of 10mg/kg ipilimumab + DITC. DTIC may negatively affect the efficacy of 10mg/kg ipilimumab, given the high discontinuation rate due to toxicity with the combination (as explained before), and given that DTIC alone never demonstrated an OS benefit. CA184-169 will also not provide additional information regarding the efficacy of ipilimumab 10mg/kg relative to DTIC.

While 10mg/kg ipilimumab may be more efficacious than 3mg/kg, there is ample data to support that outcomes with 3mg/kg are similar in first- and second-line patients, and compare favourably with DTIC, which never demonstrated an OS advantage.

It should be highlighted that the CHMP considered the benefit/risk ratio of 3mg/kg ipilimumab to be positive. The safety of the 3 mg/kg dose appears more acceptable than that of the 10mg/kg dose. [2]

Further data from other BMS studies:

An ongoing world-wide prospective, observational study in patients with advanced melanoma (IMAGE) is currently recruiting previously treated patients as they initiate second-line therapy with either 3mg/kg ipilimumab or another approved treatment. The IMAGE study will soon be extended to recruit patients receiving 3mg/kg ipilimumab as first-line therapy. The CHMP has approved the revised protocol for the study extension in March 2014. This study will provide supportive evidence for the efficacy of the 3mg/kg dose in the first-line setting. It should however be noted that, while the decision of patients to be included in the study is entirely independent of any treatment decision, recruitment requires funding access to be available. We expect that initial data from territories where first-line access is granted will be available from 2016.

Section 3: Additional evidence for treatment sequencing of ipilimumab and vemurafenib

Summary:

- The Committee noted that there are uncertainties around the plausibility of assumptions and inputs in the economic model, i.e.:
  - that the treatment sequencing of vemurafenib and ipilimumab would have an impact on the cost-effectiveness analysis, as this calculation entailed using arbitrary or adjusted OS curves for each line of treatment;
  - that additional data on sequencing would be valuable to obtain more accurate estimates.
- This section presents additional evidence on sequencing which substantiates the treatment sequencing assumptions for ipilimumab and vemurafenib.
  - The data suggest that in BRAF mutation-positive patients who have non-bulky, asymptomatic disease and a normal LDH concentration, immunotherapy with ipilimumab may be considered as first-line therapy.
  - The data further suggest that BRAF inhibitors are as effective after immunotherapy as they are prior to immunotherapy, and that ipilimumab should be considered first-line if a BRAF mutation-positive patient could benefit from immunotherapy.
  - We conclude that a recommendation for ipilimumab at first-line would allow clinicians to refer patients for a treatment with ipilimumab when appropriate, based on a patient's individual clinical presentation and prognosis.
- It further clarifies that results from ongoing trials, whilst they will provide additional guidance to clinicians regarding the optimal treatment of patients, will only be of limited value for the present decision problem.

Context:

The active comparators in this appraisal are ipilimumab, a modulator of T-cell activity, and vemurafenib, an inhibitor of a specific activating mutation in the BRAF signalling pathway. Immunotherapies and targeted agents have very different mechanisms of action, of which the Committee is aware of. The AC expressed specific concerns regarding the evidence available for the efficacy of ipilimumab and vemurafenib used sequentially in BRAF mutation-positive patients (i.e. ipilimumab first-line followed by vemurafenib second-line and vice versa), and that it would be valuable to have additional data on sequencing in order to obtain more accurate estimates.

The Committee noted that several ongoing trials explore treatment sequences relating to vemurafenib and ipilimumab.

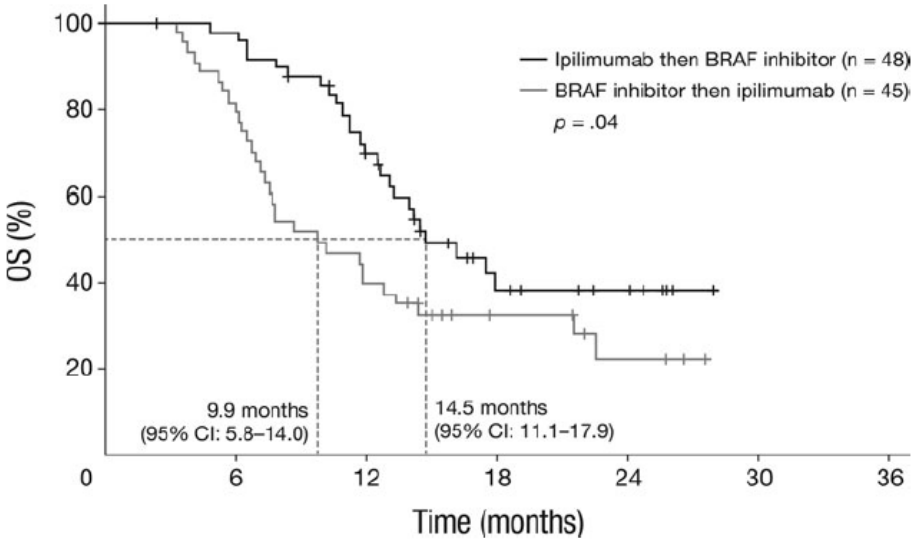
Additional evidence to substantiate treatment sequencing assumptions for ipilimumab and vemurafenib:

At present, data on the sequencing of ipilimumab and vemurafenib are scarce. However in the last few months relevant additional evidence has become available.

Ascierto et al.[15] report results from a retrospective, multicenter analysis in 93 patients, which showed that the median OS was significantly longer (14.5 months vs. 9.9 months; p=0.04) in patients who received therapy with ipilimumab (at the licensed dose of 3mg/kg) prior to a BRAF inhibitor (either vemurafenib or dabrafenib) than in those who received a BRAF inhibitor prior to ipilimumab (see Figure 13). Given the similarities in OS and PFS for patients treated with vemurafenib and dabrafenib, these patients were pooled together in this study.[16, 17]

Additional experience reported by Ackerman et al., based on a retrospective analysis of 274 consecutive patients from 5 Melanoma Centres enrolled between 2009 and 2012 in the United States and Australia, is consistent with the reported data and shows longer survival among patients treated with immunotherapy prior to a BRAF inhibitor.[18]

Figure 13: OS for patients who received a BRAF inhibitor followed by ipilimumab or ipilimumab followed by a BRAF inhibitor (Ascierto et al. 2014)[15]



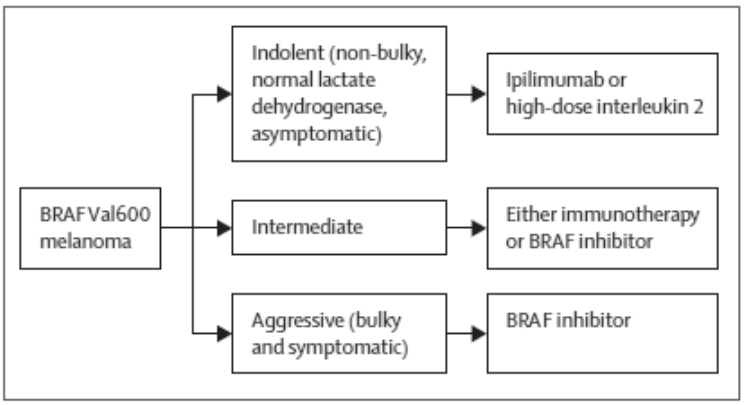
Note: 93 patients had received sequential treatment with both treatments and were eligible for analysis, comprising 48 (52%) patients who received BRAF inhibitors upon disease progression with ipilimumab and 45 (48%) patients who received ipilimumab upon disease progression with a BRAF inhibitor.

CI, confidence interval; OS, overall survival.

Based on the available data, Jang (2013) concludes that disease progression is often rapid after the onset of resistance to vemurafenib treatment.[17] In this setting subsequent treatment with ipilimumab may be inappropriate as patients are often too poorly to complete the treatment schedule of 4 doses. Due to the absence of prospective clinical data Jang proposes to follow expert advice in order to guide the choice of treatment sequence.

Experts suggest treatment with a BRAF inhibitor first in patients with symptomatic, bulky, rapidly growing disease, or with high serum LDH concentrations. These patients are less likely to benefit from immunotherapy and can achieve rapid short-term improvement in symptoms with a selective BRAF inhibitor. In BRAF mutation-positive patients who have non-bulky, asymptomatic disease and a normal LDH concentration, immunotherapy with ipilimumab could be considered first, followed by vemurafenib if and when patients show signs of clinical and radiographic disease progression. This approach could maximise the potential for patients to achieve a durable response from immuno-therapy without apparently compromising their ability to respond to vemurafenib or other BRAF-inhibiting therapies (Figure 14). It would also enable clinicians to choose the most appropriate treatment strategy for their patients based upon individual patient prognoses.

Figure 14: Suggested initial treatment for metastatic melanoma patients with confirmed BRAF V600 mutation[17]



Clinical trials might be appropriate for each category

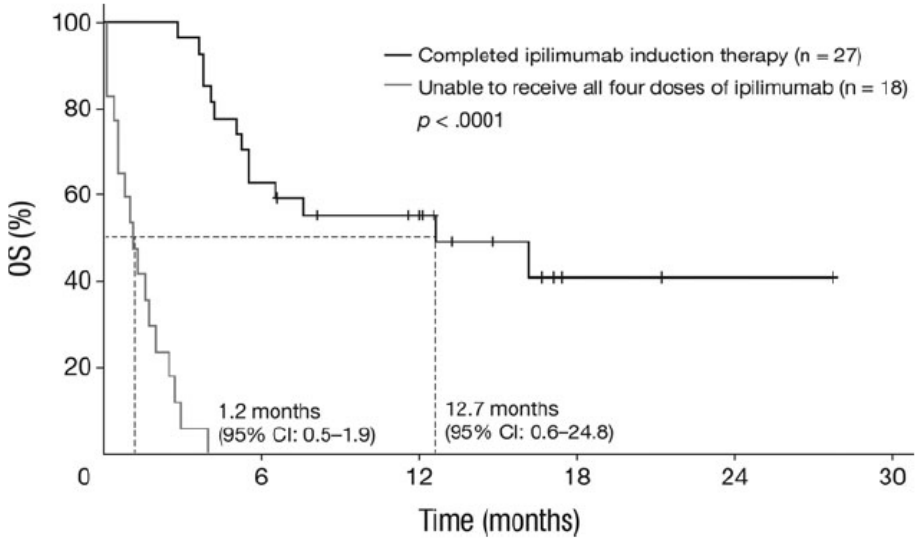
The clinical experts present at the first AC meeting stated that, based on their experience with ipilimumab, they would not expect the efficacy of ipilimumab to vary between first-line and second-line. They said that ipilimumab is most effective when patients are able to receive all 4 scheduled doses. Therefore ineffective prior treatments with chemotherapy that "waste" valuable time will also reduce the potential of responding to ipilimumab.

Ascierto et al. 2014 come to the same conclusion, i.e. patients who progressed after initial treatment with a BRAF inhibitor and were unable to complete all 4 doses of ipilimumab treatment in second-line, have considerably worse prospects than patients who are able to receive all 4 doses of ipilimumab induction treatment (Figure 15).[15]

The results reported by Ascierto et al. cannot be used to make quantitative inferences on the outcomes for different sequences of treatment, as the selection of patients to receive either ipilimumab or a BRAF inhibitor first-line will be based, in part, on their prognosis. However, the study demonstrates that there is a place for ipilimumab in the first-line treatment of BRAF mutation-positive disease for a subgroup of patients. It also shows that clinicians understand the benefits offered by each individual treatment and are quite capable of choosing the most suitable option for their patients to maximise the chance of achieving a durable response and prolonged survival.

A recommendation for ipilimumab at first-line would allow clinicians to refer patients for a treatment with ipilimumab when appropriate, based on the patient's individual clinical presentation and prognosis.

Figure 15: OS from the end of BRAF inhibition (Ascierto et al. 2014)[15]



CI, confidence interval; OS, overall survival.

A further recent publication (Flaherty et al. 2014), reported outcomes of a single-arm, open-label, Expanded Access Study of vemurafenib in patients with metastatic melanoma in the United States.[19] Out of 241 subjects, 68 (28%) patients received ipilimumab prior to vemurafenib and 173 (72%) were ipilimumab-naïve. The objective response rate observed for patients who received vemurafenib after ipilimumab was comparable to those who were naïve to prior ipilimumab. This demonstrates that due to its very different mode of action, response to vemurafenib is not influenced by previous treatment with ipilimumab.

This is supported by data reported by Ackerman et al. that show that the response rates to BRAF inhibitor treatment are similar regardless of whether given before or after ipilimumab (66% and 57%, respectively, p=0.31), indicating that the action of the BRAF inhibitor is the same in both scenarios.[18]

Despite the limitations of the analyses presented above, the data suggest that BRAF inhibitors are as effective after immunotherapy as they are prior to immunotherapy, and that ipilimumab should be

considered first-line if a BRAF mutation-positive patient could benefit from immunotherapy. This assumption was supported by the Clinical Experts at the Committee meeting:

"For patients who are BRAF V600 mutation-positive, the Committee heard that vemurafenib was likely to remain the standard first-line treatment option especially in those with a high disease burden, but understood that ipilimumab would be valuable as a first-line option in approximately 20–30% of patients with small-volume indolent disease for whom vemurafenib could be reserved as rescue treatment later in the pathway." - ACD, Paragraph 4.1

<u>Clarifying what data will become available from ongoing sequencing and combination trials:</u>

Several trials are currently ongoing which will help define the optimal sequence strategy for patients with BRAF-mutant, metastatic melanoma. A summary table of ongoing sequencing and combination trials is provided in Appendix 2.

One BMS-sponsored study explores the effect of sequencing vemurafenib prior to ipilimumab (Trial CA184-240; ClinicalTrials.gov identifier NCT01673854). In this trial, patients who are not progressing after 6 weeks are switched from vemurafenib to ipilimumab. While this trial does not investigate the scenario of switching treatment upon progression, and also does not use the licensed ipilimumab dose (patients receive 10mg/kg), it will provide valuable information regarding efficacy and safety of ipilimumab in patients who may require a fast tumour response first before being able to benefit from immunotherapy. Whilst results of this trial (expected in 2015) will be of limited relevance to the decision problem, all sequencing (and combination) trials will provide additional information to clinicians regarding the optimal treatment of patients. However it is likely that the optimal sequence or combination may differ from patient to patient.

The US Cooperative Group trial (4613) is comparing the combination of dabrafenib plus trametinib followed by the combination of nivolumab plus ipilimumab and vice versa.[18] The results of this trial are also not considered relevant to the present decision problem.

Trials looking at the combined use of ipilimumab and vemurafenib are also underway. Two studies investigating various combinations of BRAF inhibitors with immunotherapies aim to improve complete response rates and median overall survival of patients (ClinicalTrials.gov identifier NCT01656642 and NCT01767454). An earlier BMS Phase 1 trial (Trial CA184-161; ClinicalTrials.gov identifier NCT01400451), investigating the combined application of vemurafenib with ipilimumab, had to be discontinued due to severe liver toxicity.[16]

Until these various trials have completed clinicians will have to base their treatment decisions on the available evidence and experience, and judge appropriate options for patients on individual prognoses.[18]

Section 4: Clarification of effect of concomitant DTIC on clinical efficacy of ipilimumab

Summary:

- The Committee discussed the plausibility of the assumption that ipilimumab plus dacarbazine would have the same therapeutic effect as ipilimumab alone. The Committee concluded that on the basis of the data available it could not be confident that the addition of dacarbazine had not enhanced the efficacy of ipilimumab first-line in the CA184-024 trial.
- This section clarifies why it is reasonable to assume that DTIC did not enhance the efficacy of ipilimumab.
- The effect of concomitant DTIC on clinical efficacy of ipilimumab is considered less relevant given that concomitant DTIC has not been and will not be used with ipilimumab 3mg/kg (the only licensed dose of ipilimumab) and therefore its impact should not be regarded as critical.

Context:

The Appraisal Committee raised concerns that the concomitant use of DTIC in the CA184-024 clinical trial is not representative of the licensed regimen for ipilimumab treatment. The Committee concluded that on the basis of the data available it could not be confident that the addition of dacarbazine had not enhanced the efficacy of ipilimumab first-line in the CA184-024 trial.

Clarifying the effect of concomitant DTIC on clinical efficacy of ipilimumab:

Whilst we recognise that it is important to address the Committee's uncertainties, it should be noted that the issue raised in this section, i.e. the effect of concomitant DTIC on clinical efficacy of ipilimumab, is considered less relevant. This is due to the fact that concomitant DTIC has not been and will not be used with ipilimumab 3mg/kg (the only licensed dose of ipilimumab) and therefore its impact should not be regarded as critical.

Nevertheless, as noted by the Committee, the efficacy outcomes for DTIC are not well supported by clinical evidence. DTIC has never demonstrated a survival advantage in clinical trials and the clinical experts present at the Committee meeting emphasised that patients would be given as few courses of DTIC as possible, before moving patients onto ipilimumab. A recommendation for ipilimumab at first-line would not only remove the generally ineffective chemotherapy "hurdle" but also ensure that patients regain valuable time to increase the potential of responding to ipilimumab.

The poor efficacy profile for DTIC was also acknowledged by the decision summary published by the Cancer Drugs Fund, who commented: *"The panel understood the very limited efficacy of dacarbazine in melanoma and that there currently appeared to be a low threshold for clinicians to switch from 1st line dacarbazine to 2nd line ipilimumab 3mg/kg, as it is a much more effective therapy."* [14]

As noted by the Clinical Experts, and accepted by the Committee, there is no biological reason to expect that concomitant DTIC would increase response to ipilimumab.

Referring to Section 2, it is expected that the increased toxicity associated with ipilimumab 10mg/kg in combination with DTIC in the CA184-024 trial reduced the chances of patients receiving all 4 scheduled doses of ipilimumab. As the number of ipilimumab doses received has been shown to be significantly associated with durable response (HR=1.874 for 1-2 vs. 4 doses, p=0.022; and HR=1.593 for 3 vs. 4 doses, p=0.0114)[2], this reduced number of doses likely results in reduced efficacy.

In addition, in the EPAR it is noted that *"Ipilimumab PK [Pharmacokinetics] was not significantly affected by concomitant dacarbazine, prior systemic anti-cancer therapy [...]; thus, major differences in exposure between combination treatment and monotherapy or between pre-treated patients and non-pretreated patients are not expected. This supports the* ***efficacy of ipilimumab monotherapy regardless of concomitant*** *or prior* ***DTIC*** *treatment and the relevance of the results observed in a*

previously treated population to the first-line setting. Ipilimumab 3mg/kg induced a sustained activation of T cells for both the untreated and previously treated subjects; ***co-administration of DTIC did not affect the increase in absolute lymphocyte count by ipilimumab****. There is no pharmacological or biological rationale to suspect a different activity for ipilimumab treatment in the first or the next line setting, because the mechanism of action of ipilimumab is general stimulation of the immune-system, which is rather aspecific."* [2]

We therefore consider it as extremely unlikely that DTIC has enhanced the efficacy of the ipilimumab regimen used in the CA184-024 trial.

Section 5: Factual inaccuracies identified by BMS in the ACD

The following factual inaccuracies were identified in the appraisal consultation document:

Paragraph number in ACD	Comment
2.1	“recommended dose” – should read “licensed dose”
3.5	The document states “The manufacturer provided details of pre-specified subgroups of patients within the trials including median age (60 years and 66 years for the ipilimumab plus dacarbazine and ipilimumab groups respectively), sex of patients (74.3% and 56.8% male for the ipilimumab plus dacarbazine and ipilimumab groups respectively), stage of metastasis, time since diagnosis and lactate dehydrogenase level” when discussing trial MDX010-08. This data is actually baseline characteristics of the patient population of MDX010-08. Pre-specified subgroup analysis is presented but for the CA184-024 trial population.
3.15	The key limitation of the indirect comparison/MTC analyses in regard to the assumptions of proportional hazards is not referred to at all in the discussion of the analysis in section 3.15. This should be noted as per the manufacturer submission and ERG report.
3.16	“The model assumes that the per-cycle risk of death to be equal for ipilimumab, dacarbazine and vemurafenib...” – This is incorrect. Risks of death were not assumed to be equal.
3.17	“...because the manufacturer determined that disease progression was the most meaningful way of estimating quality of life.” – This is incorrect. Disease progression was not found to be significantly associated with patient utility. Quality of life was modelled on time to death.
3.26	This paragraph concludes that there is no evidence for the comparison, but that the manufacturer is likely to have overestimated the survival benefit of ipilimumab. This claim is unfounded if a clear comparison cannot be made.
3.27	ERG using MTC to check consistency of results ... “directly favoured ipilimumab”. It is not clear what the ERG have done to check consistency.
3.31	“utilities did not capture positive treatment effect” – The treatment effect included is an average value, and will include any positive treatment effect associated with treatment with ipilimumab and vemurafenib.
4.3	Last sentence – “CA184-069” should read “CA184-169”

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Appendix

Appendix 1: Detailed results for the "Section 1 base case"

Interim results for new components, Section 1

The interim results after realising the components are presented below for the conventional 3-state cancer model, as preferred by the ERG. As the results are for interim steps to realise the "Section 1 base case", these results cannot be viewed as scenarios in their own right.

Table 14: Interim results component A – Adjusted MDX010-20 ipilimumab data for use in a first-line setting

Comparison vs. ipilimumab – 3-state model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	Net benefit*
Ipilimumab	£[redacted]	3.2326	2.2566					
DTIC	£[redacted]	2.0018	1.4611	£[redacted]	1.2309	0.7955	£47,899	£[redacted]
Vemurafenib	£[redacted]	3.0125	2.1658	£[redacted]	0.2201	0.0908	£62,495	£[redacted]

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £50,000 versus DTIC (end of life), £30,000 versus vemurafenib

Table 15: Interim results component B - Adjustment of BRIM-3 vemurafenib OS curve to account for the effect of second-line ipilimumab

Comparison vs. ipilimumab – 3-state model

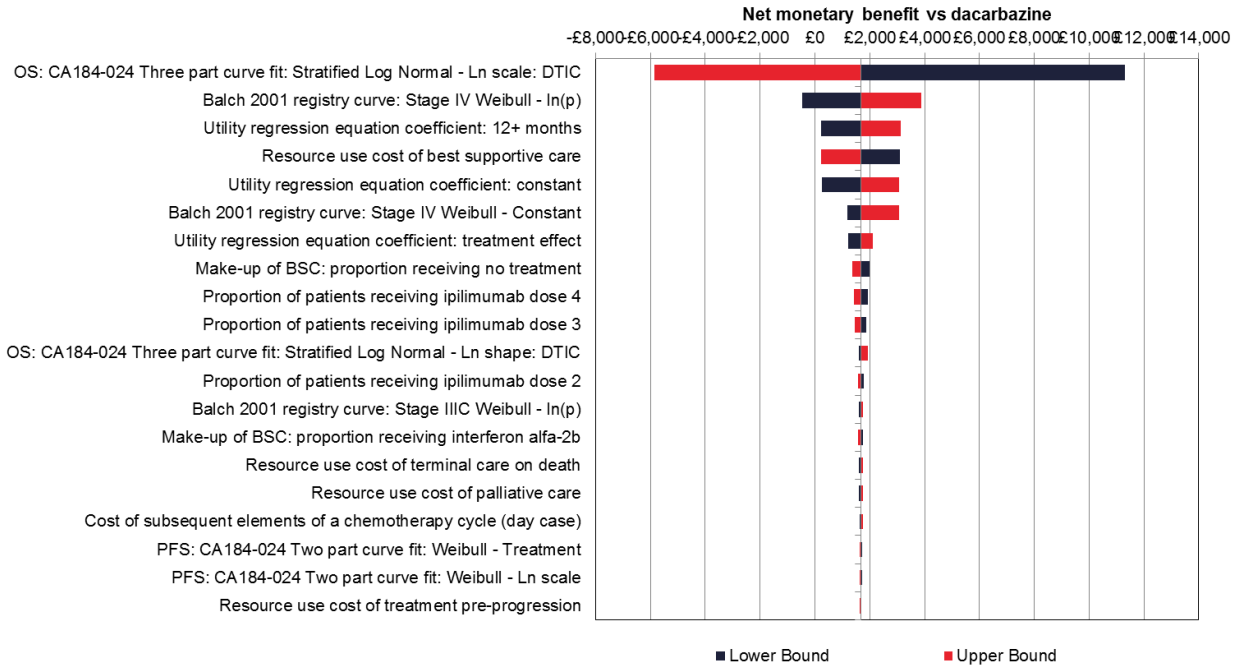
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	Net benefit*
Ipilimumab	£[redacted]	3.2326	2.2566					
DTIC	£[redacted]	2.0018	1.4611	£[redacted]	1.2309	0.7955	£47,899	£[redacted]
Vemurafenib	£[redacted]	2.6644	1.9415	£[redacted]	0.5682	0.3151	£22,450	£[redacted]

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years
*Willingness to pay thresholds: £50,000 versus DTIC (end of life), £30,000 versus vemurafenib

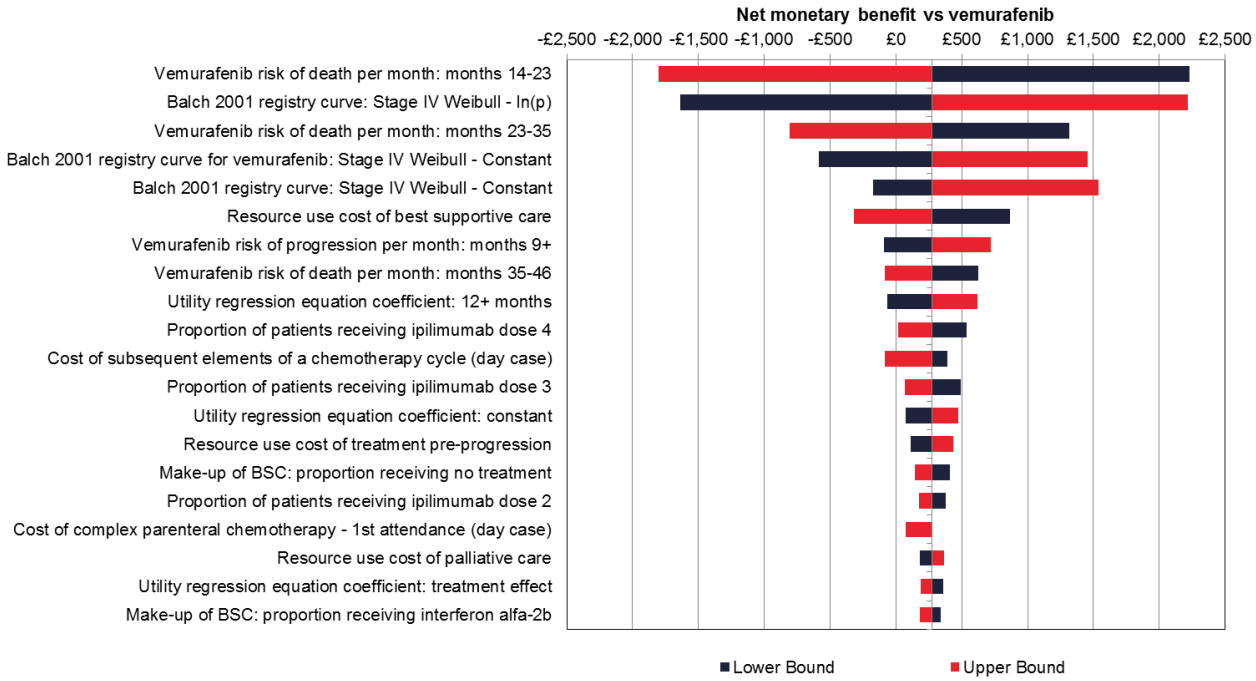
Deterministic sensitivity analysis

Tornado diagram

Comparison versus DTIC



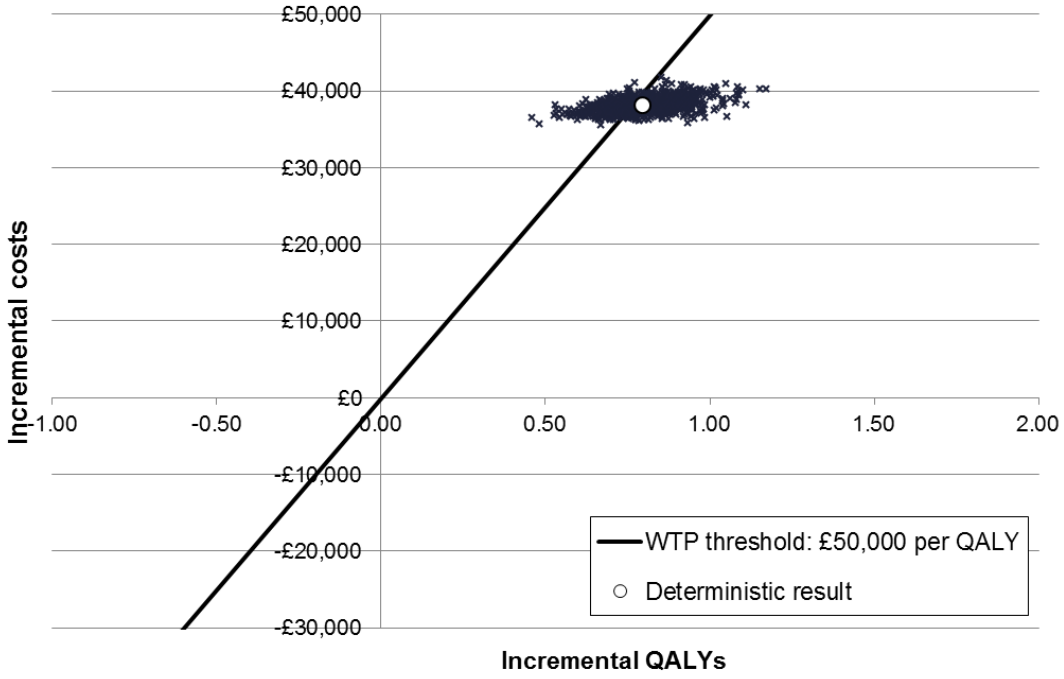
Comparison versus vemurafenib



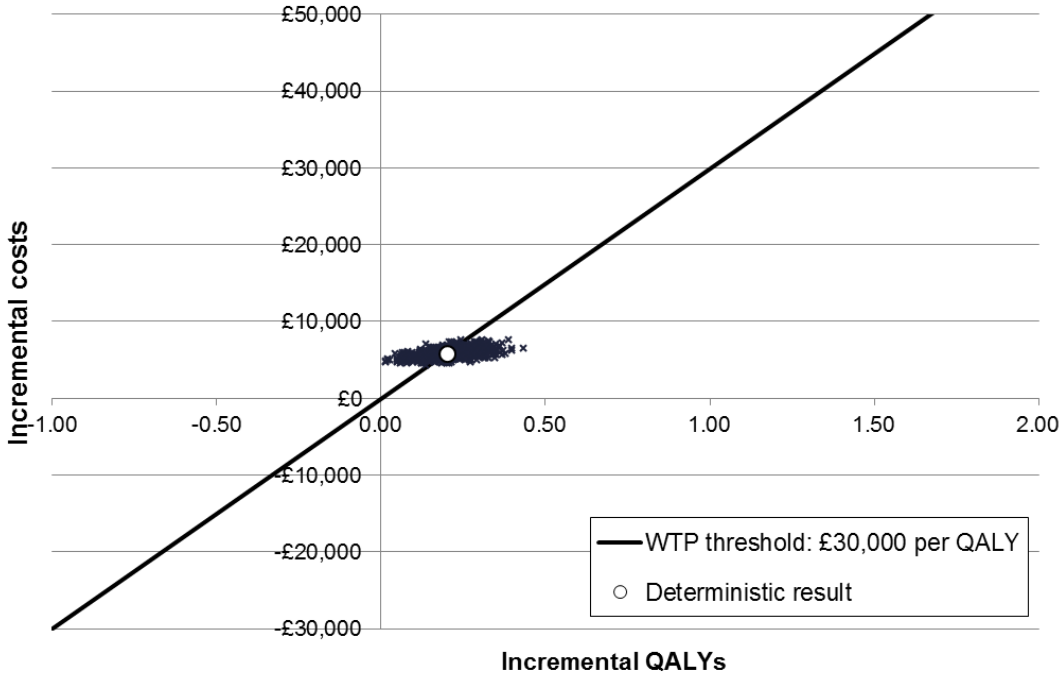
Probabilistic sensitivity analysis

Cost-effectiveness plane

Comparison versus DTIC



Comparison versus vemurafenib



Cost-effectiveness acceptability curve

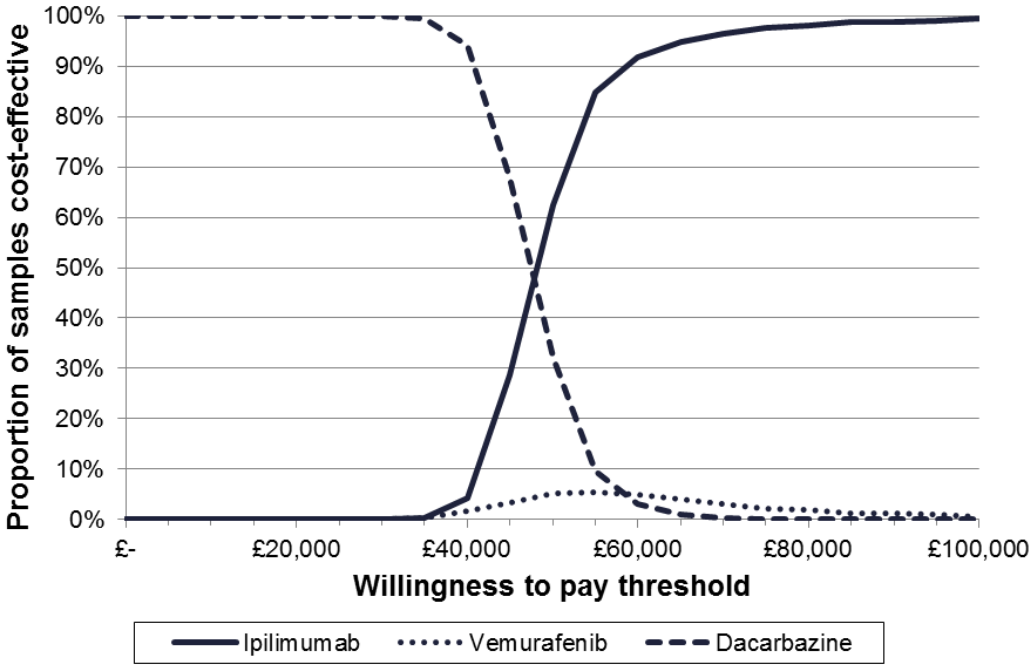


Table 16: Mean results from probabilistic sensitivity analysis

Treatment	Total		Incremental		Cost per QALY gained
	Cost	QALYs	Cost	QALYs	
Ipilimumab	£[redacted]	2.259			
DTIC	£[redacted]	1.455	£[redacted]	0.803	£47,482
Vemurafenib	£[redacted]	2.051	£[redacted]	0.208	£28,024

Table 17: Results for scenario analyses around the "Section 1 base case"

Parameter	Base Case	Sensitivity Analysis	Ipilimumab vs.			
			DTIC		Vemurafenib	
			ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*
"Section 1 base case" (3-state model)			£47,899	£[redacted]	£28,642	£[redacted]
ERGs preferred base case (3-state model)			£42,449	£[redacted]	£28,980	£[redacted]
Varying the time horizon						
Time horizon	40 Years	10 Years	£66,575	£[redacted]	£78,375	£[redacted]
		20 Years	£50,444	£[redacted]	£32,074	£[redacted]
		30 Years	£48,121	£[redacted]	£28,897	£[redacted]
Treatment Pathway						
Source of best supportive care definition	MELODY study	Leeds survey	£45,715	£[redacted]	£24,935	£[redacted]
		Oxford Outcomes report	£47,486	£[redacted]	£28,135	£[redacted]
Source of adverse event incidence data	CA184-024 clinical trial	338 Observational study	£48,692	£[redacted]	£31,947	£[redacted]
Varying the approach to modelling dosing						
Patient weight data used	Weighted average	Named patient programme	£47,775	£[redacted]	£28,153	£[redacted]
		UK trial participants	£48,919	£[redacted]	£32,666	£[redacted]
Dosing calculation	Method of moments	Cost per mg	£43,577	£[redacted]	£11,591	£[redacted]
		Round up to nearest full vial	£45,935	£[redacted]	£20,892	£[redacted]
Varying the approach to modelling utilities						
Source of utility estimates	TTD and treatment effect regression CA184-024	Time to death utilities CA184-024	£47,359	£[redacted]	£28,864	£[redacted]
		Time to death utilities MDX010-20	£51,578	£[redacted]	£31,114	£[redacted]

Appendix 2: Summary of ongoing sequencing and combination trials

The table below summarises the two BMS-sponsored studies combining ipilimumab and vemurafenib and two studies combining ipilimumab and dabrafenib listed on clinicaltrial.gov.

Table 18: Summary of ongoing sequencing and combination trials

NCT #	Title	Recruit-ment	Conditions	Interventions	Sponsor	Age Groups	Phase	Enroll-ment	Funded By	Study Type	Start Date	Primary Comple-tion Date	Comple-tion Date
01673854	Phase II Safety Study of Vemurafenib Followed by Ipilimumab in Subjects With V600 BRAF Mutated Advanced Melanoma (sequential administration)	R	Previously Untreated Unresectable Stage IIIC and Stage IV Melanoma	Ipilimumab, Vemurafenib	BMS	Adult	Ph. 2	45	Industry	I	Oct-12	Dec-14	Mar-15
01767454	Study of Dabrafenib +/- Trametinib in Combination With Ipilimumab for V600E/K Mutation-positive Metastatic or Unresectable Melanoma (concurrent administration)	R	Unresectable Stage IIIC and Stage IV Melanoma	Ipilimumab, Dabrafenib, Trametinib	GSK	Adult	Ph. 1	72	Industry	I	Feb-13	Dec-14	Dec-14
01940809	Ipilimumab With or Without Dabrafenib, and/or Trametinib in Treating Patients With Melanoma That is Metastatic or Cannot Be Removed By Surgery (sequential administration)	R	Unresectable Stage IIIC and Stage IV Melanoma	Ipilimumab, Dabrafenib, Trametinib	US NCI	Adult	Ph. 1	40	NIH	I	Aug-13	Feb-15	
01400451	Phase I Trial of Vemurafenib and Ipilimumab in Subjects with V600 BRAF Mutation-Positive Metastatic Melanoma (concurrent administration)	C	Stage IV Melanoma	Ipilimumab, Vemurafenib	BMS, Roche, Genen-tech	Adult	Ph. 1	50	Industry	I	Nov-11	Apr-13	Jan-14

R: recruiting, C: completed, BMS: Bristol-Myers Squibb, GSK: GlaxoSmithKline, NCI: National Cancer Institute, Ph.: phase, I: Interventional
Source: clinicaltrial.gov as of Feb 28, 2014F