Bristol-Myers Squibb Pharmaceuticals Ltd

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Ipilimumab for previously untreated unresectable malignant melanoma

Single technology appraisal (STA)

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Abbreviations

AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
APC	antigen presenting cell
BAD	British Association of Dermatologists
BIC	Bayesian information criterion
BRAF (V600)	a human gene that makes a protein, B-Raf
BSC	best supportive care
CHMP	Committee for Medicinal Products for Human Use
CTL	cytotoxic T-lymphocyte
CTLA-4	cytotoxic T-lymphocyte antigen 4
DTIC	dacarbazine
EC	European Commission
EMA	European Medicines Agency
EPAR	European public assessment report
ESMO	European Society for Medical Oncology
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
GI	gastrointestinal
HR	hazard ratio
HRQL	health-related quality of life
ICER(s)	incremental cost-effectiveness ratio(s)
IrAE(s)	immune-related adverse event(s)
LDH	lactate dehydrogenase
LYG	life years gained
mg	milligrams
MHC	major histocompatibility complex
ml	millilitres
MTC	mixed treatment comparison
N/A	not applicable
NE	not estimable
NCCN	The National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	overall survival
PFS	progression free survival
PSS	personal social services
QALY(s)	quality-adjusted life year(s)
RCT	randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single technology appraisal
TA	technology appraisal
TAA	tumour associated antigen
TCR(s)	T-cell receptor(s)
TTR	time to response
UK	United Kingdom
ULN	upper limit of normal
US	United States

Executive summary

Ipilimumab (Yervoy®) is a fully human monoclonal immunoglobulin antibody (IgG1κ) under appraisal for the first-line treatment of patients with previously untreated unresectable melanoma. It offers a novel way to stimulate the body's own immune system to fight cancer. It has an innovative mode of action compared with other cytotoxic and immunotherapeutic agents, known as T-cell mediated immunopotentiation. Meaning, when the immune system detects a foreign antigen (in this context the tumour), an immune response is launched and the foreign antigen attacked and destroyed by T-cells. This response is self-limiting and controlled through CTLA-4 (cytotoxic T-lymphocyte antigen 4). By blocking CTLA-4 activity, ipilimumab stops the immune response from being switched off which allows the number and production of active T-cells to increase so they are then able to target and destroy the tumour more effectively. Ipilimumab's mechanism of action is therefore fundamentally different to conventional cancer treatments.

On the 25th March 2011, the US Food and Drug Administration approved 3 mg/kg ipilimumab for advanced melanoma, including previously untreated patients. This was based on the Phase III pivotal studies MDX010-20[10, 11] and CA184-024[20]. The European Commission (EC) issued a Marketing Authorisation for ipilimumab for the treatment of adult patients with previously-treated advanced (unresectable or metastatic) melanoma on 13th July 2011. The EU license was based on the results of the pivotal trial MDX010-20[10, 11] and supported by the high level results from CA184-024[20]. In both studies, the 2-year OS rates were similar: 24% and 29%, respectively, despite different eligibility (treatment naive or pre-treated) and different regimens (3 mg/kg ipilimumab or 10 mg/kg ipilimumab plus dacarbazine). On 2nd August 2012, Bristol-Myers Squibb submitted an application to the European Medicines Agency to extend the indication of ipilimumab to previously untreated adult advanced melanoma patients at a proposed posology of 3mg/kg, to integrate its first-line therapeutic option. A positive opinion from the Committee for Medical Products for Human Use (CHMP) was received on 19th September 2013. This is awaiting approval by the European Committee for a marketing authorisation (expected November 2013)

Metastatic melanoma is associated with a short-term life expectancy (6-9 months); many patients (estimated at 40%) will only receive first-line therapy, Historically, traditional chemotherapy (dacarbazine [DTIC]) has been the first-line treatment of choice for melanoma but (a) demonstrates low response rates of short duration and (b) has never demonstrated an overall survival (OS) benefit in clinical trials.[1, 2] More recently, BRAF inhibitors have been used and have shown a very rapid effect on tumours. Unfortunately, however, responses to the BRAF inhibitors vemurafenib and dabrafenib do not seem to be durable in practice, possibly due to the development of resistance and tumour relapse.[3] Also, these agents are specifically targeted at the BRAF V600 mutation that is only present in approximately 50% of melanoma patients.[4] As a consequence, there is still a high unmet medical need for effective first-line treatment of advanced melanoma. The CHMP also recognised the significant unmet need that still exists for melanoma patients. Ipilimumab is a first-line therapeutic option that has the potential to offer a durable, long-term survival benefit

to patients with advanced melanoma, regardless of BRAF mutation status; fulfilling this significant unmet need.

The recommended induction regimen of ipilimumab is 3 mg/kg administered as intravenous infusion over a 90-minute period every 3 weeks for a total of 4 doses. Each ml of concentrate for solution for infusion contains 5 mg ipilimumab. One 10 ml vial contains 50 mg of ipilimumab (list price: £3,750; considering PAS agreed during TA268: £[redacted]). One 40 ml vial contains 200 mg of ipilimumab (list price: £15,000; considering PAS agreed during TA268: £[redacted]).

An expansive evidence base is presented for ipilimumab across a range of dosing regimens in the target indication of relevance to this submission with up to 5-year data supporting the use of ipilimumab as a first-line therapy:

- CA184-024 (n=502): pivotal phase III RCT investigating the clinical efficacy of ipilimumab 10mg/kg + DTIC compared with DTIC monotherapy in previously untreated advanced melanoma patients.
- Pooled chemotherapy-naïve dataset (n=78): analysis of data from three phase II and one phase III RCT investigating the clinical efficacy of ipilimumab 3mg/kg in chemotherapy-naïve advanced melanoma patients.
- MDX010-08 (n=72): phase II RCT investigating the clinical efficacy of ipilimumab 3mg/kg + DTIC compared with ipilimumab 3mg/kg monotherapy in chemotherapy-naïve advanced melanoma patients.
- CA184-332 (n=61) and CA184-338 (n=120): retrospective observational studies from the United States investigating the “real-world” effectiveness of ipilimumab 3mg/kg monotherapy in previously untreated advanced melanoma patients.

Although the principal limitation of the clinical evidence base is that there are no direct comparative efficacy trials for ipilimumab 3mg/kg vs. DTIC therapy in previously untreated, advanced melanoma patients, there is considerable clinical evidence to support the efficacy and side effect profile in the 3 mg/kg posology. In CA184-024, ipilimumab 10mg/kg + DTIC shows a statistically significant improvement in overall survival compared with DTIC monotherapy [HR 0.72 (0.59-0.87)] in previously untreated patients with advanced melanoma, with an overall survival rate at 5 years of 18.2% vs. 8.8% and a mean survival time at 5 years of 91.1 vs. 66.6 weeks. This survival benefit is extrapolated to the ipilimumab 3mg/kg posology with comparative efficacy observed irrespective of dosing regimens. This is supported by the fact that the median OS is equivalent between ipilimumab 10mg/kg + DTIC treatment (CA184-024); ipilimumab 3mg/kg + DTIC treatment (MDX010-08) and ipilimumab 3mg/kg monotherapy treatment in MDX010-08, the two observational studies and the pooled chemotherapy-naïve dataset: 11.2 to 14.3 months. The median OS is further equivalent between trials with a maintenance phase of treatment (CA184-024) and those without (MDX010-08; CA184-332; CA184-338): 11.2 to 14.3 months. Furthermore, indirect comparison and mixed-treatment comparison analyses show comparative efficacy ($p>0.05$) between ipilimumab and BRAF inhibitor therapies. Ipilimumab clinical benefit is observed irrespective of dosing with comparative efficacy shown between ipilimumab 10mg/kg + DTIC; ipilimumab 3mg + DTIC; and ipilimumab 3mg/kg monotherapy; median overall survival of 11.2 to 14.3 months in the first-line setting.

Ipilimumab already has an extensively documented adverse event profile which is primarily immune-related. These immune-related adverse events (irAEs) are predictable, well characterised, and generally medically manageable with topical and/or systemic immunosuppressants which do not affect the clinical activity of ipilimumab. Management of irAEs is usually paired with omission of dosing for mild or moderate events and permanent discontinuation for severe irAEs. 2-year survival analyses confirm consistency of the ipilimumab adverse event profile throughout treatment and no continuation of irAEs post treatment discontinuation. Similar safety profiles were observed across clinical trials of first-line use of ipilimumab in advanced melanoma patients, though reduced rates of irAEs are observed with ipilimumab 3mg/kg compared with the 10mg/kg dose, favouring its use in the 3 mg/kg posology.

Tolerability of ipilimumab 3mg/kg as a first-line therapeutic in patients with advanced melanoma is further confirmed by 76% of patients completing induction therapy in clinical practice.

Based on the evidence presented in this submission, we feel ipilimumab offers:

- A potential treatment option for this significant unmet need.
- An innovative mechanism of action that does not restrict use based on BRAF mutation status,
- An extensive clinical evidence base that confirms its potential for survival benefit and consistency of its manageable safety profile, regardless of BRAF mutation status.

Ipilimumab should therefore be considered a step change in first-line therapy of advanced melanoma; worthy of additional merit not only for its novel mechanism of action but also the data package provided to demonstrate these claims.

The presented data demonstrate that ipilimumab is highly cost-effective against the historical standard of care (dacarbazine) and against the only mutation specific therapy that is currently recommended by NICE (vemurafenib). Study data are consistent in showing that patients achieve durable long-term survival in a condition where, historically, the prognosis is poor. Clinical survival data from a pooled analysis of 1,861 ipilimumab-treated patients in 12 studies (2 phase III trials, 8 phase II trials and 2 observational studies across different doses and treatment regimens), relating to the long-term survival associated with ipilimumab therapy, are impressive, with approximately 20% of advanced melanoma patients surviving up to 10 years (section 4). Thus, ipilimumab offers an exciting, potential treatment for advanced melanoma where currently very limited treatment options exist.

Cost-effectiveness was demonstrated through the development of partitioned survival model to estimate the costs and benefits of first-line ipilimumab treatment over a life-time horizon. The model calculates the outcomes of patients in terms of overall survival and time spent on treatments within the current UK treatment pathway. As patients progress through the lines of treatment included in the model (first, second and third line), they incur treatment-specific costs, including drug, administration, adverse events and resource use. Health-related quality of life (HRQL) is measured using a time to death approach, based upon analysis of data from the EORTC-QLQ-

C30 collected within the CA184-024 trial. In order to present the most relevant comparisons, the treatment pathways modelled are dependent on patients' BRAF V600 mutation status. The model was populated and validated using the two key data sets for ipilimumab side by side: previously untreated patient data from trial CA184-024, and the pooled analysis of chemotherapy-naïve patients receiving ipilimumab at 3mg/kg.

In a BRAF V600 mutation-negative population, the model estimates that patients treated first-line with ipilimumab gain an additional 1.20 years of life (0.80 QALYs) compared with dacarbazine, resulting in an ICERs of £16,958 per QALY gained (Table 1). In a BRAF V600 mutation-positive population, patients treated first-line with ipilimumab vs. vemurafenib gain an additional 0.31 LYs (0.18 QALYs) at less costs (-£12,625), meaning ipilimumab is the dominant strategy. The comparison with dacarbazine in the same populations results in additional 1.14 LYs, 0.75 QALYs and an ICER of £31,559 (Table 2). As we believe that ipilimumab satisfies end of life criteria vs. dacarbazine, it can be considered as highly cost-effective at the usual ICER cut-offs applied under this process. The presented results include data from CA184-024 for ipilimumab (results for both data sets, CA184-024 and pooled analysis, are presented in Section 7.7). Despite different eligibility (treatment-naïve or chemotherapy-naïve) and different regimens (10 mg/kg ipilimumab plus dacarbazine or 3 mg/kg ipilimumab), the two data sets yield consistent outcomes.

Table 1: Base-case cost-effectiveness results (including patient access schemes for ipilimumab and vemurafenib)

	BRAF V600 mutation-negative		**BRAF V600 mutation-positive**		
	Ipilimumab	**Dacarbazine**	**Ipilimumab**	**Dacarbazine**	**Vemurafenib**
CA184-024 data for ipilimumab					
Technology acquisition cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Other costs	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Total costs	£57,760	£44,267	£68,033	£44,267	£80,658
Total costs difference	-	£13,492	-	£23,766	-£12,625
LYG	3.35	2.15	3.29	2.15	2.98
LYG difference	-	1.20	-	1.14	0.31
QALYs	2.35	1.56	2.31	1.56	2.13
QALY difference	-	0.80	-	0.75	0.18
ICER	**-**	**£16,958**	**-**	**£31,559**	**Dominant**
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio					

Table 2: Incremental cost-effectiveness results (BRAF V600 mutation-positive patients)

Technology (and comparators)	**Total cost**	**Total QALY**	**Incr. cost**	**Incr. QALY**	**ICERs versus baseline**	**Incremental analysis**
Dacarbazine	£44,267	1.56				N/A
Ipilimumab	£68,033	2.31	£23,766	0.75	**£31,559**	**£31,559**
Vemurafenib	£80,658	2.13	£12,625	-0.18	**£63,534**	**Dominated**
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

The key driver of the cost-effectiveness results is the improved survival seen with ipilimumab. The data package (consisting of 2 phase III, 5 phase II trials and 2 observational studies) shows a much larger proportion of patients receiving

ipilimumab exhibit a durable long-term survival benefit, beyond what would be expected with dacarbazine or vemurafenib.

Sensitivity analysis demonstrated that the model was robust to variations in the underlying assumptions - at all values within the 95% CI of the parameters and for all scenarios tested, ipilimumab remains a cost-effective use of healthcare resources. Probabilistic sensitivity analysis showed a 96% probability of being the most cost-effective treatment in a BRAF V600 mutation-positive population at a willingness-to-pay threshold of £50,000 per QALY gained.

The estimated total number of new patients treated with first-line ipilimumab in England and Wales is 338 in 2014, increasing to 663 in 2018. These numbers consider existing patients receiving ipilimumab in its current, NICE approved pre-treated indication, implying a 'shift' from second- to first-line (given that patients treated with ipilimumab first-line are unlikely to receive it again in second-line; Section 2.2). The budget impact of NICE approval of ipilimumab in first-line is estimated to be around £[redacted] in 2014 and around £[redacted] in 2018.

Summary

Ipilimumab is an immunotherapy with an innovative mode of action that offers a paradigm shift in the effective treatment of melanoma, regardless of BRAF V600 mutation status. It provides superior disease control by having a more durable, longer term survival benefit, than the currently recommended first-line options.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Yervoy®

Approved name: ipilimumab

Therapeutic class: Antineoplastic agents, monoclonal antibodies

1.2 What is the principal mechanism of action of the technology?

Conventional anticancer therapies act (generally) through cytotoxicity. This means they are toxic to all types of cells, but destroy the cancer cells "preferentially" because these are fast growing and rapidly dividing. As a consequence, such conventional chemotherapeutic agents have side effects that also affect "normal" rapidly growing cells (for example hair follicles – so a common side effect of these agents is hair loss).

However, in recent years, other approaches to treat cancer have been investigated. Specifically there has been an enormous increase in our knowledge regarding the relationship between cancer and the host's immune system. It is now recognised that there are a number of immunostimulatory and immunosuppressive forces present in the tumour environment. Once the tumour starts to grow, the immunosuppressive processes tend to outweigh the immunostimulatory processes – and these can be targeted by appropriately designed immunotherapies.

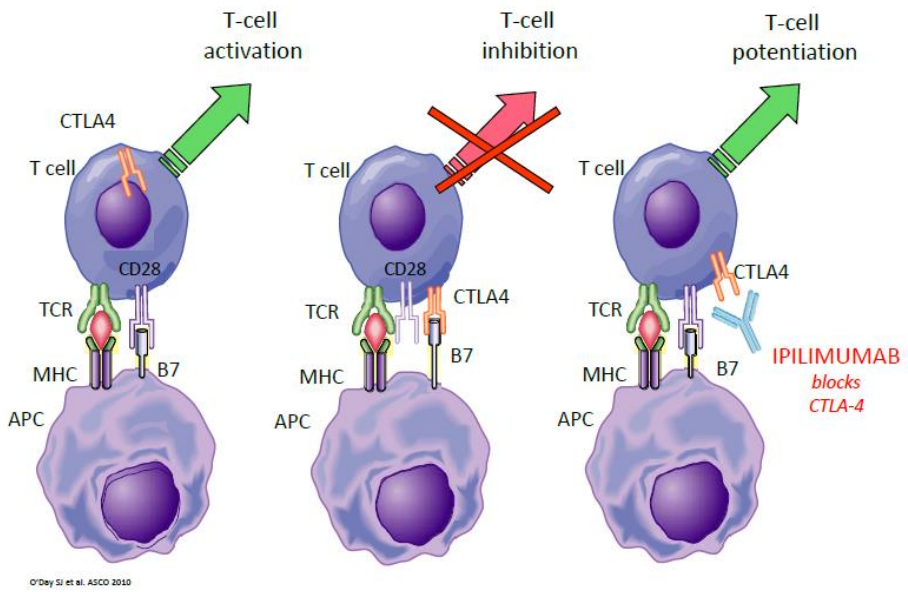
Ipilimumab (Yervoy®) is a fully human monoclonal immunoglobulin antibody (IgG1κ) that works in a novel way to stimulate the body's own immune system to fight cancer. It has an innovative mode of action compared with other cytotoxic and immunotherapeutic agents, known as T-cell mediated immunopotentiation.

When the immune system detects a foreign antigen, an immune response is launched. An important element of this response is the production of 'helper' T-cells; these are powerful white blood cells regulated by molecular switches that can turn the immune response 'on' or 'off'. Ipilimumab works by blocking the activity of one such molecule, CTLA-4 (cytotoxic T-lymphocyte antigen 4), which is thought to play a role in 'switching off' the immune system's response. Ipilimumab interferes with the interaction of CTLA-4 with B7 (CD80 or CD86) molecules on antigen presenting cells, causing blockade of the inhibitory function of CTLA-4. By blocking CTLA-4 activity, ipilimumab stops the immune response from being switched off which allows the number and production of active T-cells to increase so they are then able to target and destroy the tumour. Ipilimumab's mechanism of action is hence fundamentally

different to other cancer treatments, in that it does not directly target the tumour but activates the immune system to kill the cancer cell.

The mode of action of ipilimumab is illustrated in Figure 1.

Figure 1: Ipilimumab - mode of action



1. **T-cell activation** occurs as a result of 2 steps: (a) binding of T-cell receptor to the major histocompatibility complex (MHC) on the antigen presenting cell (APC) and b) binding of CD28 to B7 on the APC. This leads to CTLA-4 being expressed on the surface of the T-cell within 2-3 days following activation.
2. Up-regulation of CTLA-4 on the surface of cytotoxic T cells results in the inhibition of proliferation of these cells (**T-cell inhibition**) because B7 preferentially binds to CTLA-4 over CD28. This feedback loop means that continuous T-cell activation is prevented, thus avoiding “self-damage”.
3. **T-cell potentiation** is a reversal of this T-cell inhibition. It is caused by ipilimumab binding to CTLA-4 thereby blocking the inhibition process described above. The result is that cytotoxic T-cells are potentiated, carry on proliferating, infiltrate the tumour and destroy it.

What does this mean in practice?

As ipilimumab is an immunostimulatory agent (i.e. through its mode-of-action it stops the immune response from being switched off), the clinical effects seen in ipilimumab patients are slightly different from those usually seen in cancer patients treated with conventional therapies.

In clinical trials, the effects of cancer therapies are assessed by measuring specific outcomes such as “progression-free survival” (PFS) - how long the patient lives without their tumour growing/getting worse - and “overall survival” (OS) - how long patients continue to live before they die. Depending on the cancer type, PFS and OS can be a matter of months or can be a number of years. PFS assessments are made on tumour size at specific time-points defined in the clinical trial protocol. In some cases, an anti-cancer therapy can prolong PFS but have no effect on OS.

Ipilimumab has a novel mode of action and consequently patients, who receive it, generally do not follow conventional response patterns. Typically, chemotherapeutic agents can “shrink” a tumour, meaning that the overall tumour burden decreases

within a few weeks of initiating cytotoxic therapy, and if this shrinkage is large enough it would be classified as a response to the therapy. However, with ipilimumab, because the tumour is "stimulated" immunologically it appears to get larger for a short period of time (due to an influx of inflammatory cells), after which it begins to shrink. Thus, in conventional clinical trial assessment terms, the patient appears to have progressed. However, this is incorrect - the tumour is actually responding to the ipilimumab therapy. Thus, these early assessments do not truly capture the clinical picture, because ipilimumab's mode-of-action takes time to demonstrate clinical efficacy.[5] Patients on ipilimumab who ultimately achieve a positive clinical outcome may appear to have 'progressed' when assessed in the early stages of treatment. PFS is therefore not an accurate measure of the eventual response to ipilimumab.[6]

This is a crucial difference between ipilimumab and other cancer treatments with different modes-of-action.

Although the tumour burden with ipilimumab can increase in some patients in the short term (before it decreases), current data suggest this has minimal impact on patient's health-related quality of life (HRQL).[7]

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On 2nd August 2012, Bristol-Myers Squibb submitted an application to the European Medicines Agency (EMA) to extend the indication of ipilimumab to previously untreated adult advanced melanoma patients, the indication of interest for this submission. Ipilimumab) received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 19th September 2013 for the treatment of advanced (unresectable or metastatic) melanoma in adults. This is awaiting approval by the European commission for a marketing authorisation, expected November 2013.

Ipilimumab already holds a marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.[8]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

To be confirmed, as the EPAR is not available yet.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The current indication for Ipilimumab in the EU is "for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy."

It is anticipated that this will be extended to "for the treatment of advanced (unresectable or metastatic) melanoma in adults", to integrate its first-line therapeutic option.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Within the next 3 months, additional efficacy, safety and survival data from two ongoing, retrospective, observational studies (CA184-332 and CA184-338) that are collecting data are expected. These studies are investigating the "real-world" efficacy of ipilimumab 3mg/kg in advanced melanoma patients who have not received prior therapy or been treated in a clinical trial. Therefore these data are valuable to the subject of this submission. The planned full cohort of these two studies will be approximately 390 patients with at least one year of follow-up data. Some of these patients will show survival rates up to 2-years. We have included the results from an interim analysis of these two studies in this submission (section 6.8).

Within the next 12 months, data from a follow-up study (CA184-025) for patients previously enrolled in ipilimumab studies CA184-004 and CA184-022 may become available. The purpose of the study is to provide and evaluate the continued use of ipilimumab in patients who obtained clinical benefit in their parent study. Further information on this can be found at http://www.clinicaltrials.gov under the identifier: NCT00162123.

There are other ongoing ipilimumab studies for which data may become available in the next 12 months. However, these use different doses of ipilimumab and other drug combinations to this submission, and therefore are not highlighted here.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Ipilimumab is already available in the UK.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

To date, ipilimumab has been approved in the following countries/regions:

- For second-line treatment (i.e. previously treated) patients: Australia, Brazil, Canada, European Union, Iceland, Israel, Liechtenstein, New Zealand, Norway, Puerto Rico, Switzerland.

- And in both first-line (i.e. previously untreated) and second-line (i.e. previously treated) patients: Argentina, Chile, Colombia, Mexico, US.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

It is anticipated that the Scottish Medicines Consortium (SMC) will conduct a health technology appraisal of 'ipilimumab for previously untreated unresectable malignant melanoma' in 2014. The date of completion of this assessment is yet to be confirmed.

NICE have already completed a Technology Appraisal of 'Ipilimumab in previously treated unresectable stage III or IV malignant melanoma' in November 2012 and recommended ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy.[9] The SMC also gave a positive recommendation in this indication in April 2013 (SMC ID: 779/12).

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Details of the unit costs of ipilimumab are provided in Table 3.

Table 3: Unit costs of ipilimumab

Pharmaceutical formulation	Concentrate for solution for infusion
Acquisition cost (excluding VAT)	List price: 50mg/10ml = £3,750 200mg/40ml = £15,000 The PAS that was agreed with NICE during TA268 will apply, therefore NHS acquisition costs (excl. VAT) are: 50mg/10ml = £[redacted] 200mg/40ml =£[redacted]
Method of administration	Intravenous infusion
Doses	Induction dose: 3mg/kg every 3 weeks for a total of 4 doses.
Dosing frequency	Induction: every 3 weeks for a total of 4 doses.
Average length of a course of treatment	3 months
Average cost of a course of treatment	£[redacted] using the PAS price based upon: • 3mg/kg dose equating to an average of 5.23 x 50mg vials per patient (section 7.5.5) • Number of patients receiving each dose during induction and re-induction taken from the clinical trials (section 7.5.5) • Data from the CA184-024 trial
Anticipated average interval between courses of treatments	Clinicians may consider re-induction treatment. In the MDX010-20 clinical trial only a small percentage of patients (40/676 [6%]) received re-induction treatment. The median time of re-induction from first treatment was 1 year (range 6 months to 4.2 years).[10, 11]
Anticipated number of repeat courses of treatments	Clinicians may consider re-induction treatment. In the MDX010-20 clinical trial, 6% (40/676) had one re-induction, 1% (7/676) had a second re-induction and 0.1% (1/676) had a third re-induction course of treatment.[10, 11]
Dose adjustments	No dose adjustments are used. For adverse event handling, doses are either omitted or treatment is discontinued.

PAS = Patient Access Scheme

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No, there are no stipulated additional tests or investigations needed.

However, ipilimumab use should be avoided in patients with severe active autoimmune disease where further immune activation could be potentially life threatening and it should be used with caution in patients with a history of autoimmune disease, after carefully considering the potential risk-benefit on an individual basis.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Yes, the Summary of Product Characteristics (SPC) specifies that patients should be assessed for any signs or symptoms of immune-related adverse reactions (e.g. diarrhoea, enterocolitis, dermatitis, neuropathy, and endocrinopathy) during treatment with ipilimumab. Patients should have liver and thyroid function tests evaluated at baseline and before each dose of ipilimumab.[8]

In general, for severe adverse events (AEs), ipilimumab should be permanently discontinued and systematic high-dose corticosteroid therapy with or without additional immunosuppressive therapy may be required. For mild-moderate immune related AEs, the next ipilimumab dose should be omitted and corticosteroids may be required. Detailed guidance on handling AEs can be found in the SPC.[8]

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None.

2 Context

2.1 *Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.*

Malignant melanoma is the most aggressive cancer of the skin with approximately 10% of cutaneous melanomas metastasised at primary presentation.[12] There is still a high unmet medical need for effective first-line treatment of advanced melanoma, given the absence of approved, effective and life-prolonging therapies.

Demographics

Melanoma occurs more commonly in fair-skinned people and there is strong evidence that ultraviolet light exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at greatly increased risk. The mean age of diagnosis is 50 years, which is earlier than for most other cancers, but ~13% to 20% of cases occur in young adults aged between 15 and 39 years.[13, 14]

The disease

The cells that become cancerous in melanoma are the melanocytes and are found in the skin. Melanoma of the skin or cutaneous melanoma is the most common type of melanoma. This, together with nodular melanoma and lentigo maligna melanomas make up 90% of all diagnosed melanomas. Acral lentiginous melanoma and a few very rare types together make up the other 10%. Cutaneous melanoma may invade and destroy nearby tissue and metastasise by spreading to other parts of the body. In its early stages, it is normally asymptomatic and, if detected before it has spread, can be curable. However, at presentation, 10% of cutaneous melanomas will have already metastasised.

Staging

Melanoma is considered ‘advanced’ if it has spread to nearby lymph nodes (stage III) or to other parts of the body (stage IV). It is classified in metastatic substages, which encompass unresectable stage III disease, with regional lymph node involvement or distant metastatic disease (stage IV) with location either in soft tissue or distant lymph nodes (M1a), lung (M1b), or any visceral organ and/or increased lactate dehydrogenase (LDH) levels in the serum, indicating aggressive tumour growth (M1c).[15]

Survival

Prognostic factors in patients with advanced melanoma include, age, gender, primary tumour characteristics, tumour burden and LDH level.[1, 15] When diagnosed early, the chance of survival is considered relatively high. Early recognition of melanoma and accurate diagnosis presents the best opportunity for cure by surgical resection of the tumour. For stage III disease, when regional lymph nodes are involved, the 5-year survival rate ranges from 20% to 73%[14], depending on the presence of ulcerations and the number of lymph nodes involved. Stage IV disease, when melanoma has

spread outside of the regional lymph nodes to distant sites, is associated with an extremely poor prognosis; the 5-year survival rates are low and associated with poor quality of life, which further decreases in the 12 months prior to death.[16-18] The median survival is 6-9 months.[19]

Treatment of advanced melanoma

People with unresectable stage III or IV (metastatic) disease are usually managed by a specialist oncologist. Historically, first-line standard of care normally involved the administration of dacarbazine (DTIC) chemotherapy. But more recently, patients will undergo a molecular analysis of their tumour to determine the mutational status of the BRAF V600 gene, in order to identify those suitable for treatment with BRAF inhibitors (e.g. vemurafenib and dabrafenib). However, licensed therapeutic options are still limited for first-line treatment and entry into clinical trials remains an option for patients with advanced melanoma. Radiotherapy, other immunotherapies, targeted agents and combination chemotherapy continue to be studied in randomised clinical trials.

High unmet medical need

Because of the severity of their disease, and their short-term life expectancy (6-9 months[19]) many patients (estimated at 40% in CA184-024[20]) will only receive first-line therapy for metastatic melanoma as they do not survive long enough to receive second-line therapy.

Since the 1970s DTIC (traditional chemotherapy) historically has been the treatment of choice for melanoma but (a) demonstrates low response rates of short duration and (b) has never demonstrated an OS benefit in clinical trials.[1, 2]

More recently, BRAF inhibitors have been used and have been shown to have a very rapid effect on tumours. Unfortunately, however, responses to the BRAF inhibitors vemurafenib and dabrafenib do not seem to be durable in practice, possibly due to the development of resistance and tumour relapse.[3] In addition, these agents are specifically targeted at a mutation that is only present in approximately 50% of melanoma patients[4], and so are not suitable for all individuals.

As a consequence, with the only alternative, DTIC also demonstrating low response rates with short duration and no overall survival benefit[1, 2], there is still a high unmet medical need for effective first-line treatment of advanced melanoma.

Ipilimumab has already been approved for second-line use, and has demonstrated long-term benefits in a significant number of patients in this setting who otherwise have very limited therapeutic options.[9] Similarly, patients who have been diagnosed with melanoma and are eligible for first-line treatment also face a paucity of choice with regards to effective treatment. As an innovative immunotherapeutic drug, based on the evidence presented in this submission, we feel ipilimumab offers an effective, treatment which fulfils this significant unmet need.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Based on a population size of 56,792,422 people in England and Wales and an incidence rate of 0.021%, the expected incidence in 2011 was 11,898.[21] Of these, approximately 10% are expected to be diagnosed with advanced melanoma (stage IIIc-IV).[14] Assuming the incidence of melanoma increases at a rate of 3.5% per year[22], this corresponds to around 1,190 patients in England and Wales potentially eligible for treatment in 2014.

Approximately 40-50% of patients with cutaneous melanoma tumours present with oncogenic mutations in BRAF (BRAF V600 mutation-positive patients).[4] By implication, 50-60% of patients do not present with oncogenic mutations in BRAF, i.e. are BRAF V600 mutation-negative.

When estimating the likely number of patients to be treated with ipilimumab, it is necessary to take into account the considerable proportion of patients that are unlikely to be treated with ipilimumab. For example:

- The clinician may not consider a patient well enough to receive ipilimumab and/or the patient may not wish to receive ipilimumab.
- Active treatment may not be appropriate for some patients and supportive care is offered instead.
- There will also be a number of clinicians who may decide, upon results of BRAF V600 mutation testing, to treat with BRAF targeted therapies, such as vemurafenib or dabrafenib, even though ipilimumab's efficacy is independent of BRAF V600 mutation status. The clinician may also decide to treat some patients with DTIC.
- Entry of patients into clinical trials remains an option.

Taking these considerations into account alongside the expected market share of ipilimumab, we estimate the likely number of patients to be treated with first-line ipilimumab in England and Wales to be around 338 in 2014.

Patients that are treated with ipilimumab first-line are not likely to receive it again as second-line therapy. Therefore the estimated first-line patient numbers presented here incorporate patients who would currently be expected to receive ipilimumab as second-line according to the NICE approved pre-treated indication (implying a 'shift' from second-line to first-line).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Early recognition of melanoma and accurate diagnosis presents the best opportunity for cure by surgical resection of the tumour. Prognostic factors in patients with advanced melanoma include, age, gender, primary tumour characteristics, tumour burden and LDH level.[1, 15]

Stage IV disease, when melanoma has spread outside of the regional lymph nodes to distant sites, is associated with a median survival of 6-9 months[19] and an extremely poor prognosis; the 5-year survival rates are low and associated with poor quality of life, which further decreases in the 12 months prior to death.[16-18]

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Clinical Guidelines

- The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Melanoma 2013 (v2). National Comprehensive Cancer Network, Inc.[23]
- Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up (2012)[24]
- Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline - Update 2012[25]
- Revised UK Guidelines for the management of cutaneous melanoma 2010, British Association of Dermatologists (BAD)[26]
- Royal College of Physicians and British Association of Dermatologists. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. No 7. 2007[27]
- Cutaneous Melanoma. A national clinical guideline- No.72. Scottish Intercollegiate Guidelines Network (2003) [28]

NICE Guidance

Cancer Service Guidance

- NICE Guidance on Cancer Services, May 2010, ‘Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community’ (2010 partial guidance update, although this update did not include melanoma; see 2006 guidance below).[29]
- NICE Guidance on Cancer Services, February 2006, ‘Improving outcomes for people with skin tumours including melanoma: the manual (2006 guidance).[30]
- NICE Guidance on Cancer Services, March 2004, ‘Improving supportive and palliative care for adults with cancer’: the manual.[31]

NICE Technology Appraisals

- NICE Technology Appraisal 269 (TA269). 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma', Dec 2012.[32]
- NICE Technology Appraisal 268 (TA268). 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma, Dec 2012.[9]
- Scheduled for appraisal: 'Dabrafenib for the treatment of BRAF V600 mutation-positive, unresectable, advanced or metastatic melanoma' [ID605]; and 'Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAF V600 mutation-positive melanoma' [ID605].

NICE Clinical Guidance

- NICE Clinical Guideline No 104, (in preparation), 'Diagnosis and management of metastatic malignant disease of unknown primary origin', July 2010, review anticipated July 2013.
- NICE Clinical Guideline No. 27, June 2005, 'Referral guidelines for suspected cancer'.[33]

NICE Public Health Guidance

- NICE Public Health Guidance No.32, 2011, 'Skin cancer prevention: information, resources and environmental changes: guidance'.[34]

No specific subgroups are addressed within this submission as ipilimumab is not restricted for use.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

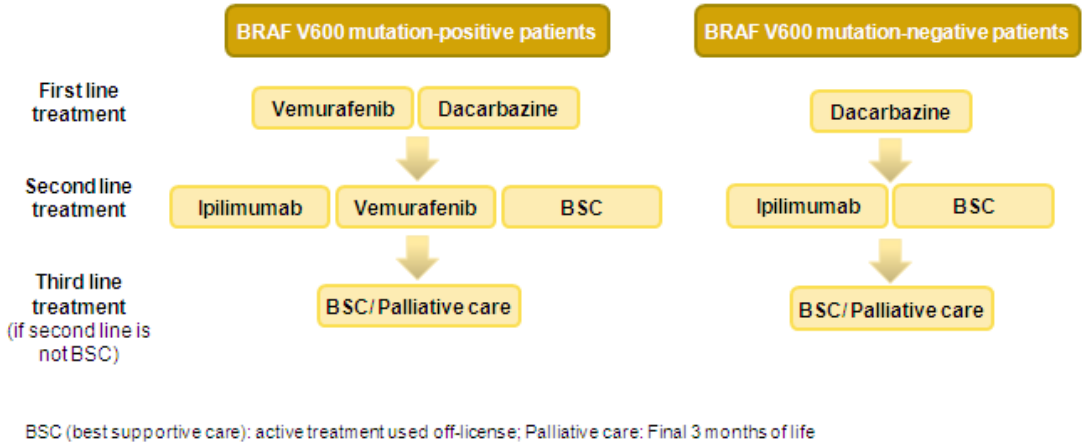
The treatment options for unresectable melanoma include[30]:

- Chemotherapy - is often used for patients with melanoma. There is no evidence to support the use of adjuvant chemotherapy following surgery.
- Radiotherapy - this has a very limited role in the management of patients with melanoma, as it is generally regarded as a radioresistant tumour. It is occasionally used for localised metastases and in the palliative setting.
- Vaccines - use is still experimental.
- No active treatment (Best Supportive Care [BSC]) - occasionally, for some patients, no active treatment with supportive care may be the most appropriate course of action.

When a patient has unresectable stage III or stage IV disease, the mainstay of treatment is systemic therapy. Traditionally, first-line therapy normally involved the administration of DTIC chemotherapy. Recent additions to systemic first-line therapies include vemurafenib [and dabrafenib (which has just been licensed)], for

patients with BRAF V600 mutation-positive tumours. The current clinical pathway of care is presented in Figure 2.

Figure 2: Current clinical pathway of care for the treatment of advanced (unresectable or metastatic) melanoma[30]



Footnote: While vemurafenib is both a first- and second-line treatment option, it is highly unlikely that having been used first-line, vemurafenib would subsequentially be used second-line.

Licensed therapeutic options are still limited for first-line treatment and entry into clinical trials remains an option for patients with advanced melanoma. Radiotherapy, other immunotherapies, targeted agents and combination chemotherapy continue to be studied in randomised clinical trials. However, not all patients are eligible for available clinical trials (i.e. do not meet the inclusion criteria - for example being fit enough to receive a treatment).

More recent melanoma treatment guidelines have been published from the European Society for Medical Oncology (ESMO)[24] and a European consensus-based interdisciplinary guideline from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organisation of Research and Treatment of Cancer.[25]

The ESMO Guidelines recommend that patients with metastatic melanoma should have the tumour screened for the presence of BRAF V600 mutation. Treatment options for the first- and second-line setting include ipilimumab, an anti-CTLA4 antibody, for all patients and vemurafenib, a BRAF inhibitor, for patients with BRAF V600 mutation-positive melanoma. They acknowledge that at the time of the guidelines, ipilimumab is approved only as second-line therapy by the EMA. If clinical trials or the approved new targeted compounds are not available, cytotoxic drugs such as DTIC could be used.

The European consensus-based interdisciplinary guideline states general principles for management of metastatic melanoma. Mutation testing of tumour tissue is a prerequisite for treatment decisions. BRAF V600 mutation-positive patients should be offered treatment with BRAF inhibitors or relevant experimental drugs in the context of clinical trials. Patients, whose disease progresses on first-line treatment, should be offered ipilimumab or other immunotherapies in the context of clinical trials. At the time of these guidelines, ipilimumab was only licensed in the second-line setting.

Chemotherapy (e.g. DTIC) should be considered for patients whose tumours do not have the BRAF V600 mutation and those who progress on BRAF inhibitors or immunotherapies. In summary, there is a clear unmet need for effective treatment options for advanced metastatic melanoma.

How does ipilimumab change the existing treatment pathway?

Currently, people with unresectable stage III or IV (metastatic) disease are treated with either DTIC or vemurafenib (only if the tumour is positive for the BRAF V600 mutation). Up to now ipilimumab has only been licensed and recommended by NICE for previously treated patients and is therefore used in the second-line setting, where it shows a long-term, durable survival benefit irrespective of mutation status.

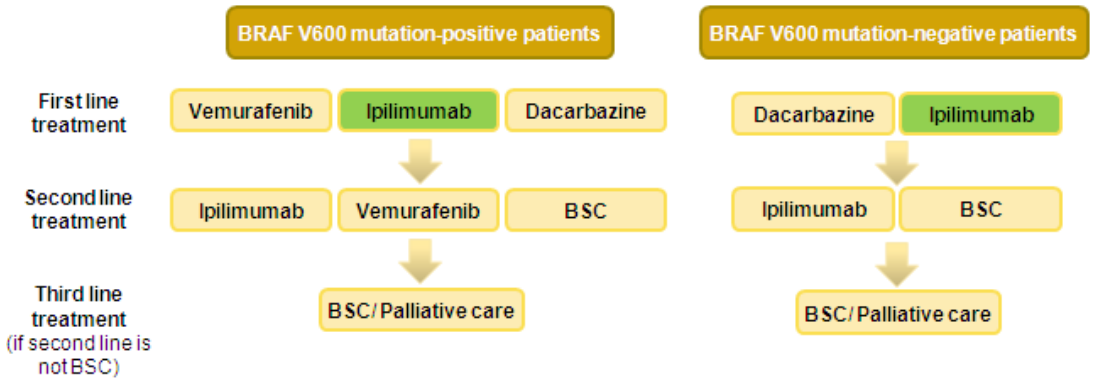
DTIC has demonstrated low response rates with short duration and a low overall survival benefit.[35] Responses to vemurafenib may not be durable and the majority of people who receive it develop resistance and tumour relapse.[3] This means that despite advances with targeted therapies there continues to be a significant unmet need for a durable, long-term survival benefit for first-line therapy of patients with advanced melanoma regardless of mutation status.

Results of clinical research with ipilimumab show promising long-term survival benefits with ipilimumab in patients with melanoma, with some individuals surviving up to 5 years and longer (10 years).[10, 11, 20, 36-38] This is an exciting outcome, given that previously the median survival has been 6-9 months.[19]

Ipilimumab has received CHMP approval and is anticipated to obtain a broader licensed indication in the near future. Ipilimumab therefore will offer a valuable first-line treatment option regardless of BRAF V600 mutation status.[39]

The future clinical pathway of care for advanced melanoma could look like that presented in Figure 3.

Figure 3: Future clinical pathway of care for the treatment of advanced (unresectable or metastatic) melanoma



BSC (best supportive care): active treatment used off-license; Palliative care: Final 3 months of life

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

In current clinical practice, there are no effective first-line treatments for melanoma which offer durable long-term survival benefit to all patients, i.e. irrespective of BRAF V600 mutation status.

2.7 Please identify the main comparator(s) and justify their selection.

The main comparators for this appraisal are therapeutics currently approved for first-line use in advanced melanoma in the UK, as identified by the NICE scope:

- DTIC: All patients with melanoma
- Vemurafenib: Patients with BRAF V600 mutation-positive melanoma

In addition to the NICE scope, we have included dabrafenib in BRAF V600 mutation-positive patients as a clinical comparator, as it is licensed for monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and is currently scheduled for a NICE technology appraisal (ID605).

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The unique immune-based mechanism of action of ipilimumab means that the most common drug-related AEs are immune-related in nature (irAEs). These are well characterised and are generally medically manageable with topical and/or systemic immunosuppressants.

Specific events are managed with symptomatic therapy (e.g. loperamide for diarrhoea) and/or oral steroids (e.g. prednisolone) for grade 1-2 events and high dose oral/IV corticosteroids (e.g. methylprednisolone) for grade 3-4 events, or in a minority of cases, other immunosuppressants (e.g. infliximab, mycophenolate mofetil) for steroid unresponsive irAEs as appropriate.[8] If an endocrinopathy occurs it may require ongoing hormone replacement therapy, which may be life-long. Such treatment of irAEs has been shown not to impact the development or maintenance of ipilimumab clinical activity in advanced melanoma.[40]

Management of irAEs is usually associated with omission of dosing for mild or moderate events and permanent discontinuation for severe irAEs.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Ipilimumab will be administered in the hospital setting, usually in outpatient chemotherapy suites as ‘day case’. Most hospitals have established oncology units that already provide the staffing and infrastructure for administration of cancer

treatments. No additional infrastructure is envisaged for the administration of ipilimumab.

Liver function tests and thyroid function tests should be evaluated at baseline and before each dose of ipilimumab.

The MELODY outcomes research study was used to inform resource estimates and costs.[41, 42]

2.10 Does the technology require additional infrastructure to be put in place?

It is anticipated that the administration of ipilimumab will utilise the existing NHS infrastructure, therefore there is no need for additional infrastructure.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equality issues are foreseen.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

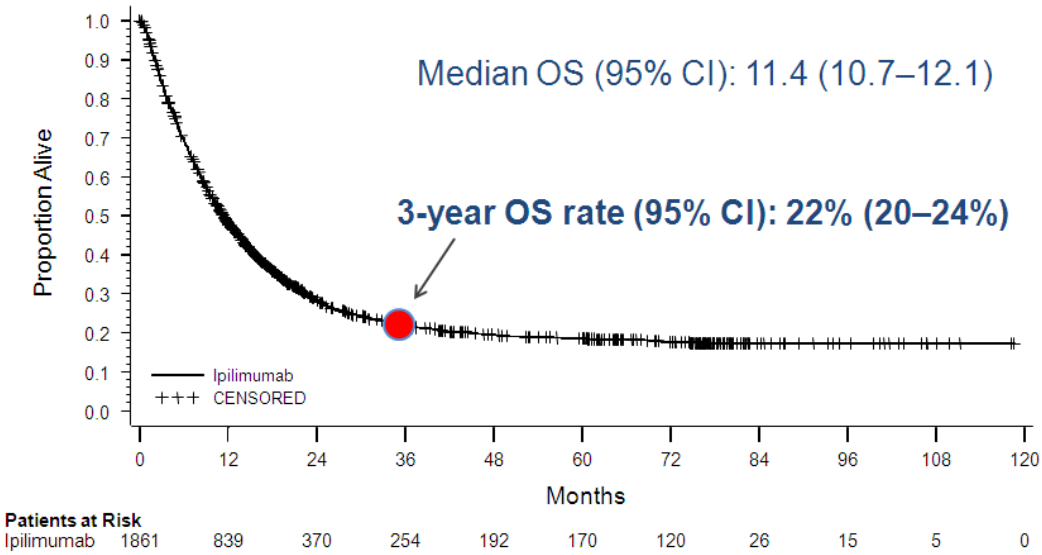
4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

At the advanced (unresectable or metastatic) stage of melanoma survival is poor with low 5-year survival rates[14] and a median survival of 6-9 months[19]; associated with poor quality of life that further decreases in the 12 months prior to death.[16-18] Over the past 25 years a great number of therapies have been investigated, yet none has significantly improved overall survival for advanced melanoma patients. This was demonstrated in a meta-analysis of over 70 treatments across 40 clinical trials highlighting the continued unmet need for effective treatment in advanced disease.[1]

It is against this backdrop that ipilimumab has been developed. The first of its class (licensed in 2010), ipilimumab is a new form of immunotherapy that initiates a CTLA-4 blockade, which in simple terms means the immune system has the potential to increase the number of active T cells targeting and attacking the malignant tumour cells (see section 1.2). This innovative mode of action is fundamentally different to that of traditional cytotoxic agents.

Clinical survival data from a pooled analysis of 1,861 ipilimumab-treated patients in 12 studies (2 phase III trials, 8 phase II trials and 2 observational studies across different doses and treatment regimens), relating to the long-term survival associated with ipilimumab therapy, are impressive, with approximately 20% of advanced melanoma patients surviving up to 10 years as presented in Figure 4[38].

Figure 4: Survival profile associated to ipilimumab therapy in advanced melanoma patients (n=1,861)[38]



In the meantime, the identification of a molecular target for melanoma treatment has led to the development of BRAF inhibitor therapies: vemurafenib and dabrafenib.

These treatments have shown a significant survival benefit in advanced melanoma patients compared with the historical standard of care (DTIC), but can only be used if molecular analysis confirms tumours possess the BRAF V600 mutation. In addition, the durability of effect with these therapies is still under investigation, meaning long-term data from pivotal trials are currently unavailable. Interestingly, reports suggest patients demonstrate progressive disease within 6-8 months after starting vemurafenib or dabrafenib therapy in practice.[3, 4]

Thus, ipilimumab is the only novel therapeutic option for advanced melanoma that offers a durable long-term survival benefit.

This clinical benefit is observed across a range of dosing regimens, with an extensive evidence base supporting ipilimumab's use as a first-line therapy with up to 5-year data available from:

- the randomised phase III study, CA184-024;
- the randomised phase II study, MDX010-08;
- a pooled analysis of chemotherapy-naïve patients randomized to 3 mg/kg ipilimumab monotherapy in three phase II studies, MDX010-08, CA184004, and CA184022, and one phase III study, MDX010-20; and
- interim results from two retrospective observational studies, CA184-332 and CA184-338, which assess ipilimumab's "real-world" effectiveness.

Data from the pivotal phase III study in previously untreated patients, CA184-024, shows a statistically significant improvement in survival times compared with historical standard of care (DTIC), with an overall survival rate at 5 years of 18.2% vs. 8.8% and a mean survival time at 5 years of 91.1 vs. 66.6 weeks.[43]

Post-hoc analysis of HRQL data for patients treated with ipilimumab as first-line therapy shows that ipilimumab does not have a significant negative impact on quality of life (Section 7.4). Quality of life (in terms of utility) remains close to that of the age matched general population for patients who survive at least an additional six months. Furthermore, ipilimumab is administered as 4 single doses within a 12 week treatment period and does not have the daily pill burden of the BRAF inhibitors.

Consideration of the evidence base shows ipilimumab for first-line therapy of advanced melanoma meets NICE's End of Life criteria:

- advanced melanoma patients have a short life expectancy with a median survival of 6-9 months[19]; this was previously assessed as true in TA269
- ipilimumab offers an extension to life, normally of at least an additional 3 months compared with standard of care: restricted mean analysis (carried out on patient level data from the 5 year cut of CA184-024) shows a survival gain of 5.7 months over the 5 year trial;
- estimated advance melanoma patient population eligible for first-line therapy is small: expected patient numbers of ~338 in 2014; this was previously assessed as true in TA269

In summary, ipilimumab is the first of a new class of therapies that offers durable long-term survival benefits when used as a first-line therapy for advanced melanoma. This is demonstrated in an expansive evidence base of clinical trials (negating the need for extrapolation to allow long-term effect analyses). Due to its stimulation of the body's own immune system, ipilimumab is not restricted for use, and has comparable clinical activity in BRAF V600 mutation-positive and -negative melanoma.

For these reasons, ipilimumab should be considered a step change in first-line therapy of advanced melanoma; worthy of additional merit for not only its novel mechanism of action but also the data package provided to demonstrate these claims.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Not applicable.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable.

5 Statement of the decision problem

The decision problem that this submission addresses is presented in Table 4.

Table 4: Scope and decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with previously untreated advanced (unresectable or metastatic) malignant melanoma.	People with previously untreated advanced (unresectable or metastatic) malignant melanoma.	No difference.
Intervention	Ipilimumab	Ipilimumab	No difference.
Comparator(s)	DTIC, Vemurafenib (in BRAF V600 mutation-positive patients)	DTIC, Vemurafenib (in BRAF V600 mutation-positive patients)	No difference.
Outcomes	Overall survival, adverse effects of treatment, HRQL.	Overall survival, adverse effects of treatment, HRQL.	No difference.
Economic analysis	Cost effectiveness of treatments expressed in terms of incremental cost per quality-adjusted life year. Time horizon for estimating clinical and cost effectiveness sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs from an NHS and Personal Social Services perspective.	Cost effectiveness in incremental cost per quality-adjusted life year. Life-time horizon (40 years). Costs from an NHS and Personal Social Services perspective.	No difference.
Subgroups to be considered	None	None in addition to the BRAF V600 mutation-positive sub-population.	No difference.
Special considerations, including issues related to equity or equality	None	None	No difference.

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of HTA	Reference case	Section in 'Guide to the methods of TA'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)

6 Clinical evidence

Summary

- An extensive evidence base supports the use of ipilimumab as first-line treatment of patients with advanced melanoma:
  - CA184-024: pivotal phase III randomised controlled trial (RCT) in previously untreated advanced melanoma patients that investigates the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy compared with DTIC monotherapy
  - MDX010-08: phase II RCT in chemotherapy-naïve advanced melanoma patients that investigates the efficacy of ipilimumab 3mg/kg monotherapy compared with ipilimumab 3mg/kg in addition to DTIC therapy
  - Pooled chemotherapy-naïve dataset: combined data from three phase II RCTs (MDX010-08, CA184004, and CA184022) and one phase III RCT (MDX010-20) in chemotherapy-naïve advanced melanoma patients that reports the efficacy of ipilimumab 3mg/kg monotherapy
  - CA184-332 and CA184-338: retrospective, observational studies investigating the “real-world” effectiveness of ipilimumab 3mg/kg monotherapy in previously untreated advanced melanoma patients
- Ipilimumab provides an innovative mechanism of action that stimulates the body’s own immune system to fight cancer cells.
- Ipilimumab use is not restricted by BRAF V600 mutation status.
- Ipilimumab shows a durable biological effect and currently offers the only long-term survival profile in previously untreated patients with advanced melanoma:
  - 5-year data demonstrate a significant improvement in mean survival of 24.5 weeks compared with historical standard of care (DTIC)
  - 10 year data from a poled analysis study also supports the long-term survival effect of ipilimumab
- Ipilimumab has a predictable, manageable, adverse event profile, which is normally reversible with immunosuppressant therapy which has no impact on the clinical activity of ipilimumab.
- Normally we would expect there to be a deleterious effect on patients’ quality-of-life when treated with standard chemotherapy. Unlike other treatments, ipilimumab has a minimal treatment-related effect on the quality of life.
  - HRQL for ipilimumab treated patients who survive at least a further six months post ipilimumab therapy remain close to that of the age matched general population for patients

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

To help answer the research question *"what is the clinical efficacy and tolerability of ipilimumab and comparator therapies for the treatment of adult patients with previously untreated advanced malignant melanoma?"* the following databases were searched in the week commencing 6th May 2013 to identify relevant sources of information:

- Medline
- Embase
- The Cochrane Library
- Cochrane Database of Systematic Reviews (CDR)
- Cochrane Central Register of Controlled Trials (CCRT)
- Health Technology Assessment Database (HTA)
- Database of Abstracts of Reviews of Effects (DARE)
- Cinahl
- ClinicalTrials.gov (searched w/c 13th May 2013)

In addition, 2009-2012 conference proceedings of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the European Association of Dermato-Oncologists (EADO), Perspectives in Melanoma (PiM) and Society for Melanoma Research (SMR) were searched in the week commencing 13th May 2013.

Reference lists of previous systematic reviews/meta-analyses and clinical guidelines identified were hand-searched to highlight any further relevant studies.

Furthermore, unpublished data by Bristol-Myers Squibb were reviewed for relevance to the research question.

Ipilimumab use is not restricted by BRAF V600 mutation status so no exclusion criteria were placed against either BRAF V600 mutation-positive or -negative melanoma. Comparator therapies therefore included those used in either melanoma type. Dabrafenib was included in the list of comparator therapies alongside currently approved therapies (DTIC and vemurafenib) as NICE guidance of its use in BRAF V600 mutation-positive malignant melanoma is currently in development.

Given that the earliest melanoma trial was published in 1972, a date limit of 1970 to present day (May 2013) was justified.

No other restrictions were applied to the systematic searches.

Details of the search strategy used are provided in section 10.2, appendix 2.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Prior to the recent approval of vemurafenib use for patients with BRAF V600 mutation-positive malignant melanoma, only chemotherapy was approved for the treatment of advanced malignant melanoma in the EU. Therefore, both treatment-naïve and chemotherapy-naïve patients were included in order to fully capture the untreated patient population of interest in this submission.

Studies were included that evaluated any of the named interventions (either as monotherapy or in combination) in comparison to any other named intervention. Prior to statistical analysis, studies excluded on account of a comparator arm outside of the named interventions list were assessed for potential inclusion in the subsequent mixed-treatment comparison (MTC) based on network strengthening.

In order to conduct preliminary assessment, at least the abstract of identified citations had to be available in English. Eligibility criteria used in the clinical search strategy are listed in Table 5.

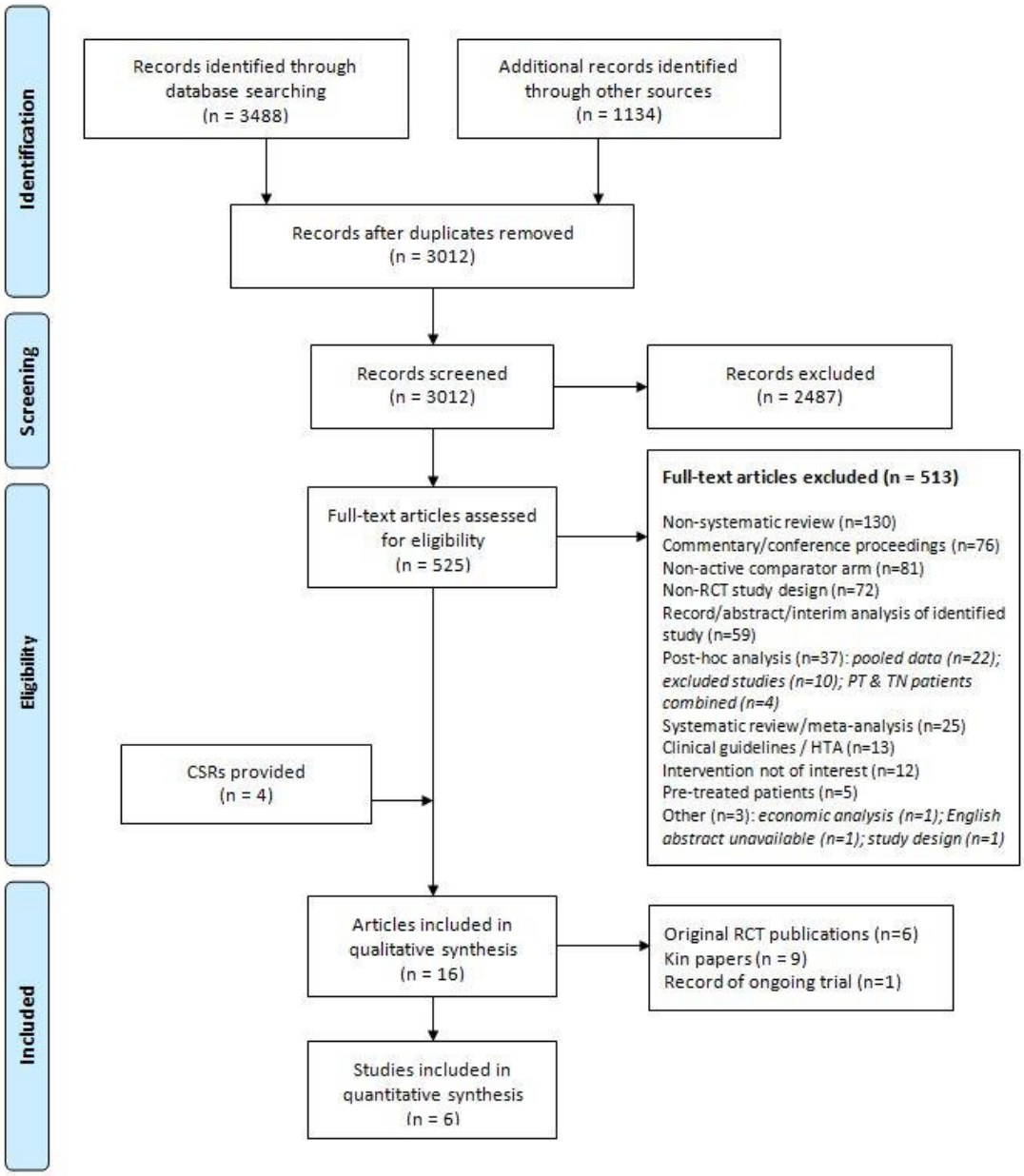
Table 5: Eligibility criteria used in clinical search strategy

Inclusion criteria
Population • Adult patients with previously untreated (chemotherapy-naïve) advanced (unresectable or metastatic) malignant melanoma *Interventions* • Ipilimumab • DTIC • Vemurafenib • Dabrafenib *Outcomes* • Survival (OS or PFS) • Response (overall response rate, time to response, duration of response, disease control) • Safety (adverse effects of treatment) • Health-related quality of life (HRQL) *Study design* • RCTs *Restrictions* • Date = 1970-present day (May 2013) • Language = English abstract
Exclusion criteria
Population • Paediatric patients • Pre-treated patients • Stage 0 – II melanoma *Interventions* • Treatments used off-licence *Study design* • Prospective non-RCTs • Observational studies

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

A flow diagram of the systematic review process is presented as a PRISMA (preferred reporting information in systematic reviews and meta-analyses) in Figure 5.

Figure 5: PRISMA flow diagram of the systematic search process



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Secondary publications of original RCTs were included in the final set of articles included in qualitative synthesis when they gave additional information on a clinical outcome or the patient population of interest. Characteristics of secondary publications are listed in Table 6.

Table 6: Characteristics of secondary publications (kin papers)

Trial no. (acronym)	Original reference	Kin paper reference	Format	Summary of additional information
CA184-024	Robert et al. 2011[20]	BMS 2012[7]	Clinical Study Report	PFS TTR HRQL
		Maio et al. 2012[44]	Abstract	Updated OS
		Maio et al. 2012[45]	Abstract	Updated OS
		Thomas et al. 2012[46]	Abstract	Updated safety
MDX010-08	Hersh et al. 2011[47]	BMS 2009[48]	Clinical Study Report	OS
CA184-004	Hamid et al. 2011[49]	BMS 2009[50]	Clinical Study Report	Chemotherapy-naïve subgroup analysis
CA184-022	Wolchok et al. 2010[51]	BMS 2008[52]	Clinical Study Report	Chemotherapy-naïve subgroup analysis
CA184-169	NCT01515189_2013[53]	-	-	-
BREAK-3	Hauschild et al. 2012[54]	-	-	-
BRIM-3	Chapman et al. 2011[55]	McArthur et al. 2011[56]	Abstract	Updated OS
		Chapman et al. 2012[57]	Abstract	Updated OS
HRQL, Health-related quality of life; OS, overall survival; PFS, progression free survival; TTR, time to response				

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 7 provides the list of relevant RCTs identified by the clinical search.

Table 7: List of relevant RCTs identified by the clinical search

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
CA184-024	Ipilimumab 10mg/kg + DTIC	DTIC	Adult patients with previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions and a life expectancy of ≥3 months.	Robert et al. 2011[20]
MDX010-08	Ipilimumab 3mg/kg + DTIC	Ipilimumab 3mg/kg	Adult patients with unresectable metastatic melanoma who had not received prior chemotherapy and had a life expectancy of ≥3 months.	Hersh et al. 2011[47]
CA184-004	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg	Adult patients with stage IV or unresectable stage III malignant melanoma and a life expectancy of ≥4 months. Previously treated and treatment-naïve patients eligible but only the chemotherapy-naïve subgroup of interest in this review.	Hamid et al. 2011[49]
CA184-022	Ipilimumab 3mg/kg	Ipilimumab 0.3mg/kg Ipilimumab 10mg/kg	Adult patients with stage IV or unresectable stage III malignant melanoma and a life expectancy of ≥4 months. Previously treated patients eligible but only the chemotherapy-naïve subgroup of interest in this review.	Wolchok et al. 2010[51]
CA184-169	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg	Adult patients with stage IV or unresectable stage III malignant melanoma. Previously treated and treatment-naïve patients eligible but only the treatment naïve subgroup of interest in this review.	NCT01515189_2013[53]
BREAK-3	Dabrafenib	DTIC	Adult patients with measurable metastatic melanoma (stage IV or unresectable stage III) that tested positive for the BRAF V600 mutation and had not received previous antitumor therapy other than interleukin-2.	Hauschild et al. 2012[54]
BRIM-3	Vemurafenib	DTIC	Adult patients with previously untreated stage IIIC or stage IV melanoma that tested positive for the BRAF V600 mutation and a life expectancy of ≥3 months.	Chapman et al. 2011[55]

DTIC, dacarbazine

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

In the RCTs identified, ipilimumab 3mg/kg monotherapy has not directly been compared with any of the comparators included in the scope.

There are however four RCTs identified (CA184-024, MDX010-08, CA184-004 and CA184-022) that, when taken into consideration collectively, provide comparative efficacy evidence for ipilimumab 3mg/kg vs. DTIC (the appropriate comparator for BRAF V600 mutation-negative patients) in previously untreated advanced (unresectable or metastatic) melanoma:

CA184-024 is a large phase III trial that compared the combination of ipilimumab 10mg/kg + DTIC to DTIC directly.[20] In turn, ipilimumab 3mg/kg + DTIC combination therapy was compared with ipilimumab 3mg/kg monotherapy in the phase II trial, MDX010-08.[47]

Though combination arms included different ipilimumab doses, clinical equivalence of ipilimumab 3mg/kg demonstrated long-term survival with lower rates of adverse events, thus offering a promising risk/benefit ratio.

Ipilimumab 3mg/kg and ipilimumab 10mg/kg has been directly considered in two phase II trials: CA184-004 and CA184-022 that included both pre-treated and treatment naïve patients and is being formally investigated in the ongoing phase III trial: CA184-169.[49, 51, 53]

The clinical benefit of ipilimumab 3mg/kg monotherapy as a first-line therapy option for advanced melanoma patients is supported by the EMA who have approved a licence extension for ipilimumab 3mg/kg monotherapy to untreated as well as pre-treated patients.[58]

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

CA184-169 is an ongoing study and not due for completion before December 2016. No preliminary results are available at this stage and thus this trial has been excluded from further discussion.[53]

Preliminary survival analysis conducted on the chemotherapy-naïve subgroups of interest from CA184-004 and CA184-022 was deemed inappropriate for use due to the low patient numbers in each treatment arm that met the criteria for inclusion in this submission (Table 8).[50, 52] The decision was therefore made to remove both studies from further discussion in accordance with expert opinion.

Table 8: Chemotherapy-naïve patient numbers from CA184-004 and CA184-022

	CA184-004, n	CA184-022, n
Ipilimumab 0.3mg/kg	-	6
Ipilimumab 3mg/kg	17	8
Ipilimumab 10mg/kg	19	4

For completeness, survival analyses of subgroups from both trials are presented in appendix A.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

In light of the limited RCT evidence directly investigating the clinical efficacy of ipilimumab 3mg/kg monotherapy in untreated patients, the following additional non-RCT evidence is included to support its use in the first-line setting (Table 9):

- Interim results from two retrospective, observational studies (CA184-332 and CA184-338)[59, 60], which are currently ongoing in the US and were specifically designed to assess outcomes in patients who have been prescribed 3mg/kg in the first-line setting.[61] These studies are of relevance as they are conducted in a “real world” population without traditional clinical trial exclusion criteria.
- An analysis of a pooled chemotherapy-naïve dataset from clinical trials is presented.[8, 61] This pooled dataset comprises chemotherapy-naïve patients from CA184-004, MDX010-08, CA184-022 (phase II RCTs) and MDX010-020 (a phase III RCT comparing the clinical efficacy of ipilimumab 3mg/kg monotherapy to its combination with the synthetic vaccine gp100 and gp100 monotherapy.[11]

Table 9: List of relevant non-RCT evidence

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
CA184-332	Ipilimumab 3mg/kg	Adult patients with previously untreated advanced malignant melanoma who were prescribed ipilimumab 3mg/kg.	To assess the clinical efficacy (survival) and safety of ipilimumab 3mg/kg when used as first-line therapy.	Patt et al, 2013[59]	Provide evidence in a 'real world' population. Supports the use of ipilimumab 3mg/kg in the first-line setting.
CA184-338	Ipilimumab 3mg/kg			Margolin et al, 2013[60]	
Pooled chemo-therapy-naïve dataset (from clinical trials)	Ipilimumab 3mg/kg	Adult patients with treatment naïve or chemotherapy-naïve advanced malignant melanoma who participated in a clinical trial where they were randomised to treatment with ipilimumab 3mg/kg monotherapy.	To assess the clinical efficacy (survival) of ipilimumab 3mg/kg when used as first-line therapy.	BMS_2013[61]	Supports the use of ipilimumab 3mg/kg in the first-line setting.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Three of the four RCTs identified of relevance to the decision problem were phase III trials: CA184-024, BREAK-3 and BRIM-3. Of these phase III trials, only CA184-024 was double-blind in design with BREAK-3 explicitly stating its open-label nature and BRIM-3 assumed to be the same given that the intervention and control arm have

different modes of administration (oral vs. intravenous).[20, 54, 55] The fourth RCT, MDX010-08, is a phase II, open-label study.[47]

On confirmation of progression, patients randomised to DTIC could crossover to the experimental treatment arm in both trials investigating BRAF inhibitors. This was pre-planned in BREAK-3 but added into the protocol after interim analysis in BRIM-3.[54, 55] One of the ipilimumab trials was also cross-over in design with patients receiving ipilimumab monotherapy in MDX010-08 being additionally treated with DTIC on confirmation of progression.[47]

Ipilimumab dosing differed across trials with the agent being administered at doses of either 3mg/kg or 10mg/kg. Clinical equivalence between these doses has been illustrated in both untreated and pre-treated melanoma patients in CA184-004 and CA184-022, and is being formally investigated in the ongoing phase III trial CA184-169.[49, 51, 53] DTIC was administered at doses reflecting clinical practice.[20, 47, 54, 55]

The treatment schedule for ipilimumab therapy also differed between trials: patients enrolled in MDX010-08 were treated for ipilimumab induction therapy defined as 3mg/kg every 4 weeks for a total of 4 doses (which deviated from the UK licence terms being 3 mg/kg, every 3 weeks for a total of 4 doses); the study protocol for CA184-024 included a maintenance phase of therapy post-induction of ipilimumab where responsive patients received ipilimumab every 12 weeks. Review of Kaplan–Meier curves from ipilimumab trials in untreated patient populations shows such a maintenance phase of therapy does not significantly impact the survival profile of ipilimumab therapy (see section 6.8).

The primary outcome measure of clinical efficacy was survival (OS and/or PFS) in all phase III trials.[20, 54, 55] Survival of patients enrolled in MDX010-08 was a secondary outcome of the original study, but was a named primary outcome in the associated MDX010-028 protocol under which survival was actually assessed.[48]

In the initial design of CA184-024, PFS was to be the primary endpoint. However, emerging data from the early phase II ipilimumab trials suggested that conventional definitions of disease progression and response incompletely captured clinical benefit among subjects who appear to have favourable survival due to the novel mechanism of action of ipilimumab.[6] Subsequently, in an amendment approved by the US FDA before the treatment assignments were revealed, the primary endpoint was changed from PFS to OS. No change in the size of the study was required since it was already fully powered to assess OS.[48]

Median follow-up times are less than 12 months for trials investigating the clinical efficacy of vemurafenib and dabrafenib.[54, 55, 57, 62] Conversely, a long-term clinical and safety profile is available for ipilimumab with CA184-024 presenting a median follow-up time of ≥37 months.[7, 20]

The comparative summary of methodology of the RCTs is provided in Table 10.

Table 10: Comparative summary of methodology of the RCTs

	CA184-024	MDX010-08	BREAK-3	BRIM-3
Location	111 sites in Africa, Australia, Europe, North America and South America.	12 sites in the US.	70 sites in 12 countries worldwide.	104 centres in 12 countries worldwide.
Design	Multinational, randomised, double-blind, phase III study designed to assess if ipilimumab addition to standard therapy (DTIC) improves overall survival in patients with previously untreated metastatic melanoma.	Multicentre, randomised, open-label, phase II, cross-over study designed to evaluate the efficacy and safety of ipilimumab addition to standard therapy (DTIC) in patients with chemotherapy-naïve metastatic melanoma.	Multinational, randomised, open-label, phase III, cross-over study designed to compare dabrafenib to standard therapy (DTIC) in patients with previously untreated metastatic melanoma with the BRAF V600 mutation.	Multinational, randomised, phase III, cross-over study designed to assess if vemurafenib prolongs survival in comparison to standard therapy (DTIC) in patients with previously untreated metastatic melanoma with the BRAF V600 mutation.
Method of randomisation	A centralised randomisation scheme was used to assign subjects in a 1:1 ratio. Randomisation was stratified according to baseline M stage; ECOG performance status; and study site.	A centralised randomisation scheme was used to assign subjects in a 1:1 ratio. Randomisation was stratified using a random block size of 2 or 4.	A centralised, computerised, interactive voice activated response randomisation scheme was used to assign subjects in a 3:1 ratio. Randomisation was stratified according to baseline M stage.	Randomisation was used to assign subjects in a 1:1 ratio. Randomisation was stratified according to baseline M stage; ECOG performance status; geographic region; and serum lactate dehydrogenase.
Method of blinding	Patient; care provider; outcome assessor on site	Open-label study: treatment was not blinded	Not reported.	Independent review committee only.
Intervention **Comparator**	Ipilimumab 10mg/kg + DTIC 850mg/m^2 (n=250) DTIC 850mg/m^2 (n=252)	Ipilimumab 3mg/kg + DTIC 1000mg/m^2 (n=36) Ipilimumab 3mg/kg (n=40)	Dabrafenib (n=187) DTIC 1000mg/m^2 (n=63)	Vemurafenib 960mg (n=337) DTIC 1000mg/m2 (n=338)
Treatment schedule	Induction phase: treatment on weeks 1, 4, 7 and 10; DTIC only on weeks 13, 16, 19 and 22 Maintenance phase: ipilimumab or placebo every 12 weeks (responsive patients only)	Ipilimumab (both groups): weeks 1, 5, 9 and 13 DTIC: weeks 1, 4, 7, 10, 13 and 16	Dabrafenib: twice daily DTIC: every 3 weeks	Vemurafenib: twice daily DTIC: every 3 weeks

	CA184-024	MDX010-08	BREAK-3	BRIM-3
Primary outcomes	Overall survival	Objective response rate (CR + PR)* Safety *RECIST assessments performed every 4 weeks after criteria for response were first met	Progression-free survival (investigator assessed)	Overall survival Progression-free survival
Secondary outcomes	Progression-free survival Overall response rate (CR + PR)* Disease control rate (CR + PR + SD)* Time to response Duration of response Safety HRQL: (EORTC) QLQ-C30 at baseline and weeks 4, 7, 12, 24, 36, 48 *RECIST assessments performed at week 12 and in responsive patients at weeks 16, 20 and 24 and every 6 weeks through week 48. Then every 12 weeks.	Duration of response Stable disease rate* Survival Lymphocyte subpopulations Pharmacokinetics *RECIST assessments performed every 4 weeks after criteria for response were first met	Progression-free survival (IRC assessed) Overall survival Objective response rate (CR + PR)* Progression-free survival post cross-over Duration of response HRQL Safety and tolerability Support of a BRAF mutation assay validation *RECIST assessments performed at weeks 6 and 12 and every 9 weeks thereafter	Confirmed response rate (CR + PR)* Time to response Duration of response Number of participants with AEs *RECIST assessments performed at weeks 6 and 12 and every 9 weeks thereafter
Duration of follow-up	37 months post last patient enrolment	Median, months: Ipilimumab + DTIC: 20.9 Ipilimumab: 16.4	Median, months: Dabrafenib: 5.0	*Initial analysis* Median, months: Vemurafenib: 3.8 DTIC: 2.3 *Extended analysis* Median, months: Vemurafenib: 10.5 DTIC: 8.4

AEs, adverse events; CR, complete response; DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group; HRQL, health-related quality of life; IRC, independent review committee; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours ;SD, stable disease; US, United States

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

The eligibility criteria in CA184-024, MDX010-08, BREAK-3 and BRIM-3 are summarised in Table 11.

The major difference between trials is the inclusion of only BRAF V600 mutation-positive patients in BRIM-3 and BREAK-3, whereas the ipilimumab trials patents regardless of mutation status.[20, 54, 55] This is due to the fact that both vemurafenib and dabrafenib target the BRAF pathway and thus have no effect in BRAF V600 mutation-negative patients. Ipilimumab's novel mode of action stimulates the body's own immune system to fight cancer cells and its use is not therefore restricted by the BRAF V600 mutation status of advanced melanoma patients.

Post-hoc analysis of study CA184-004 that enrolled both pre-treated and untreated patients investigated whether the clinical activity of ipilimumab would be affected by the BRAF V600 mutation status of the tumours. Based on retrospective analysis of 69 patients for whom data on disease control and BRAF V600 mutation status were available, rates of objective responses and stable disease were comparable across patients with BRAF V600 mutation-positive tumours and those with BRAF V600 mutation-negative tumours.[39]

An additional difference between trials is within the treatment history of patients enrolled: CA184-024 and BRIM-3 did not allow any prior anti-tumour therapy; BREAK-3 patients were allowed prior immunotherapy with interleukin-2; and MDX010-08 patients were chemotherapy-naïve and had not received immunotherapy, melanoma vaccine or anti-CTLA-4 antibody in the past 5 years.[20, 47, 54, 55] As discussed in section 6.2.1, all are considered of relevance to the decision problem.

Furthermore, subset analysis of an additional ipilimumab study, MDX010-020, which investigated the clinical efficacy of ipilimumab monotherapy or in combination with gp100, showed the survival benefit associated to ipilimumab therapy was not affected by treatment history. Specifically, overall survival benefit was observed for subjects regardless of prior immunotherapy (yes vs. no) and number of prior therapies.[63] A large independent academic meta-analysis of 42 clinical trials in metastatic melanoma also showed that whether or not a patient received prior therapy was not a predictor for OS.[1] Finally, the exposure-response results from the phase II ipilimumab program confirmed that prior therapy was not a significant covariate for OS from ipilimumab.[63]

Table 11: Eligibility criteria in CA184-024, MDX010-08, BREAK-3 and BRIM-3

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
CA184-024	≥18 years of age; previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions; an ECOG performance status of 0 or 1; a life expectancy of ≥16 weeks.	Prior treatment for metastatic disease; evidence of brain metastasis (as confirmed on imaging); primary ocular or mucosal melanoma; autoimmune disease; concomitant treatment with immunosuppressive agents or long-term use of systemic glucocorticoids (except for the management of AEs during the course of the study) was not allowed.
MDX010-08	≥18 years of age; histologic diagnosis of unresectable metastatic melanoma; progressive disease defined by Response Evaluation Criteria in Solid Tumours (RECIST); ≥1 measurable lesion; life expectancy ≥12 weeks; discontinued any other melanoma therapy ≥4 weeks before enrolment.	Any other prior malignancy; history or clinical evidence of autoimmune disease; treatment with an immunosuppressive drug, melanoma vaccine, anti-CTLA-4 antibody, or chemotherapy within the past 5 years (except for regional chemotherapy); active infection requiring therapy; chronic active hepatitis B or C virus infection, or human immunodeficiency virus reactivity.
BREAK-3	Histologically confirmed, measurable metastatic melanoma (stage IV or unresectable stage III) with BRAF V600 mutation by central testing using an investigational-use-only assay; 18 years of age or older; ECOG performance status of 0 or 1; adequate haematological, hepatic, renal, and cardiac function.	Previous anti-tumour therapy for unresectable or metastatic melanoma other than interleukin 2; surgery, radiotherapy, or immunotherapy within 4 weeks; history of HIV infection; glucose-6-dehydrogenase deficiency; previous malignancy within the past 5 years; CNS metastases unless patients were without evidence of active CNS metastases for more than 3 months after surgery or stereotactic radiosurgery; corrected QT interval of 480 ms or more; acute coronary syndrome, coronary angioplasty, placement of stents, or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks; abnormal cardiac valve morphology grade 2 or higher on ECHO cardiography; known cardiac metastases.
BRIM-3	Unresectable, previously untreated stage IIIC or stage IV melanoma that tested positive for the BRAF V600 mutation on real-time polymerase-chain-reaction assay; ≥18 years of age; life expectancy of ≥3 months; ECOG performance status of 0-1; adequate hematologic, hepatic, and renal functions.	History of cancer within the past 5 years (except for basal- or squamous-cell carcinoma of the skin or carcinoma of the cervix) or metastases to the central nervous system, unless such metastases had been definitively treated more than 3 months previously with no progression and no requirement for continued glucocorticoid therapy; concomitant use of any other anticancer therapy was not allowed.

AEs, adverse events; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, Human immunodeficiency virus
Source: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Demographic and other baseline characteristics of participants were generally comparable and well balanced both within and across RCTs (Table 12).

Average age ranged from 50-65 years, >50% of enrolled patients were male and ~90-100% of all participants were white in all RCTs, directly reflecting the melanoma population observed in clinical practice.[20, 47, 54, 55]

Known prognostic factors were also similar in presentation across trials at baseline: approximately 70% of enrolled patients had an ECOG performance status of 0 in all RCTs and elevated serum lactate dehydrogenase levels were observed in ~30-60% of patients.[20, 47, 54, 55]

While metastasis stage showed the largest variability, over 50% of patients in all RCTs presented with advanced disease (i.e. stage M1c where the tumour has metastasised to vital organs other than the lungs, or there are distant metastases with elevated LDH). However, the number of patients randomised to each treatment arm was stratified for this prognostic factor in all phase III trials.[20, 47, 54, 55]

Table 12: Baseline characteristics of participants in CA184-024, MDX010-08, BREAK-3 and BRIM-3 across randomised groups

	CA184-024		MDX010-08		BREAK-3		BRIM-3	
	Ipi + DTIC (n=250)	**DTIC (n=252)**	**Ipi + DTIC (n=35)**	**Ipi (n=37)**	**Dab (n=187)**	**DTIC (n=63)**	**Vem (n=337)**	**DTIC (n=338)**
Age, median years (range)	57.5*	56.4*	60 (27-82)	66 (25-82)	53 (22-93)	50 (21-82)	56 (21-86)	52 (17-86)
Male, n (%)	152 (60.8)	149 (59.1)	26 (74.3)	21 (56.8)	112 (59.9)	37 (58.7)	200 (59.4)	181 (53.6)
White, n (%)	249 (99.6)	251 (99.6)	31 (88.6)	34 (91.9)	187 (100)	63 (100)	333 (98.8)	338 (100)
ECOG performance status, n (%)	0 = 177 (70.8) 1 = 73 (29.2)	0 = 179 (71.0) 1 = 73 (29.0)	NR	NR	0 = 124 (66.3) ≥1 = 62 (33.2)	0 = 44 (69.8) ≥1 = 16 (25.4)	0 = 229 (68.0) 1 = 108 (32.0)	0 = 230 (68.0) 1 = 108 (32.0)
Metastasis stage, n (%)	M0 = 6 (2.4) M1a = 37 (14.8) M1b = 64 (25.6) M1c = 143 (57.2)	M0 = 8 (3.2) M1a = 43 (17.1) M1b = 62 (24.6) M1c = 139 (55.2)	M1a = 6 (17.1) M1b = 12 (34.3) M1c = 16 (45.7)	M1a = 8 (21.6) M1b = 8 (21.6) M1c = 21 (56.8)	M0 = 6 (3.2) M1a = 23 (12.3) M1b = 34 (18.2) M1c = 124 (66.3)	M0 = 1 (1.6) M1a = 10 (15.9) M1b = 12 (19.0) M1c = 40 (63.5)	M0 = 20 (5.9) M1a = 34 (10.1) M1b = 62 (18.4) M1c = 221 (65.6)	M0 = 13 (3.8) M1a = 40 (11.8) M1b = 65 (19.2) M1c = 220 (65.1)
Duration of melanoma, months	36.6	40.4	23.2	46.3	NR	NR	NR	NR
Lactate dehydro-genase, n (%)	≤ULN = 157 (62.8) >ULN = 93 (37.2)	≤ULN = 140 (55.6) >ULN = 110 (43.7)	≤ULN = 27 (77.1) >ULN = 8 (22.9)	≤ULN = 27 (73.0) >ULN = 10 (27.0)	≤ULN = 119 (63.6) >ULN = 67 (35.8)	≤ULN = 43 (68.3) >ULN = 19 (30.2)	≤ULN = 142 (42.1) >ULN = 195 (57.9)	≤ULN = 142 (42.0) >ULN = 196 (58.0)
DTIC, dacarbazine; NR, not reported; ULN, upper limit of normal; UR, unresectable								

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

An overview of primary and secondary outcomes of CA184-024, MDX010-08, BREAK-3 and BRIM-3 is presented in Table 13.

As noted in section 6.3.2, the primary outcome measure of clinical efficacy was survival in all phase III trials identified.[20, 54, 55] This was also named as a secondary outcome measure of clinical efficacy in the phase II trial.[47] Both OS and PFS are well established measures of the effects of cancer therapies and are of relevance to clinical practice where the ultimate aim is to prolong life. Overall survival is also directly referenced in the decision problem.

Long-term survival data are only available for ipilimumab therapy in untreated metastatic melanoma patients with 5 year survival data recently presented at ESMO 2013.[43]

Safety was named as a primary or secondary outcome measure in all RCTs with intensity of AEs graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) on a five-point scale (grade 1 to 5: mild, moderate, severe, life-threatening and death). [20, 47, 54, 55] This is a recognised scale, often adopted in clinical trials, and allows any safety concerns in practice to be highlighted.

Ipilimumab already has an extensively documented AE profile which is primarily immune-related. As a result, attention was paid to the detection and assessment of AEs that could represent the biological consequences of CTLA-4 inhibition in ipilimumab RCTs.

Long-term safety data are only available for ipilimumab therapy in untreated metastatic melanoma patients with safety data available from CA184-024 for patients alive beyond 2 years from study initiation.[46]

HRQL was pre-specified as an outcome measure for ipilimumab in CA184-024 and dabrafenib in BREAK-3.[20, 54] However, at the time of publication of clinical efficacy

results for dabrafenib, quality-of-life analyses was noted as ongoing and to be reported separately.[54] No subsequent HRQL publications have been identified to date and no details are therefore available on HRQL measures adopted or the outcomes of these measures.

It is documented in the single technology appraisal for vemurafenib, submitted by the manufacturer to NICE, that overall quality-of-life was assessed as an exploratory objective within BRIM-3. This was measured using the Functional Assessment of Cancer Therapy – Melanoma (FACT-Melanoma) questionnaire but due to extremely low completion rates, the resulting data has not been reported.[62]

Table 13: Primary and secondary outcomes of CA184-024, MDX010-08, BREAK-3 and BRIM-3

Trial no. (acronym)	Primary outcome(s)	Reliability/validity/ current use in clinical practice	Secondary outcomes	Reliability/validity/ current use in clinical practice
CA184-024	• Overall survival	Clinically relevant endpoint directly referenced in the decision problem. Consistent with other studies of therapeutic agents in this study population.	• Progression-free survival • Overall response rate • Disease control rate • Time to response • Duration of response • Safety • HRQL	Clinically relevant endpoints: safety & HRQL directly referenced in the decision problem. Consistent with other studies of therapeutic agents in this study population.
MDX010-08	• Objective response rate Safety	Clinically relevant endpoints: safety directly referenced in the decision problem. Consistent with other studies of therapeutic agents in this study population.	• Duration of response • Stable disease rate • Survival • Lymphocyte subpopulations • Pharmacokinetics	Clinically relevant endpoints: safety directly referenced in the decision problem. Some consistency with other studies of therapeutic agents in this study population.
BREAK-3	• Progression-free survival	Clinically relevant endpoint. Consistent with other studies of therapeutic agents in this study population	• Progression-free survival (IRC assessed) • Overall survival • Objective response rate • Progression-free survival post cross-over • Duration of response • HRQL • Safety and tolerability • Support of a BRAF mutation assay validation	Clinically relevant endpoints: OS, safety and HRQL directly referenced in the decision problem. Consistent with other studies of therapeutic agents in this study population.
BRIM-3	• Overall survival • Progression-free survival	Clinically relevant endpoints: OS directly referenced in the decision problem. Consistent with other studies of therapeutic agents in this study population.	• Confirmed response rate • Time to response • Duration of response • Number of participants with AEs	Clinically relevant endpoints. Consistent with other studies of therapeutic agents in this study population.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 14 gives a summary of statistical analyses in CA184-024, MDX010-08, BREAK-3 and BRIM-3.

Table 14: Summary of statistical analyses in CA184-024, MDX010-08, BREAK-3 and BRIM-3

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Patient withdrawals
CA184-024	To determine whether ipilimumab (10mg/kg) plus DTIC, compared with DTIC and placebo, improves overall survival.	Survival rates between treatment arms were compared with a two-sided log-rank test at a two-sided alpha level of 0.05, stratified according to metastasis stage and ECOG performance status. HR for survival and the associated two-sided 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Survival functions were estimated with the use of the Kaplan–Meier method.	The target number of events for the primary analysis was 416 deaths, which we estimated would give the study approximately 90% power to detect a 37% increase in median overall survival to 11 months with ipilimumab + DTIC, with a corresponding HR for death of 0.727, assuming a total sample of 500 patients (250 randomly assigned to each group) and a median survival of 8 months for the patients receiving DTIC + placebo.	Discontinuations due to disease progression, %: Ipi + DTIC (n=250):46.2 DTIC (n=252): 77.3 Discontinuations due to drug-related AE, %: Ipi + DTIC (n=250): 36.0 DTIC (n=252): 4.0
MDX010-08	To evaluate the efficacy and safety of ipilimumab (3mg/kg) in combination with DTIC.	The 95% confidence intervals for response and disease control rate were calculated for each treatment group. Duration of response, time to response, and duration of stable disease were analyzed using parametric and non-parametric statistics. OS was determined using the Kaplan–Meier product limit method.	By Fisher's exact test, a sample size of 23 evaluable patients in each group was required to provide 80% power to detect treatment differences (objective response rate) in a one-sided test at the 0.05 significance level.	Discontinuations due to disease progression, %: Ipi + DTIC (n=36): 41.7 Ipi 3mg/kg (n=40): 62.5 Discontinuations due to drug-related AE, %: Ipi + DTIC (n=36): 8.3 Ipi 3mg/kg (n=40): 2.5 Crossover patients: n = 13 (32.5%)

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Patient withdrawals
BREAK-3	To compare dabrafenib and DTIC chemotherapy.	HR for survival estimated using the Pike method with a two-sided 95% CI. Secondary endpoints analysed using α=0·05 and two-sided 95% CIs.	The trial was designed for 200 patients to be randomly assigned and to observe 102 progression-free survival events with statistical power of 99·7% to detect a HR of 0.33 (median progression-free survival of 2 months in patients who received DTIC and 6 months in patients who received dabrafenib). The trial design used a one-sided log-rank test with α=0·02.	Discontinuations due to disease progression, %: Dab (n=187): 35.3 Discontinuations due to AE, %: Dab (n=187): 2.7 Crossover patients: n = 28 (44.4%)
BRIM-3	To determine if vemurafenib prolongs the rate of survival compared with DTIC.	Survival rates between treatment arms were compared with a two-sided unstratified log-rank test. HR were estimated with the use of unstratified Cox regression. Event–time distributions were estimated using the Kaplan–Meier method. All reported P values are two-sided and confidence intervals are at the 95% level.	The trial was designed for 680 patients to be randomly assigned to receive either vemurafenib or DTIC. The trial had a power of 80% to detect a HR of 0.65 for overall survival with an alpha level of 0.045 (an increase in median survival from 8 months for DTIC to 12.3 months for vemurafenib) and a power of 90% to detect a hazard ratio of 0.55 for progression-free survival with an alpha level of 0.005 (an increase in median survival from 2.5 months for DTIC to 4.5 months for vemurafenib).	Discontinuations due to disease progression, %: Vem (n=337): 25.5 DTIC (n=338): 49.4 Discontinuations due to AE, %: Vem (n=337): 3.6 DTIC (n=338): 2.4 Crossover patients: n = 81 (23.9%)

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In the phase III clinical trial for ipilimumab (CA184-024), subgroup analyses were conducted based on the following demographic characteristics: M-stage, baseline LDH, age, female age, ECOG status, prior adjuvant therapy, race and gender. These analyses were pre-planned.[20]

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

CONSORT flow charts for the RCTs are presented in Figure 6 to Figure 9.

Figure 6: CONSORT flow chart of participants in CA184-024[20]

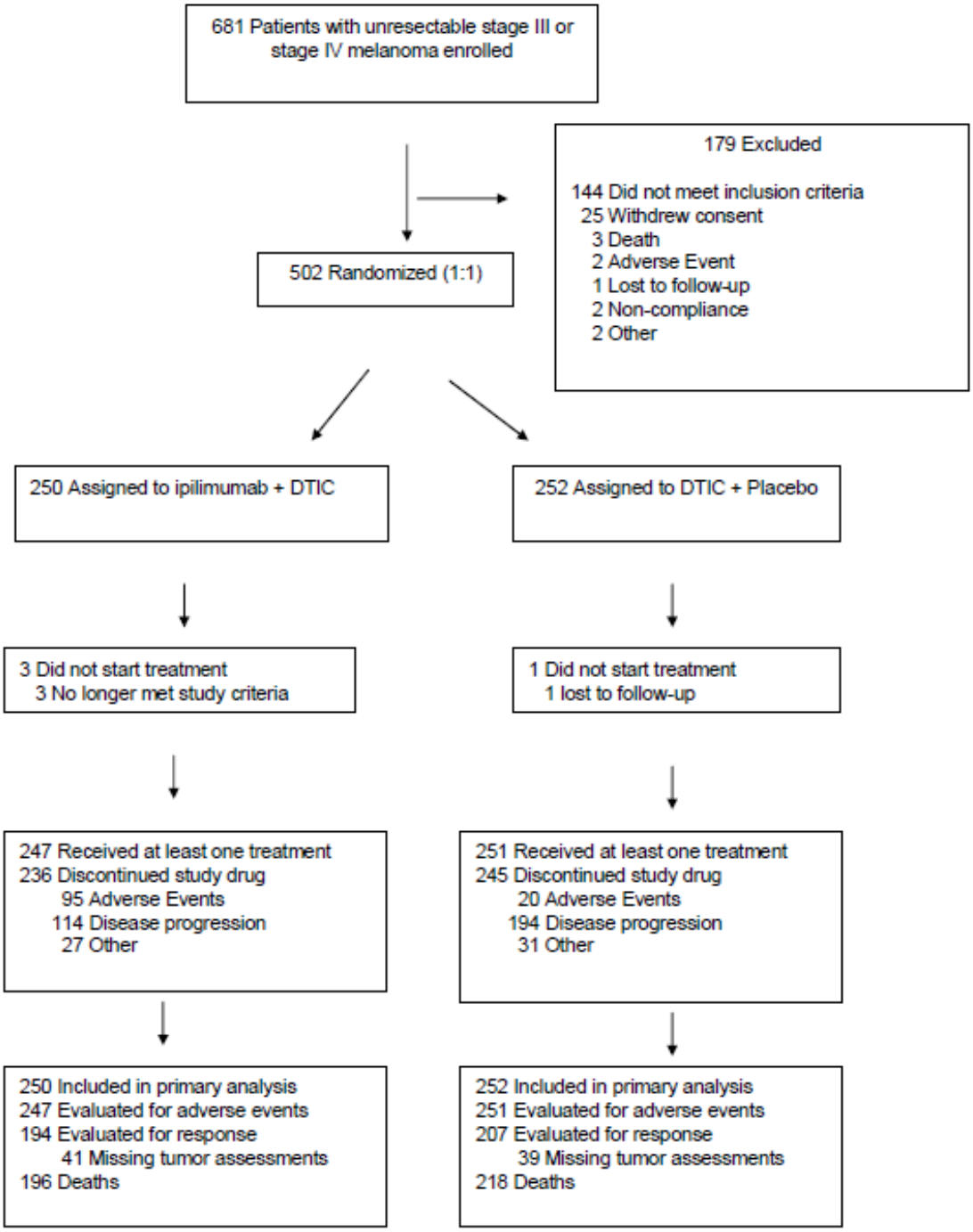
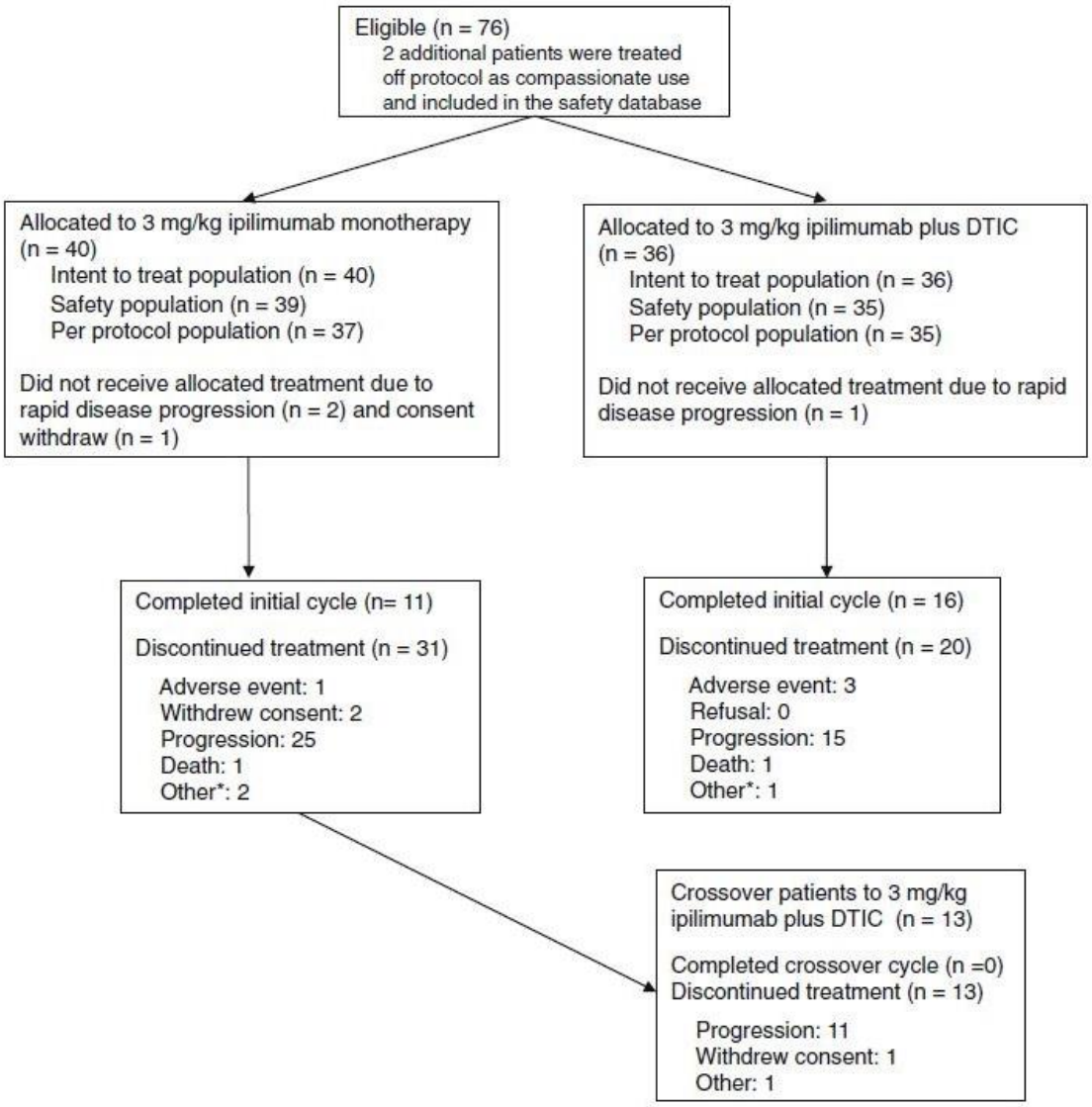


Figure 7: CONSORT flow chart of participants in MDX010-08[47]



*1 patient was withdrawn per investigator decision, 1 refused further treatment, and 1 was randomized but not treated

Figure 8: CONSORT flow chart of participants in BREAK-3[54]

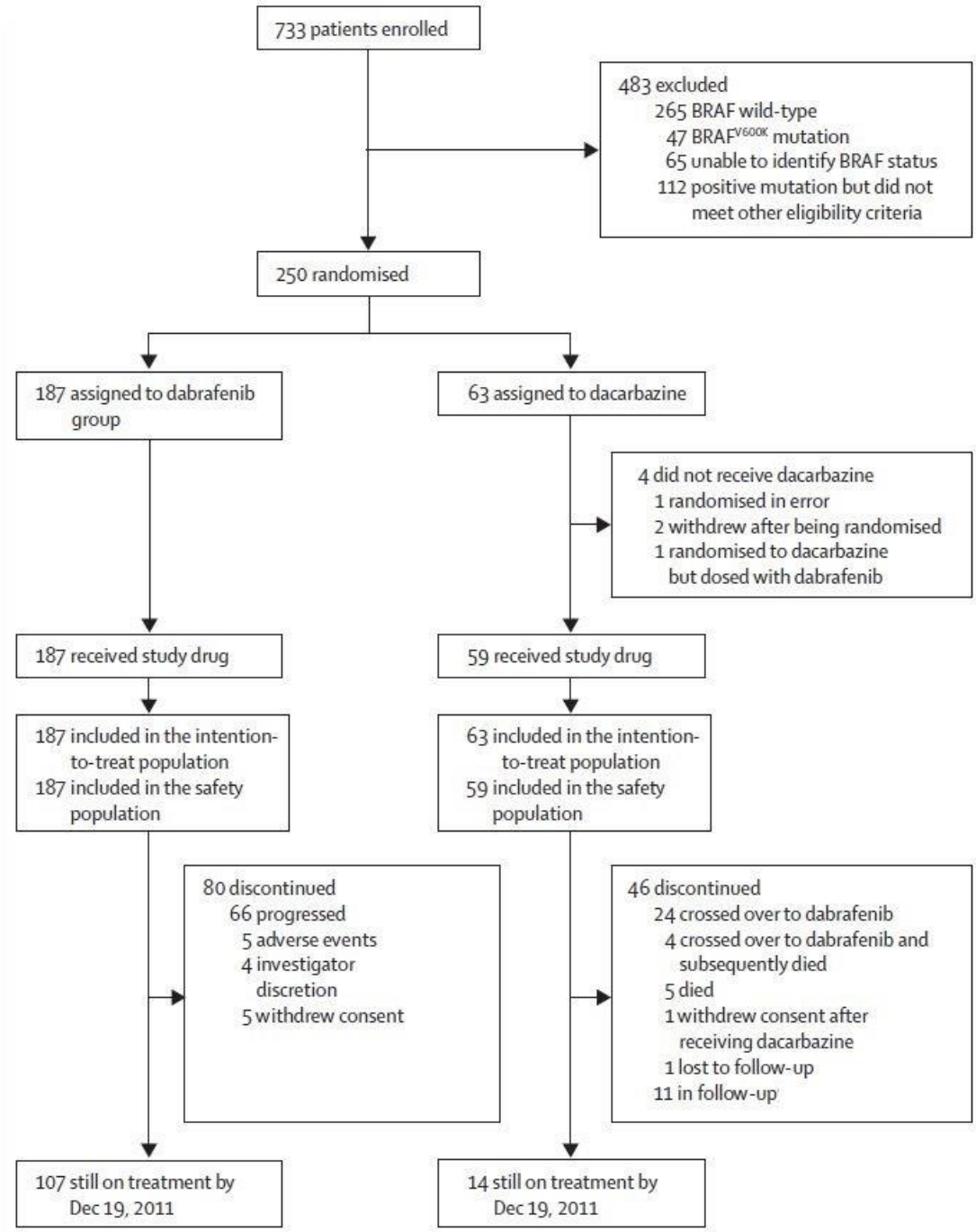
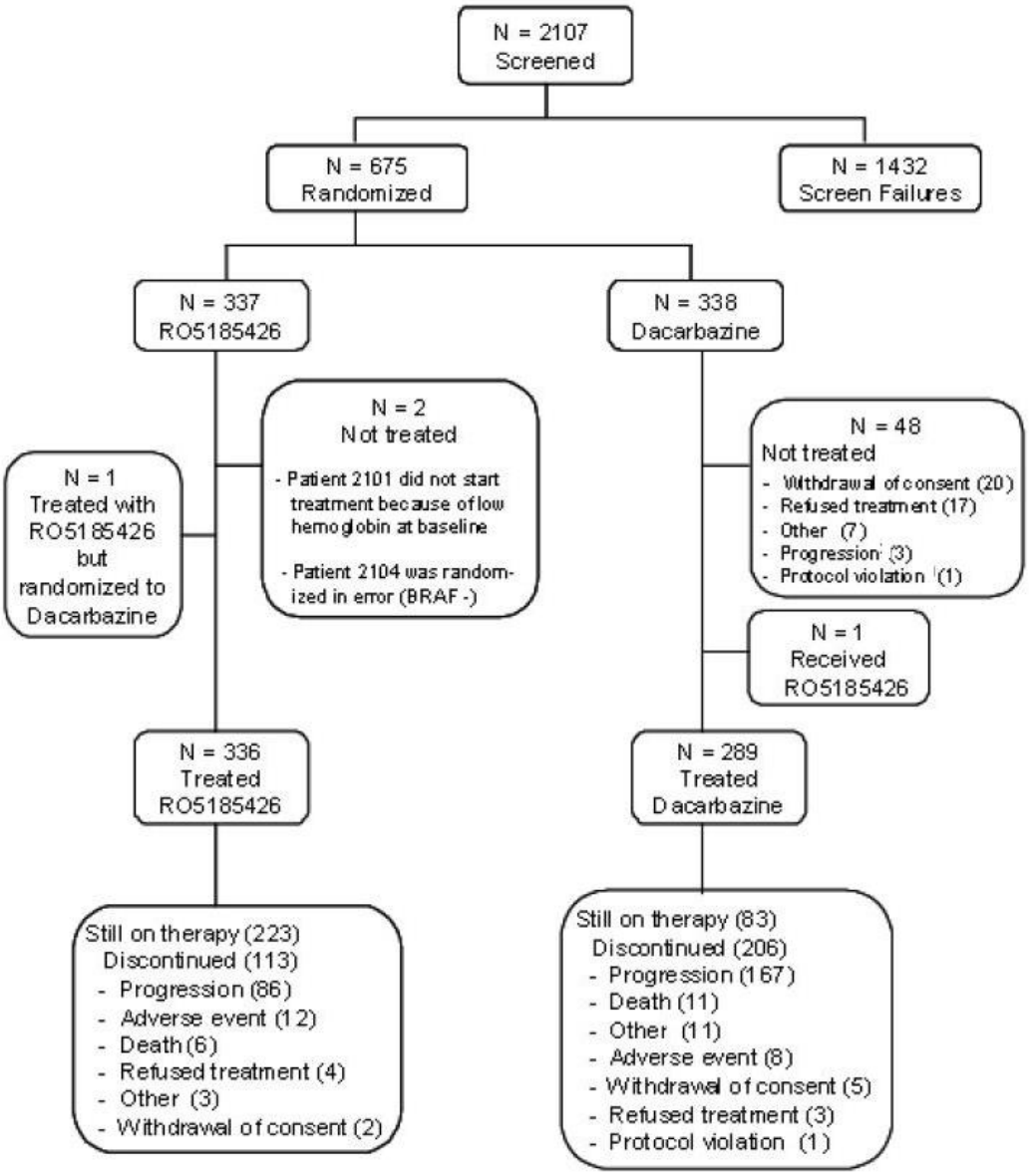


Figure 9: CONSORT flow chart of participants in BRIM-3[62]



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

Complete quality assessment is available in appendix 3, section 10.3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

The quality assessment results for CA184-024, MDX010-08, BREAK-3 and BRIM-3 can be found in Table 15.

Table 15: Quality assessment results for CA184-024, MDX010-08, BREAK-3 and BRIM-3

Trial no. (acronym)	CA184-024	MDX010-08	BREAK-3	BRIM-3
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Open-label	Open-label	Independent review committee blinded only
Was the follow up adequate?	Yes	Yes	<6 months	<12 months
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	Exploratory outcomes only
Did the analysis include an appropriate intention-to-treat analysis?	Yes	Yes	Yes	Yes

6.5 Results of the relevant RCTs

Summary

- Ipilimumab (10mg/kg) plus DTIC significantly improves overall survival compared with historical standard of care (DTIC alone):
  - CA184-024: primary survival analysis demonstrates median overall survival is significantly improved by 2.1 months; p<0.001
- Ipilimumab has a durable biologic effect, with long-term data analysis demonstrating survival efficacy is sustained over time:
  - CA184-024: post-hoc survival analysis of 5-year data demonstrates mean overall survival is significantly improved by 24.5 weeks
  - CA184-024: overall survival rates at years 1 to 5 are significantly higher than those associated to DTIC therapy by at least 10%
- Ipilimumab is associated with improved survival across patient subgroups, including those defined according to known prognostic factors.
  - CA184-024: overall survival improved regardless of baseline age, sex, performance status, LDH level and disease stage
- Ipilimumab addition to DTIC does not negatively impact health-related quality of life:
  - CA184-024: longitudinal analysis shows no significant difference (p>0.05) in EORTC QLQ-C30 functioning scales or symptom scales between treatment groups
- Concomitant DTIC therapy does not significantly influence the clinical efficacy of ipilimumab (3mg/kg) treatment:
  - MDX010-08: no significant difference (p=0.32) in median overall survival between ipilimumab (3mg/kg) + DTIC and ipilimumab monotherapy (3mg/kg) treatment arms
  - MDX010-08: no significant difference in objective response rate or disease control rate between ipilimumab (3mg/kg) + DTIC and ipilimumab (3mg/kg) monotherapy treatment arms
- Ipilimumab clinical activity is comparable across a range of dosing regimens:
  - Median overall survival equivalent between ipilimumab 10mg/kg + DTIC treatment (CA184-024) and ipilimumab 3mg/kg monotherapy treatment (MDX010-08): 11.2 vs.11.4 months
  - CA184-004 and CA184-022: no significant difference in survival analyses between ipilimumab 3mg/kg and10mg/kg treatment arms

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

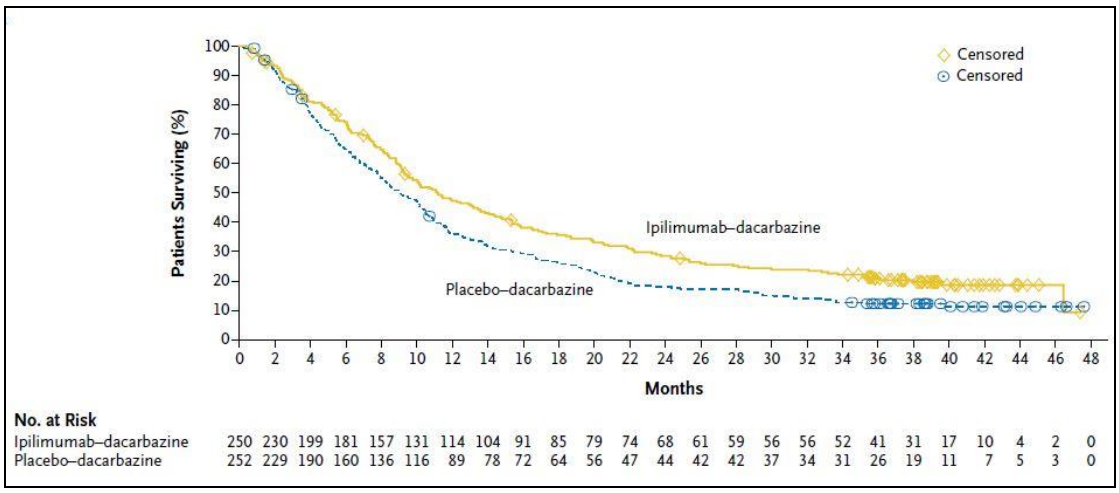
Given it is the fundamental aim of metastatic melanoma therapeutics to prolong life, the clinical efficacy measure of primary interest to the decision problem is overall survival (OS).

In intention-to-treat analyses of the 502 patients randomised in CA184-024, ipilimumab 10mg/kg + DTIC therapy significantly increased survival compared with DTIC therapy (Table 16). Primary survival analysis was performed after 414 deaths occurred, 37 months after the last patient was enrolled. Median OS times were significantly improved by 2.1 months with ipilimumab addition to DTIC therapy: 11.2 vs. 9.1 months; p<0.001. Overall survival rates also showed superiority to the ipilimumab treatment arm at all time points analysed. 1-5 year survival rates of 47.6%, 28.9%, 21.3%, 19.1% and 18.2% were observed for the ipilimumab treatment arm. These were at least 10% higher than 1-5 year survival rates of 36.4%, 17.8%, 12.1% and 9.7% and 8.8% observed for the DTIC treatment arm.[43-45] The results of this analysis for phase III study CA184-024, with 5 years of follow up, continues to demonstrate a long-term survival benefit for patients treated with ipilimumab plus DTIC compared with placebo plus DTIC.

Consistent with the results of phase II studies, survival rates appear to plateau beginning at 3 years. Patient level data analysis at 5 years shows a restricted mean survival of 91.1 weeks with ipilimumab + DTIC therapy compared with 66.6 weeks with DTIC therapy alone.

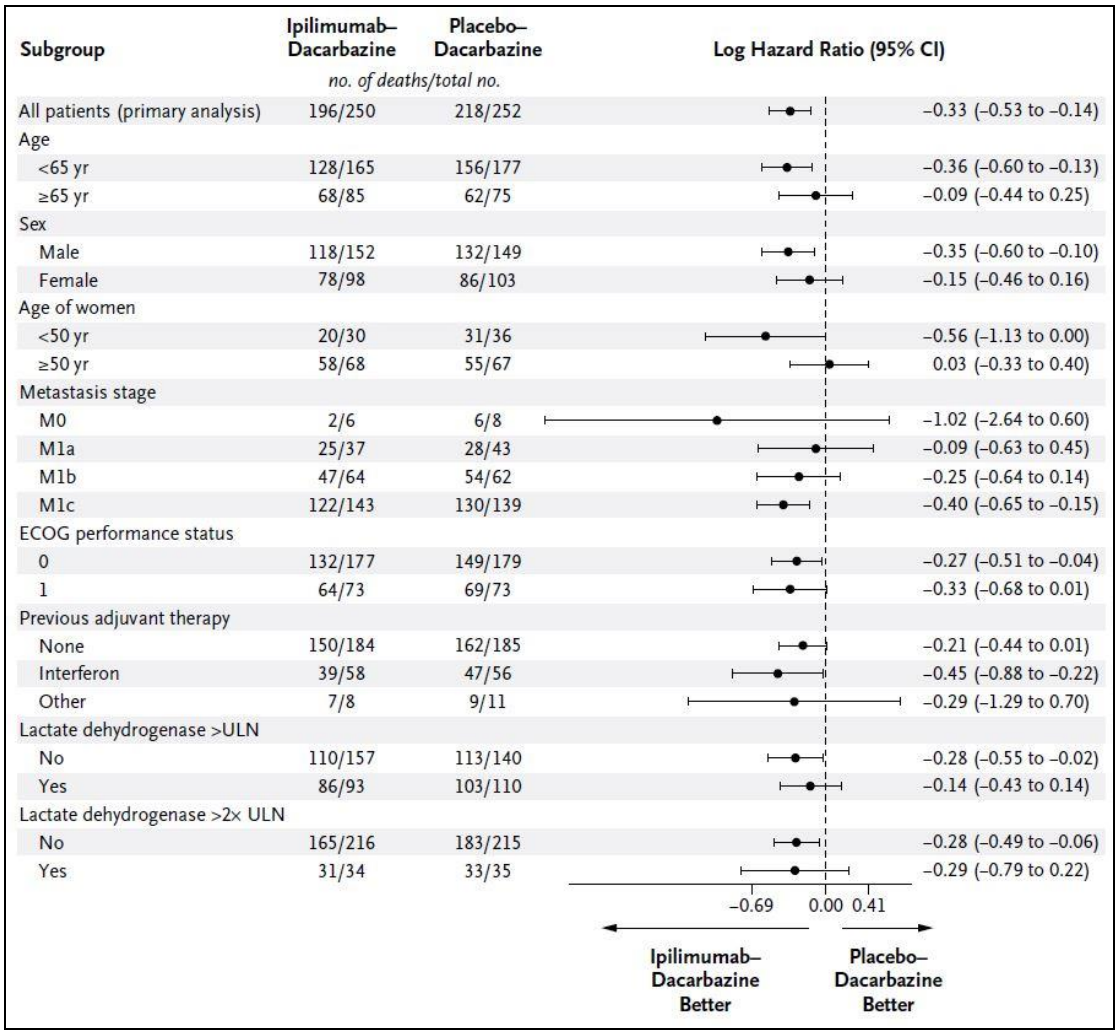
This durable biologic effect can be seen in the Kaplan-Meier survival curve (Figure 10) where separation of the treatment arms occurs at approximately 4 months, subsequently increases (representing the mechanism of action described in section 1.2) and is sustained over time.[7, 20, 43]

Figure 10: Kaplan-Meier curve for overall survival of patients enrolled in CA184-024[20]



Ipilimumab was associated with improved survival across patient subgroups, including those defined according to age, sex, ECOG performance status, baseline serum lactate dehydrogenase level, and substage of metastatic disease (Figure 11). The results of these sub-population analyses suggest a consistent survival effect with hazard ratios (HRs) favouring the ipilimumab-containing group relative to the DTIC monotherapy group.

Figure 11: Overall survival according to subgroup analysis of patients enrolled in CA184-024[20]



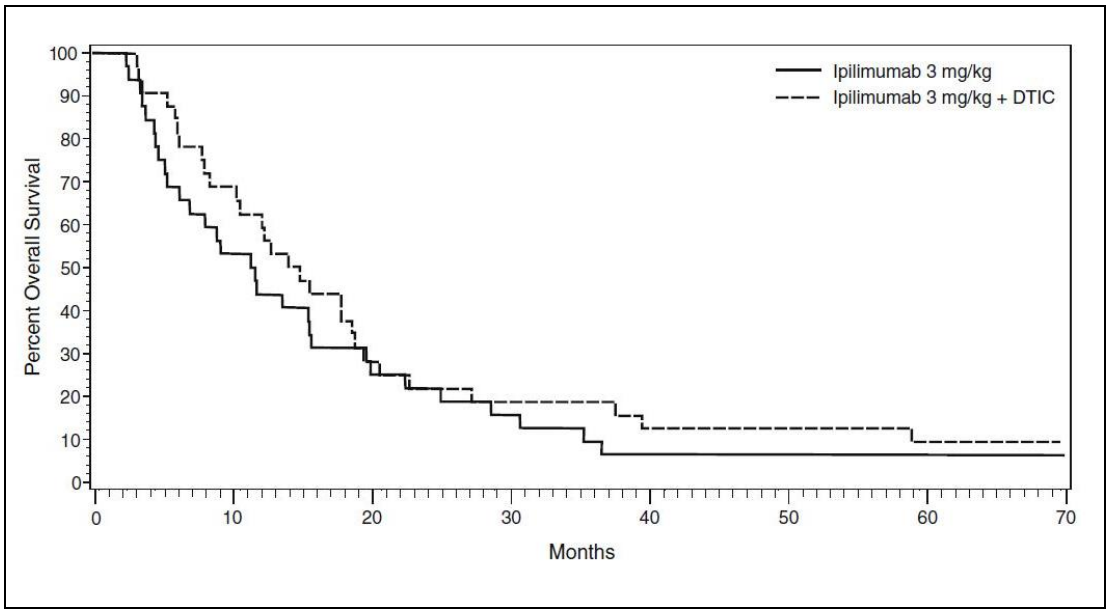
In the phase II trial MDX010-08, the combination of ipilimumab 3mg/kg + DTIC showed comparative efficacy in regards to overall survival to ipilimumab 3mgmg monotherapy. Analysis of 64 randomised patients, after a median follow-up of 20.9 and 16.4 months for ipilimumab 3mg/kg + DTIC (n=32) and ipilimumab 3mg/kg (n=32) respectively, showed no survival difference between treatment arms, supporting the conclusion that DTIC does not significantly influence the clinical efficacy of ipilimumab treatment as represented in the Kaplan-Meier curve (Figure 12) and associated time-to-event analyses (Table 16). Median OS times were 14.3 vs. 11.4 months with 1 year survival rates of 62% vs.45% in the ipilimumab 3mg/kg + DTIC vs. ipilimumab 3mg/kg treatment groups but this difference was not shown to be statistically significant: p=0.32. This analysis includes the 13 cross-over patients

who were analysed according to the treatment group to which they were originally randomised (ipilimumab 3mg/kg).[47, 48]

Of note, the median overall survival observed with ipilimumab 3mg/kg monotherapy was directly comparable with that observed with ipilimumab 10mg/kg + DTIC therapy in CA184-024 at 11.4 vs. 11.2 months.

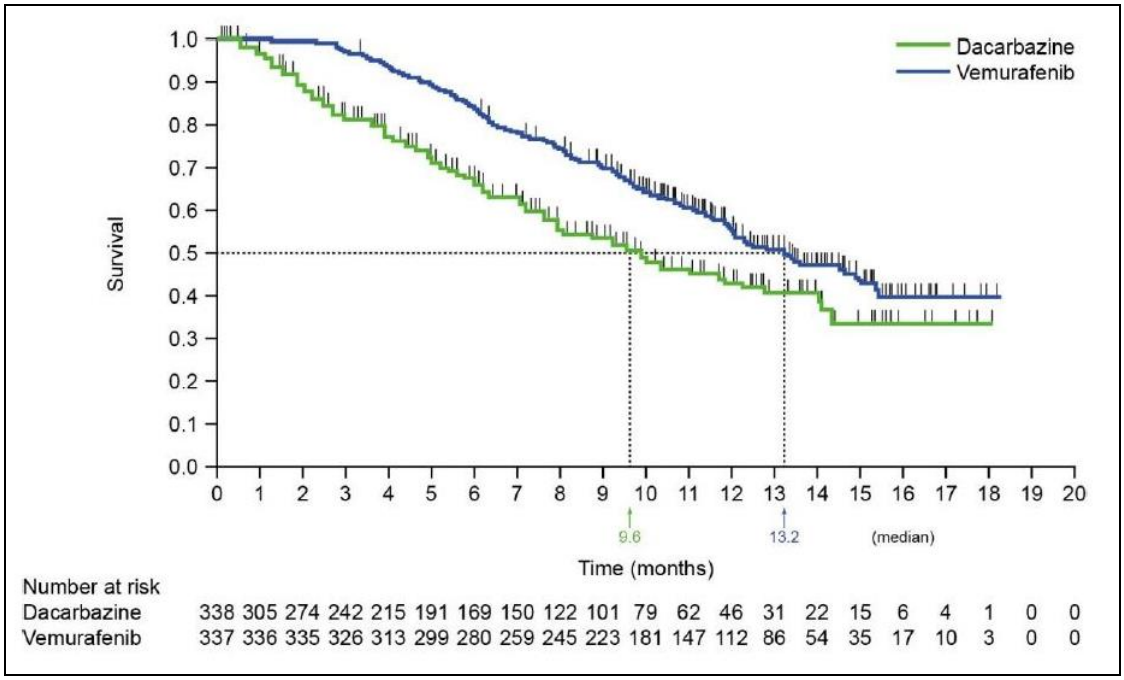
Furthermore, though the number of untreated patients enrolled in studies CA184-004 and CA184-022 deemed survival analyses of this subgroup of interest inappropriate for use; total population analyses showed no significant difference between ipilimumab 3 mg/kg and ipilimumab 10 mg/kg treatment arms in terms of median overall survival and survival rate analyses.[49, 51]

Figure 12: Kaplan–Meier curve for overall survival of patients enrolled in MDX010-08[47]



In metastatic melanoma patients with a confirmed BRAF V600 mutation, vemurafenib therapy significantly increases survival compared with DTIC therapy. This was observed in the interim and updated overall survival analyses of BRIM-3. Both sets of analyses are based on the intent-to-treat population of 672 randomised patients. At the time of the interim analysis, there was an inadequate number of patients in follow-up beyond 7 months to provide reliable Kaplan–Meier estimates of OS. Therefore only the updated analysis which is based on a median follow-up time of 10.5 months and 8.4 months in vemurafenib and DTIC treated patients respectively is presented. By this time, the median OS for the vemurafenib treatment group had been reached as shown in the Kaplan–Meier curve (Figure 13) and associated time-to-event analyses (Table 16). This analysis includes censoring at the time of cross-over for the 81 patients that received vemurafenib post randomisation to the DTIC treatment arm.[55, 57, 62]

Figure 13: Kaplan–Meier curve for updated overall survival of patients enrolled in BRIM-3[62]



Dabrafenib therapy did not demonstrate increased survival in metastatic melanoma patients with a confirmed BRAF V600 mutation compared with DTIC therapy. However, OS was a secondary outcome measure in the BREAK-3 trial and the data were not mature at the time of publication. Death rates are reported in primary analysis of this phase III trial and are therefore included in time-to-event analyses (Table 16). These data are from intention-to-treat analysis of the 250 randomised patients but are limited due to the fact that the median duration of follow-up for patients receiving dabrafenib was only 5 months at the time. It is also unclear as to whether death rates in primary analysis include any patients that crossed-over to dabrafenib treatment post-progression.[54]

Overall survival of patients enrolled in the four RCTs is presented in Table 16.

Table 16: Overall survival of patients enrolled in CA184-024, MDX010-08, BREAK-3 and BRIM-3[20]

Trial no. (acronym)	Treatment arm	Median OS, months (95% CI)	Hazard Ratio (95% CI)
CA184-024	Ipilimumab 10mg/kg + DTIC DTIC	11.2 (9.4, 13.6) 9.1 (7.8, 10.5)	0.72 (0.59, 0.87)
MDX010-08	Ipilimumab 3mg/kg + DTIC Ipilimumab 3mg/kg	14.3 (10.2, 18.8) 11.4 (6.1, 15.6)	0.75 (0.45, 1.24)
BREAK-3	Dabrafenib DTIC	NR	0.61 (0.25, 1.48)
BRIM-3	Vemurafenib DTIC	13.2 9.6	0.62 (0.49, 0.77)

NR = not reported

In CA184-024, health-related quality of life (HRQL) was measured using the EORTC QLQ C-30 questionnaire.[7, 20] This questionnaire is comprised of 15 questions on functional scales: 13 questions on symptom scales and 2 questions on global health status scale. Higher scores for all functional scales and global health status indicate better HRQL with an increase from baseline indicating improvement in HRQL. Published criteria suggests a mean change in scores of 5 to 10 points indicates “a little” change either for improvement or worsening; a mean change of 10 to 20 points is considered “moderate”; and 20 points or more is considered “very much” change.[64]

Ipilimumab therapy had no significant impact on patient HRQL, meaning there were no clinically meaningful changes observed among on-study subjects for emotional functioning, pain, insomnia, constipation, diarrhoea, and financial difficulties. “A little” change was seen for physical functioning, cognitive functioning, nausea/vomiting, dyspnoea, and appetite loss. “Moderate” declines were observed for role functioning, social functioning, global health status, and fatigue scale. In addition, longitudinal comparisons did not show any significant differences in EORTC QLQ-C30 functioning scales or symptom scales between treatment groups ($p>0.05$) (Table 17). For ipilimumab treated patients, HRQL returned close to baseline following 12 weeks of induction therapy and was maintained beyond treatment [7, 65]

These data should be reviewed in the light of the fact that we would normally expect there to be a deleterious effect on patients’ quality-of-life when treated with standard chemotherapy.

Table 17: Mean change from baseline (CFB) in EORTC QLQ-C30 scales of patients enrolled in CA184-024

	Mean CFB at week 12		Mean CFB at week 24		Mean CFB at week 36		Mean CFB at week 48	
	Ipi + DTIC (n=132)	DTIC (n=147)	Ipi + DTIC (n=63)	DTIC (n=82)	Ipi + DTIC (n=45)	DTIC (n=35)	Ipi + DTIC (n=30)	DTIC (n=25)
Physical	-7.44	-8.48	-4.34	-7.89	-2.07	-4.00	1.33	-5.07
Role	-12.88	-10.88	-6.08	-10.98	-2.96	-7.14	-1.67	-6.67
Emotional	-0.49*	1.97[$]	6.05[+]	4.74	8.40	3.43[<<]	10.00	1.39[~]
Cognitive	-6.15*	-3.97[$]	-3.23[+]	-8.74	-3.33	-7.14	-2.78	-4.86[~]
Social	-10.64*	-6.35[$]	-2.42[+]	-7.32	0.74	-3.81	1.11	-2.78[~]
Fatigue	11.20	10.77	6.88	10.49[<]	2.72	2.54	0.74	5.33
Nausea/vomiting	5.05	8.16	3.70	7.93	-2.59	-1.43	-2.78	-1.33
Pain	-1.14	5.33	-0.79	4.88	1.11	5.71	1.11	5.33
Dyspnoea	7.58	9.26**	4.76	7.82[<]	-0.78[++]	6.67	1.11	5.33
Insomnia	4.07^	-0.23^^	-3.17	4.12[<]	-5.93	-4.76	-4.60[#]	-2.67
Appetite loss	7.83	9.98	-1.06	6.10	0.74	-1.90	-6.67	0.00
Constipation	3.33*	8.28[$$]	-2.19[>]	7.82[<]	-1.48	5.71	-3.33	1.39[~]
Diarrhea	4.10*	1.36	0.00[+]	2.44	-2.96	-1.90	-1.11	4.17[~]
GHS	-10.00*	-6.45^^	-4.37[>]	-6.48[<]	3.03[>>]	-5.39[<<]	2.22	-1.81[##]

*n = 130; ^n = 131; [$]n = 147; **n = 144; ^^n = 146; [$$]n = 145; [+]n = 62; [>]n = 61; [<]n = 81; [++]n = 43; [>>]n = 44; [<<]n = 34; [#]n = 29; [~]n = 24; [##]n = 23

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

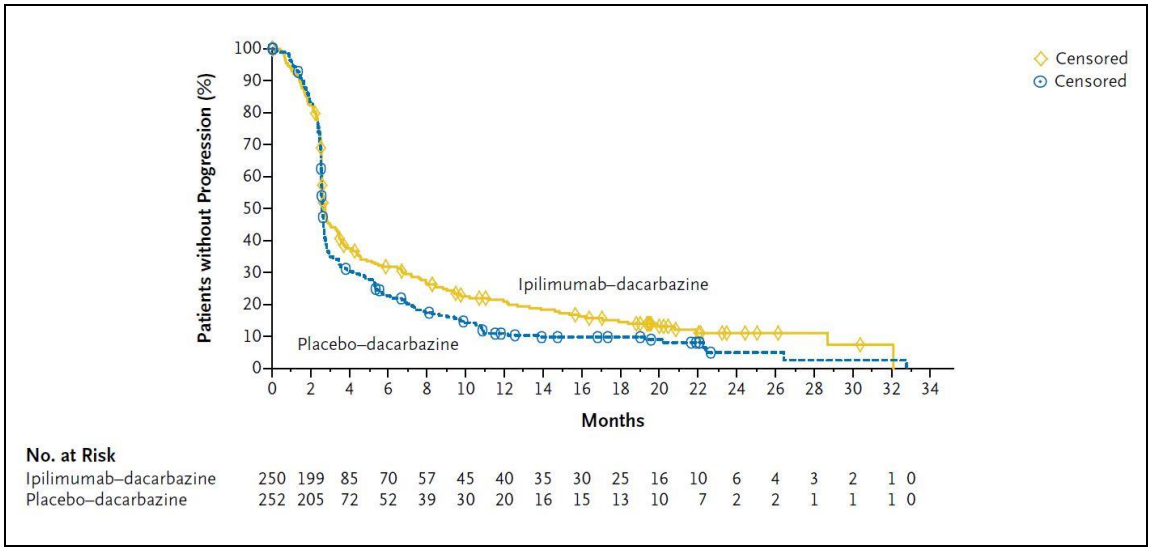
See section 6.5.1.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as either relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

In intention-to-treat analyses of the 502 patients randomised in CA184-024, ipilimumab 10mg/kg + DTIC therapy significantly increased PFS survival compared with DTIC therapy (HR: 0.76 (0.63,0.93)). The Kaplan–Meier curve for PFS is shown in Figure 14.

Figure 14: Kaplan–Meier curve for progression-free survival of patients enrolled in CA184-024[20]



The biologic effect observed in the overall survival analysis can again be seen in the Kaplan–Meier survival curve for PFS (Figure 14) where separation of the treatment arms occurs by the first measurement at 3 months, subsequently increases and is sustained over time.[20]

This durable effect was also shown in response analyses (Table 18) with the duration of response significantly increased with ipilimumab treatment addition to DTIC (19.3 months vs. 8.1 months; p=0.03). Response rates (partial and complete) were significantly superior with ipilimumab + DTIC therapy compared with DTIC monotherapy.[20] The disease control rate between the two treatment arms was not shown to significantly differ, suggesting DTIC therapy stabilises disease but ipilimumab therapy improves disease.

Table 18: Results from response outcome measures in CA184-024[20]

	Ipilimumab + DTIC (n=250)	DTIC (n=252)	P Value
Response rate, n (%)	38 (15.2)	26 (10.3)	0.03
Disease control rate, n (%)	83 (33.2)	76 (30.2)	0.41
Time to response, median months	2.6	2.7	NR
Duration of response, median months	19.3	8.1	0.03

NR = not reported

The primary outcome measure in MDX010-08 was objective response rate with an associated secondary outcome measure of disease control rate. As with the overall survival analysis, no significant difference in clinical efficacy of ipilimumab was detected based on administration as monotherapy or in combination with DTIC.[47] This further reinforces the conclusion that the addition of DTIC does not significantly influence the clinical efficacy of ipilimumab therapy.

Of the potential comparator therapies for treatment of patients with BRAF V600 mutation, both vemurafenib and dabrafenib significantly increased PFS compared with

DTIC therapy: the primary outcome of interest in both trials (alongside overall survival in the case of BRIM-3). As we would expect, given the mechanism of action associated to BRAF inhibitors, the PFS curves separate early for both treatments (Figure 15 and Figure 16).[54, 55, 62]

Figure 15: Kaplan–Meier curve for progression-free survival of patients enrolled in BRIM-3

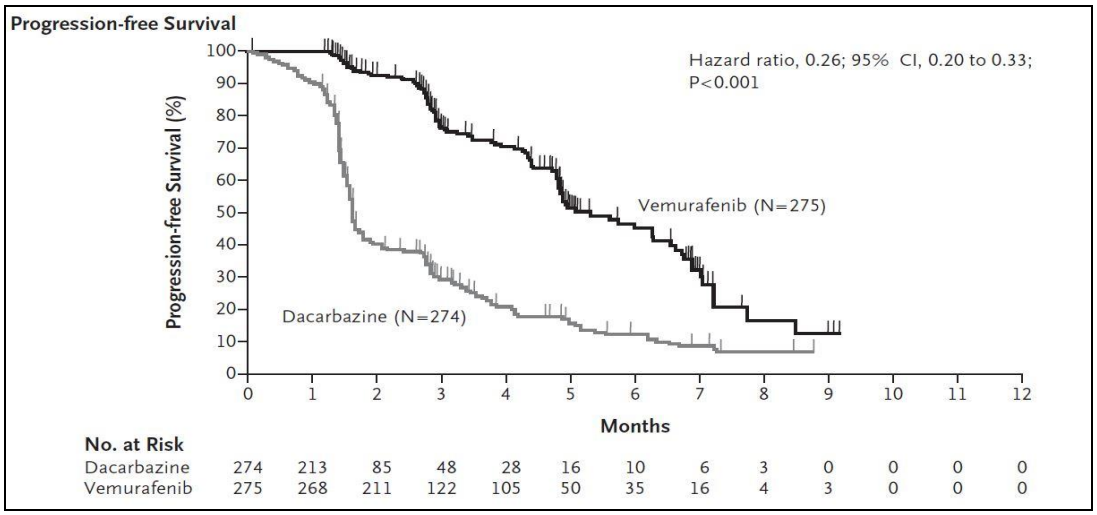
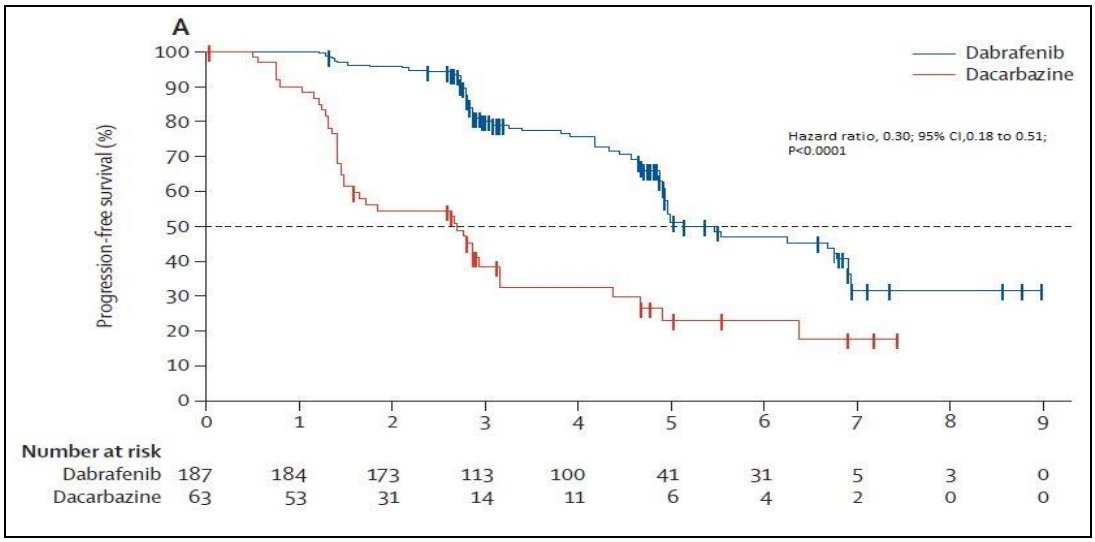


Figure 16: Kaplan–Meier curve for progression-free survival of patients enrolled in BREAK-3



Analysis was conducted on the intention-to-treat populations; however, in the case of BRIM-3 only 274 and 275 patients had been randomised to DTIC and vemurafenib therapy respectively in time to be eligible for PFS analysis on the initial data set.[54, 55, 62] This suggests that the durability of effect with regard to PFS for both BRAF inhibitors cannot be reliably assessed with estimates from the current data sets, as they only follow patients treated with dabrafenib for 5 months and with vemurafenib for 3.8 months. Measure of PFS is not included in the extended dataset analysis identified for BRIM-3.

Secondary response outcomes for both vemurafenib and dabrafenib show superiority of these treatments over DTIC therapy in regard to overall response rate, though

statistical significance was not measured for this outcome in BREAK-3 (Table 19). The time to response was under 2 months for both BRAF inhibitors; however the durability of response was less than 6 months with dabrafenib therapy and though not measured in BRIM-3, is likely to be similar with vemurafenib therapy, given the similar mechanism of action of these treatments.[54, 55, 62]

Table 19: Results from response outcome measures in BRIM-3 and BREAK-3[54, 55]

	BRIM-3			BREAK-3		
	Vem (n=219)	**DTIC (n=220)**	**P Value**	**Dab (n=187)**	**DTIC (n=63)**	**P Value**
Response rate, n (%)	106 (48.4)	12 (5.5)	<0.001	99 (52.9)*	12 (19.0)*	NR
Disease control rate, n (%)	NR	NR	NR	171 (91.4)^	34 (54.0)^	NR
Time to response, median months	1.5	2.7	NR	1.6	NR	NR
Duration of response, median months	NR	NR	NR	5.6	NE	NR

*investigator assessed; ^IRC assessed; NE = not estimable; NR = not reported

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained.

Not applicable.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The search strategy used was identical to that used in the clinical section. For details, please refer to sections 6.1 and 6.2.

Prior to statistical analysis, studies excluded on account of a comparator arm outside of the named interventions list were assessed for potential inclusion in statistical analyses. No trials were identified that gave additional links that may have strengthened the evidence base used in statistical analyses.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

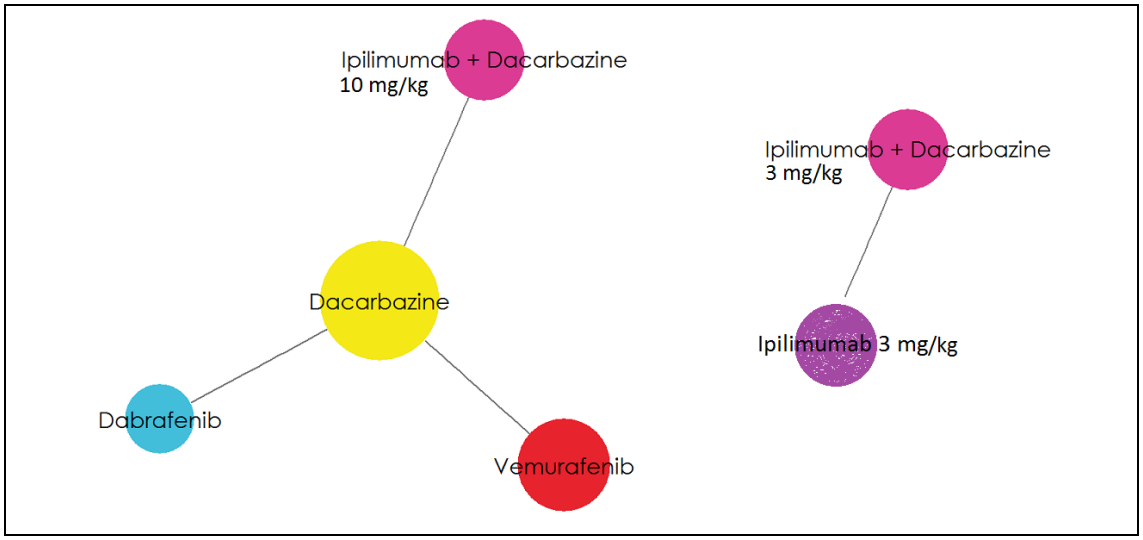
Please refer to quality assessment data presented in earlier sections (6.1 to 0).

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

The four trials that met the systematic review criteria were eligible for statistical analyses and thus an evidence network for potential Mixed Treatment Comparison (MTC) analysis was synthesised. As presented in Figure 17, ipilimumab 3 mg/kg monotherapy is disconnected from the main network of evidence as the MDX010-08 trial providing data for this treatment arm does not share a common comparator with any other RCTs identified as relevant to the target indication of this submission. Data from CA184-024, BREAK-3 and BRIM-3 could however be used to model comparative efficacy and safety of ipilimumab 10mg/kg + DTIC vs. BRAF inhibitors.

Given that the survival profile associated to ipilimumab is shown to be constant, irrespective of differences in dosing and administration (see sections 6.5, 6.8, 6.10) and its safety profile is improved with reduced dosing (see section 6.9), coupled with the fact that the addition of DTIC does not significantly impact on its clinical activity (see sections 6.5, 6.8, 6.10), outcomes from this MTC can be used as a proxy for the comparative efficacy and safety of ipilimumab 3mg/kg vs. BRAF inhibitors.

Figure 17: Network of trials for potential MTC analysis



6.7.4 For the selected trials, provide a summary of the data used in the analysis.

HRs of death are used to compare overall survival across included trials as presented in Table 20.

Table 20: Summary of data used in the MTC and indirect comparison analyses

Trial no. (acronym)	Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	Log (HR)	SE [Log(HR)]
CA184-024	Ipilimumab + DTIC vs. DTIC	0.72	0.59	0.87	-0.329	0.099
BRIM-3	Vemurafenib vs. DTIC	0.62	0.49	0.77	-0.478	0.115
BREAK-3	Dabrafenib vs. DTIC	0.61	0.25	1.48	-0.494	0.454

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

As discussed, the fundamental aim of metastatic melanoma therapeutics is to prolong life. Consequently, the clinical efficacy measure of primary interest to the decision problem is overall survival.

Commonly reported measures of overall survival are the number of patients who died in each of the treatment arms at the time of analysis or at a specified time point (for example, 1 year) and median overall survival time. Neither are ideal for use in indirect comparison or MTC analysis.

With time-to-event data, the proportion of patients who died at a specific time point has been reduced to a binary variable at an arbitrary cut-off point and does not account for either the differences in follow-up time or the differences in the length of survival time between the treatment arms.[66, 67] Furthermore, analysis using median survival times may result in an over- or under-estimation of the treatment effect and a notable loss of statistical power and is a poor choice where trials reported few events.[66]

Consequently, hazard ratios of death are used to populate the MTC analysis, in view of the fact that there are noticeable differences in follow-up times and associated event numbers between them. This method is not however without limitation given that the Kaplan–Meier survival curves do not follow the same trajectory due to differences within the mechanisms of action between ipilimumab and the BRAF inhibitors.

Respecting the RCT nature of the data used to analyse comparative efficacy of active treatments for which head-to-head trials are not available, a random-effects model was fitted utilising Bayesian methodology. This approach deviates from the assumption of a common treatment effect across the trials included within the network and models outcomes relative to trial control arms. Differences in treatment effects were assessed using pair wise comparisons, with statistical significance determined using 95% credible intervals.

In light of the fact that the connected network of evidence available for MTC analysis contains only trials with a common comparator arm; indirect comparison analyses was also conducted. Using the log of the hazard ratios of death used to populate the MTC analysis and the associated standard error, the adjusted indirect comparison of ipilimumab vs. BRAF inhibitors individually were calculated utilising the method developed by Bucher et al.[68] This method is expected to reduce the uncertainty associated to the comparative efficacy analyses by focusing the network to a single link through a common comparator arm.

Full details of the MTC methodology adopted and the code used in the analysis is presented in appendix B. Included within this appendix is additional MTC analysis of PFS. This is not detailed in full within this section as it is not of direct relevance to the decision problem.

6.7.6 Please present the results of the analysis.

Results of all pair wise comparisons are presented in grid format with those demonstrating a statistically significant difference coloured. Where the hazard ratio for a treatment listed on the left hand side of the table is significantly worse (i.e. greater hazard of death) versus treatments on the bottom of the table, the result is coloured pink; where the hazard ratio for a treatment listed on the left hand side of the table is significantly better (i.e. reduced hazard of death) versus treatments on the bottom of the table, the result is coloured blue (Figure 18). The area of the circle is proportional to the magnitude of the hazard ratio.

Figure 18: Pair wise comparisons of estimated survival determined using MTC analysis

	Dabrafenib	Ipilimumab + Dacarbazine	Vemurafenib	Dacarbazine
Dabrafenib	1	0.84	0.98	0.61
Ipilimumab + Dacarbazine	1.19	1	1.16	**0.72**
Vemurafenib	1.02	0.86	1	**0.62**
Dacarbazine	1.64	**1.39**	**1.61**	1

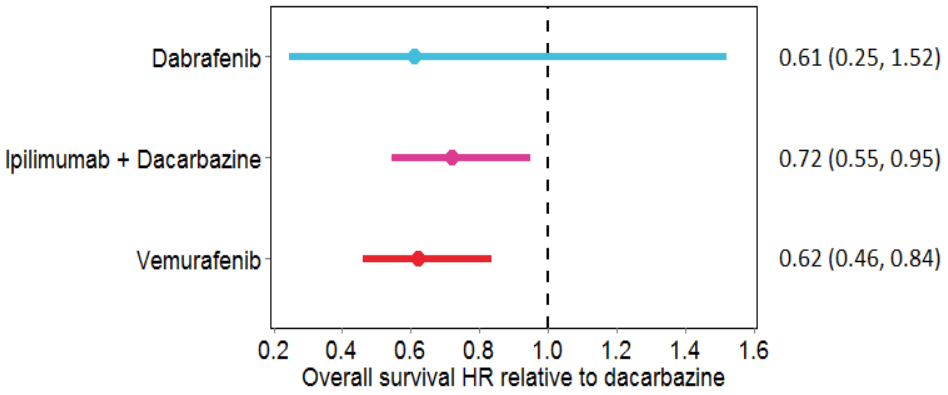
The pair wise comparisons of novel therapies compared with historical best supportive care (DTIC) are additionally presented as a forest plot with associated values. The solid circles represent the point estimate for each modelled comparison with horizontal lines representing the 95% credible intervals around the point estimate. When these are disconnected from the vertical axis of no difference (hazard ratio of 1); this denotes statistical significance vs. DTIC therapy.

Supportive adjusted indirect comparison analyses are presented as indirect hazard ratios of death with associated 95% confidence intervals.

Results

As a direct reflection of the trial programmes, ipilimumab, dabrafenib and vemurafenib therapies all show modelled superiority over DTIC monotherapy with this superiority being statistically significant for both ipilimumab + DTIC and vemurafenib (Figure 19).

Figure 19: Forest plot of estimated survival of novel therapies vs. DTIC determined using MTC analysis



Indirect comparisons, estimated using MTC analysis of the complete network of evidence, showed no significant differences in survival efficacy between ipilimumab and BRAF inhibitor treatment arms (Figure 19).

In support of the MTC outcomes, indirect comparisons calculated using the Bucher equation also showed no significant differences in survival efficacy between ipilimumab and BRAF inhibitor treatment arms (Table 21). As expected a-priori, this analysis results in estimated indirect HR of death that are nearly identical to those estimated using the complete network of evidence but reduces the associated uncertainty.

Table 21: Pair wise comparisons of estimated survival determined using the Bucher method

Comparison	Indirect Hazard Ratio	95% Confidence Interval
Ipilimumab + DTIC vs. Vemurafenib	1.16	[0.86, 1.56]
Ipilimumab + DTIC vs. Dabrafenib	1.18	[0.48, 2.93]

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

As the network presented does not include a closed loop it was not possible to assess statistical heterogeneity. A random effects model was fitted to the data to allow for between-study variation. This should not however be used as a replacement for exploration of heterogeneity in potential treatment effect modifiers.

Qualitative assessments of patient characteristics across trials are presented in section 6.3.

There are a number of limitations with this MTC analysis:

- Due to differences in the mechanisms of action between ipilimumab therapy and BRAF inhibitor therapy, Kaplan–Meier curve shapes for OS vary so the HR across trials may not be proportional. Furthermore, the ipilimumab + DTIC treatment arm from CA184-024 violates proportional hazards and thus the HR analysis adopted potentially does not accurately capture the full benefit of such therapy.
- In addition, both BRAF inhibitor trials were cross-over in design but reported HRs are not adjusted and simply incorporate censoring of patients that switched treatments (assumed for dabrafenib patients for whom cross-over handling is not described).[54, 55] The impact of this does not however appear to be substantial with survival profiles of patients randomised to control arms in the phase III trials included in MTC analysis shown to be highly homogenous with median survival times of 9.1 and 9.6 months associated to DTIC monotherapy for patients enrolled in CA184-024 and BRIM-3 respectively. Furthermore, HR of death for dabrafenib therapy vs. DTIC is calculated using number of deaths rather than median overall survival analyses.

- Key differences between patients enrolled in clinical trials included in the MTC analysis were their BRAF V600 mutation status and their treatment history. Neither are thought to be treatment effect modifiers with post-hoc analysis of ipilimumab studies showing rates of objective responses, stable disease and median survival times are comparable regardless of BRAF V600 mutation status[39, 60]; and subset analysis of MDX010-020 showing that the survival benefit associated to ipilimumab therapy is observed, irrespective of treatment history.[63]

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable.

6.7.9 Please discuss any heterogeneity between results of pair wise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

As discussed in section 6.7.6, MTC analysis reflected the trial programme for all direct comparisons investigated in included trials. However, consistency could not be officially checked for given that there are no closed loops in the network.

6.8 Non-RCT evidence

Summary

- Ipilimumab 3mg/kg monotherapy offers a "real-world" survival benefit when used as first-line therapy in patients with advanced melanoma:
  - CA184-332: primary survival analysis demonstrates median OS of 11.5 months
  - CA184-338: primary survival analysis demonstrates median OS of 14.3 months
- Ipilimumab 3mg/kg monotherapy improves OS compared with historical standard of care (DTIC):
  - CA184-332: primary survival analysis demonstrates median OS is improved by 2.4 months and 1-year survival rate is improved by 13% compared with DTIC treated patients from CA184-024
  - CA184-338: primary survival analysis demonstrates median OS is improved by 5.2 months and 1-year survival rate is improved by 24% compared with DTIC treated patients from CA184-024
  - Pooled chemotherapy-naïve dataset (MDX010-08, CA184004, CA184022 and MDX010-20): primary survival analysis demonstrates median OS is improved by 4.4 months and 1-year survival rate is improved by 10% compared with DTIC treated patients from CA184-024
- Ipilimumab clinical activity is comparable across a range of dosing regimens:
  - Median OS equivalent between ipilimumab 10mg/kg + DTIC treatment (CA184-024); ipilimumab 3mg/kg + DTIC treatment (MDX010-08) and ipilimumab 3mg/kg monotherapy treatment (MDX010-08; CA184-332; CA184-338; pooled dataset): 11.2 to 14.3 months
  - Median OS equivalent between trials with a maintenance phase of treatment (CA184-024) and those without (MDX010-08; CA184-332; CA184-338): 11.2 to 14.3 months
- Ipilimumab clinical activity is comparable in both BRAF V600 mutation-positive and BRAF V600 mutation-negative tumours:
  - CA184-332 and CA184-338: at least 50% of patients enrolled presented with BRAF V600 mutation-negative tumours
  - CA184-004: post-hoc analysis demonstrates no significant difference in efficacy between patients based on BRAF V600 mutation status
- The survival profile associated with ipilimumab therapy is consistent, irrespective of differences in dosing and administration.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

As there is limited comparative efficacy data for ipilimumab 3mg/kg monotherapy in untreated patients, additional sets of non-RCT evidence are presented to further support the comparative equivalence between survival profiles of ipilimumab + DTIC and ipilimumab 3mg/kg monotherapy observed in MDX010-08 and MTC analysis and the subsequent survival benefit of ipilimumab 3mg/kg over DTIC.

Though none of these trials directly compare the intervention with the appropriate comparator(s) with reference to the decision problem, survival outcomes have been modelled against the overall survival profile of DTIC treated patients from CA184-024: the only treatment currently available for use in both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients.

CA184-332 and CA184-338 are both retrospective observational studies of advanced melanoma patients prescribed ipilimumab 3mg/kg monotherapy as their first-line treatment in clinical practice.[59, 60] In addition, a pooled analysis of 78 chemotherapy-naïve patients randomised to receive ipilimumab 3mg/kg monotherapy across four clinical trials is presented.[8] Methodologies of the non-RCTs are presented in Table 22.[61]

Table 22: Comparative summary of methodology of the non-RCTs[8, 59-61]

	CA184-332	CA184-338	Pooled chemotherapy-naïve dataset (from clinical trials)
Location	Multiple US oncology sites.	27 sites in the US.	Multiple sites in multiple countries worldwide.
Design	Multi-site, observational, retrospective medical chart review of patient medical records, designed to understand how ipilimumab is being used in treatment-naïve unresectable or metastatic melanoma patients in routine clinical practice.	Multi-site, observational, retrospective medical chart review of patient medical records, designed to understand how ipilimumab is being used in treatment-naïve unresectable or metastatic melanoma patients in routine clinical practice.	Pooled analysis of patients randomised to ipilimumab 3mg/kg monotherapy treatment arms of three phase II trials: MDX010-08; CA184-004; CA184-022 and one phase III trial: MDX010-20 designed to further assess the survival profile of ipilimumab in previously untreated subjects.
Intervention	Ipilimumab 3mg/kg	Ipilimumab 3mg/kg	Ipilimumab 3mg/kg
Treatment schedule	Every 3 weeks for a total of 4 doses	Every 3 weeks for a total of 4 doses	Induction phase: weeks 1, 4, 7 and 10 Maintenance phase: every 12 weeks (responsive patients only from CA184-004; CA184-022) Re-induction phase: every 3 weeks (stable disease patients only from MDX010-20).
Primary outcomes	Demographic & clinical characteristics Occurrence & severity of AEs and TEAEs Patterns of care Overall survival	Demographic & clinical characteristics Occurrence & severity of AEs and TEAEs Patterns of care Overall survival	Overall survival
Secondary outcomes	Healthcare resource use	Healthcare resource use	-
Duration of follow-up	Interim analysis Median, months: 8.5	Interim analysis Median, months: 12.0	Median, months: 11.6 2 year survival rate: 32%

Though retrospective observational studies have the potential to introduce biases due to different patient selection criteria to prospective clinical trials, they also have benefits that provide confidence in the interpretation of these results. Including the fact that unlike prospective clinical trials of melanoma therapies, CA184-332 and CA184-338 did not exclude patients on the basis of factors associated with worse outcome e.g. performance status, life expectancy less than 3 months and presence of brain metastases. In addition, patients were enrolled solely on eligibility criteria with no consideration of outcome prior to inclusion.[59-61]

Pooled analyses also have the potential to introduce biases due to break of randomisation and differences in patient selection criteria across source trials. However, in this instance it allows a more meaningful analysis than subset analyses within clinical trials, due to the small number of chemotherapy-naïve subjects enrolled in CA184-004, CA184-022 and MDX010-022 individually.[61]

Complete quality assessments for each trial are presented in appendix 7, section 10.7.

Primary outcomes in all non-RCTs include overall survival: a clinically relevant endpoint and the main efficacy outcome referenced in the decision problem as discussed in section 6.3.5. In the case of CA184-332 and CA184-338, “real-world” effectiveness is addressed, allowing the survival profile of ipilimumab 3mg/kg monotherapy as first-line therapy in clinical practice to be determined.[59-61]

Eligibility criteria for patients included in the two observational studies was identical (Table 23) with no limitation based upon BRAF V600 mutation status as ipilimumab has shown comparable efficacy in both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients.[59-61]

As with the RCT trials, there is a difference between the observational studies and the pooled chemotherapy-naïve dataset in the respect that patients enrolled in CA184-332 and CA184-338 had received no prior therapy for melanoma whereas patients included in the pooled chemotherapy-naïve dataset analysis (n=78) were all chemotherapy-naïve (treatment naïve, n=37/78) but some have received prior immunotherapy (n=41/78).[59-61] As discussed, the survival benefit of ipilimumab therapy is not affected by treatment history.

Table 23: Eligibility criteria in the non-RCTs[59-61]

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
CA184-332	Diagnosis of unresectable or metastatic melanoma; age ≥18 years at the time of diagnosis; initiated first-line treatment with ipilimumab 3mg/kg monotherapy.	Prior systemic treatment for unresectable or metastatic melanoma; current or pending participation in a clinical trial or expanded access programme; current use of therapy to treat a cancer other than melanoma.
CA184-338	Diagnosis of unresectable or metastatic melanoma; age ≥18 years at the time of diagnosis; initiated first-line treatment with ipilimumab 3mg/kg monotherapy.	Prior systemic treatment for unresectable or metastatic melanoma; current or pending participation in a clinical trial or expanded access programme; current use of therapy to treat a cancer other than melanoma.
Pooled chemo-therapy-naïve dataset	Diagnosis of advanced malignant melanoma; ≥16 years.	Prior adjuvant or systemic chemotherapy treatment for advanced malignant melanoma; prior receipt of lenalidomide or thalidomide.

Demographic and other baseline characteristics of participants were generally comparable and well balanced across non-RCTs (Table 24). The only clear differences were the average duration of melanoma, treatment history and the number of patients with brain metastases:

- Duration of melanoma was higher in the pooled chemotherapy-naïve data set, presumably due to the fact that these patients may not be newly diagnosed.
- Treatment history differed with some patients receiving prior immunotherapy in the pooled data set; though we have seen prior immunotherapy does not affect the ipilimumab activity profile.
- Brain metastasis is one of the poorest prognostic features for overall survival in advanced melanoma.[69, 70] We would therefore expect median survival to be lower in observational studies than in the pooled data analysis.

BRAF V600 mutation status data are only available for the patients enrolled in CA184-332 and CA184-338 where at least 50% of patients presenting with unresectable or metastatic melanoma were BRAF V600 mutation-negative.[59, 60]

Previous post-hoc analysis of CA184-004 that enrolled both pre-treated and untreated patients shows the best overall response and disease control status achieved with ipilimumab 3mg/kg monotherapy is not affected by the BRAF V600 mutation status of the tumours.[39] Post-hoc analysis of CA184-338 supports the conclusion that tumour mutation status does not impact on the clinical activity of ipilimumab with no differences in survival function (p=0.23) observed across between BRAF V600 mutation-positive and BRAF V600 mutation-negative patients.[60]

Table 24: Baseline characteristics of participants receiving ipilimumab 3mg/kg monotherapy in the non-RCTs[59-61]

	CA184-332	CA184-338	Pooled chemo-therapy-naïve dataset (from clinical trials)
Sample size, n	61	120	78
Age, mean years	64	61.3	57.4
Male, n (%)	40 (65.6)	79 (65.8)	47 (60.3)
ECOG performance status, n (%)	0 = 39 (63.9) 1 = 16 (26.2) >1 = 3 (4.9)	0 = 49 (40.8) 1 = 62 (51.7) >1 = 7 (5.8)	0 = 45 (57.7) 1 = 30 (38.5) >1 = 3 (3.8)
Metastasis stage, n (%)	M0 = 0 M1a = 20 (29.5) M1b = 23 (37.7) M1c = 18 (29.5)	M0 = 14 (11.7) M1a = 13 (10.8) M1b = 27 (22.5) M1c = 66 (55.0)	M0 = 0 M1a = 18 (23.1) M1b = 16 (20.5) M1c = 44 (55.6)
Brain metastasis, n (%)	20 (32.8)	9 (7.5)	0
Duration of melanoma, median months	10.3	12.9	39.0
Lactate dehydrogenase, n (%)	≤ULN = 27 (44.3) >ULN = 18 (32.8)	≤ULN = 67 (55.8) >ULN = 44 (36.7)	≤ULN = 56 (71.8) >ULN = 21 (26.9)
BRAF V600 mutation, n (%)	Negative = 31 (50.8) Positive = 8 (31.1)	Negative = 76 (63.3) Positive = 21 (17.5)	NR
Prior immunotherapy, n (%)	0	16 (13.3)	41 (52.6)

ULN = upper limit of normal; NA = not applicable; NR = not reported

Given that the survival profile of ipilimumab 3mg/kg monotherapy from the three non-RCT data sets are to be compared with the DTIC therapy arm from CA184-024, it is important to see how similar baseline characteristics of patients are across these trials. Generally, patient populations were comparable though patients treated in clinical practice showed worse prognostic features including greater ECOG performance status and a higher proportion of patients presenting with associated brain metastases.[59-61]

Ipilimumab is the only novel therapeutic offering a long-term survival profile for the treatment of advanced melanoma. This survival profile is further supported by the results of all three non-RCTs.

Estimated 1-year survival rates for previously untreated and chemotherapy-naïve patients who received 3mg/kg ipilimumab in studies CA184-332 and CA184-338 and the pooled chemotherapy-naïve dataset were 49%, 60% and 54%, respectively. In all these datasets, the estimated 1-year OS rates are mature and compare favourably to the estimated 1-year survival rate for DTIC (36%).[8, 20, 59, 60]

2-year survival rates are not yet fully mature for CA184-332 and CA184-338 but are mature for the pooled chemotherapy-naïve dataset and again compares favourably to the 2-year OS rate for DTIC from CA184-024: 31.6% vs. 17.9%.[8, 20]

Median overall survival times ranged between 11.5 and 14.3 months for ipilimumab 3mg/kg monotherapy across the non-RCTs[59-61], which is comparable to the range observed for ipilimumab 3mg/kg monotherapy and ipilimumab 3mg/kg or 10mg/kg adjunctive therapy to DTIC in the RCTs described in sections 6.3 to 6.5 of 11.2–14.3 months (Table 25). This range again compares favourably to the median OS time observed with DTIC monotherapy (9.1 months), which is actually a favourable estimate of best-supportive care survival time, independently modelled to be 6.2 months in meta-analysis of 42 trials in metastatic melanoma.[1]

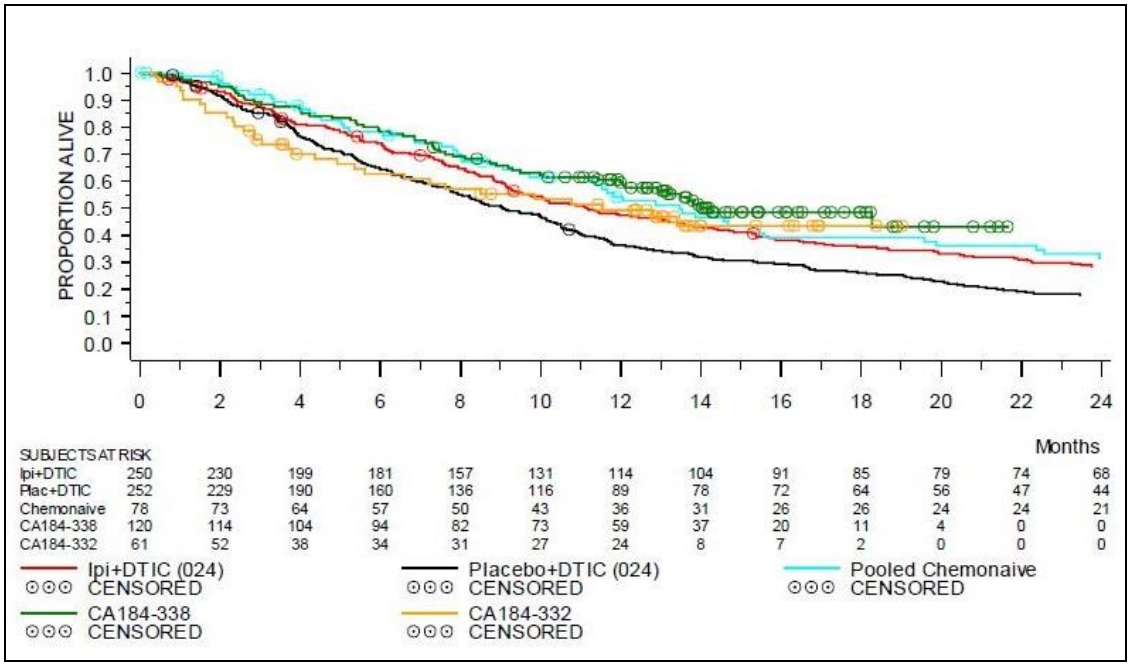
Table 25: Survival associated to ipilimumab therapy across RCTs and non-RCTs

Trial no. (acronym)	Treatment arm	Median OS, months	95% CI	1-year survival, %
CA184-024	Ipilimumab 10mg/kg + DTIC DTIC	11.2 9.1	9.4 - 13.6 7.8 - 10.5	47.6
MDX010-08	Ipilimumab 3mg/kg + DTIC Ipilimumab 3mg	14.3 11.4	10.2 - 18.8 6.1 - 15.6	45.0
CA184-332	Ipilimumab 3mg	11.5	6.6 - -	49.3
CA184-338	Ipilimumab 3mg	14.3	12.1 - -	59.5
Pooled chemo-therapy-naïve dataset	Ipilimumab 3mg	13.5	11.2 - 19.6	54.1

In addition to the ipilimumab dose administered across clinical trials, there were differences in the treatment schedule with CA184-024 and some trials from the pooled chemotherapy-naïve dataset including a maintenance phase of treatment for responding patients post ipilimumab induction. As shown in the overlay of Kaplan–Meier curves presented in Figure 20, ipilimumab provides a survival benefit compared with standard of care, irrespective of dose regimen.

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%, Table 24) 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.[59]

Figure 20: Kaplan–Meier curve for overall survival of untreated patients enrolled in CA184-024, CA184-332, CA184-338 and the pooled chemotherapy-naïve dataset[61]



In light of the differences within datasets, a Korn model was designed to benchmark survival profiles from the non-RCTs to historical OS by adjusting for key prognostic factors. This model was based on that designed by Korn et al.[1] and was validated in 2011 against 8 non-BMS phase III trials and MDX010-020.[71] Prior to its application to CA184-322, CA184-338 and the pooled chemotherapy-naïve dataset, the model was further validated by application to the DTIC monotherapy arm of CA184-024.

As shown in Figure 21, the observed OS coincided with or fell below the model predicted OS, confirming the models validity to serve as a predicted control for the current patient population of previously untreated, advanced melanoma patients.[61]

Figure 21: Observed and predicted survival with historical best supportive care (DTIC monotherapy)[61]

[redacted]

The Korn model was subsequently applied to the untreated patient populations of the non-RCTs. The observed survival profile associated to ipilimumab 3mg/kg monotherapy used as first-line treatment were markedly superior to the Korn model-predicted expected OS of these patients (Figure 22).[61]

Conclusion

The survival profile associated with ipilimumab therapy is consistent, irrespective of differences in dosing and administration, with median and 1-year OS rates in previously untreated patients similar among the different data sets. This survival profile compares favourably to that observed with DTIC monotherapy.

Not only do the OS results from CA184-332 and CA184-338 offer “real-world” efficacy data for the use of ipilimumab 3mg/kg monotherapy in untreated patients, the demographic results show at least 50% of patients presenting with unresectable or metastatic melanoma in clinical practice are BRAF V600 mutation-negative (Section 2.2). There is currently no treatment option proven to prolong overall survival in untreated patients regardless of their mutation status; ipilimumab 3mg/kg monotherapy offers this and thus meets a significant unmet need in the melanoma arena.

Figure 22: Predicted improved survival with ipilimumab 3mg/kg monotherapy in untreated patients[61]

[redacted]

6.9 Adverse events

Summary

- Ipilimumab has a well-characterised safety profile, mostly defined by mechanism of action driven immune-related adverse events (irAEs):
  - Dermatologic, gastrointestinal and hepatic irAEs were the most common across clinical trials of ipilimumab used as first-line therapy
- Ipilimumab has a consistent safety profile that is maintained throughout therapeutic phases:
  - CA184-024: 2-year survivor analyses shows the safety profile associated to continued ipilimumab therapy is constant with induction therapy
  - CA184-024: 2-year survivor analyses shows subjects who discontinue ipilimumab therapy experience few new onset or repeat occurrence irAEs
- Common irAEs are transient in nature and reversible with corticosteroids or other immunosuppressant therapies:
  - Post-hoc analysis shows medical management of irAEs does not impact the clinical activity of ipilimumab in advanced melanoma
- Serious complications associated with ipilimumab therapy are rare:
  - CA184-024: no treatment-related deaths associated to ipilimumab 10mg/kg + DTIC therapy
  - MDX010-08: one pulmonary embolism/sepsis with an outcome of death suspected to be related to treatment with ipilimumab 3mg/kg monotherapy
  - CA184-338: no treatment-related deaths associated to ipilimumab 3mg/kg monotherapy
- The frequency of irAEs of any grade rise with increasing dose of ipilimumab:
  - CA184-024: total irAEs in patients treated with ipilimumab 10mg/kg + DTIC = 77.7%; 31.6% of grade 3 and 10.1% of grade 4.
  - MDX010-08: total irAEs in patients treated with ipilimumab 3mg/kg monotherapy = 53.8%; 7.7% severe,10.3% serious/ongoing
  - CA184-338: total irAEs in patients treated with ipilimumab 3mg/kg monotherapy = 52.5%; 12.5% of grade 3 and 0.8% grade 4.
- Ipilimumab 3mg/kg monotherapy is well tolerated as a first-line treatment for patients with advanced melanoma:
  - CA184-338: 75.8% of patients completed ipilimumab induction therapy (received all 4 doses)

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Alongside activity (defined as objective response rate), MDX010-08 was primarily designed to evaluate the safety of ipilimumab alone or in combination with DTIC in patients with advanced melanoma.[47]

In addition, safety was pre-specified as a secondary outcome of interest in the phase III trial, CA184-024[20]; and occurrence and severity of AEs and treatment emergent AEs was predefined as one of the primary outcomes of interest in both observational studies: CA184-332; CA184-338.[61]

Details of trials from which safety data are herein presented can be found in sections 6.1 to 6.8.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

CA184-024

The overall tolerability of ipilimumab (10mg/kg) addition to DTIC therapy, based on events observed throughout the on-study period, is shown in Table 26 for the defined safety population of all treated patients in CA184-024. The on-site study period is defined as starting from the first date of induction dosing and ending at 70 days after the last dose of study therapy, including maintenance doses.[7, 20]

Table 26: Summary of ipilimumab tolerability from CA184-024[7, 20]

	Ipi + DTIC (N = 247)	DTIC (N= 251)
Subjects with any on-study AE[a] (n %)	244 (98.8)	236 (94.0)
Severe (grade 3/4)	139 (56.3)	69 (27.5)
Serious	170 (68.8)	121 (48.2)
Related	221 (89.5)	192 (76.5)
AEs leading to study drug discontinuation	114 (46.2)	46 (18.3)
AE with outcome of death	45 (18.2)	64 (25.5)
Related AE with outcome of death	0	1 (0.4)

[a] On-study AEs include all AEs reported between the first dose and 70 days after the last dose of study drug.
AE, adverse event; DTIC, dacarbazine; Ipi, ipilimumab

Total rates of AEs were similar between treatment groups but grade 3/4 AEs, SAEs, drug-related AEs, and AEs leading to drug discontinuation were more frequently reported in the ipilimumab + DTIC group compared with the DTIC monotherapy group. This difference is not unexpected, and is consistent with the known mechanism of action of ipilimumab resulting in increased inflammatory response. No new types of AEs were observed and no drug-related AEs with an outcome of death were reported in the ipilimumab group.[7, 20]

Discontinuations due to study-drug toxicity resulted in less than half (37%) of patients randomised to combination therapy receiving all 4 doses of ipilimumab 10mg/kg induction therapy. Post-hoc analysis showed subjects who received fewer doses had worse baseline characteristics (these included higher ECOG status and greater frequency of elevated LDH) compared with subjects who received 3 or 4 doses. This suggests that patients who have the most severe disease based on ECOG/LDH are less likely to successfully complete a full course of ipilimumab 10mg/kg therapy.

Details of all AEs and irAEs reported in CA184-024 are presented in Table 27. The event rate of total irAEs in patients treated with ipilimumab 10mg/kg + DTIC in CA184-024 was 77.7%, but the majority were mild to moderate in nature with only 10.1% of patients in this treatment arm reporting irAEs of grade 4. It is accepted that early administration of corticosteroids is crucial to the successful management of inflammatory events. Overall, ~59% of subjects in the ipilimumab group received systemic steroids. [7, 20]

Such treatment of irAEs has been shown not to impact the development or maintenance of ipilimumab clinical activity in advanced melanoma.[40]

Table 27: Total AEs and irAEs reported in CA184-024[7, 20]

	Ipilimumab + DTIC (n=247)			DTIC (n=251)		
	Total, n (%)	Grade 3, n (%)	Grade 4, n (%)	Total, n (%)	Grade 3, n (%)	Grade 4, n (%)
All adverse events, regardless of cause						
Any event	244 (98.8)	99 (40.1)	40 (16.2)	236 (94.0)	45 (17.9)	24 (9.6)
Gastrointestinal disorders	90 (36.4)	10 (4.0)	0	62 (24.7)	0	0
Dermatologic						
Pruritus	73 (29.6)	5 (2.0)	0	22 (8.8)	0	0
Rash	61 (24.7)	3 (1.2)	0	17 (6.8)	0	0
Hepatic						
Increase in alanine aminotransferase	82 (33.2)	40 (16.2)	14 (5.7)	14 (5.6)	2 (0.8)	0
Increase in aspartate aminotransferase	72 (29.1)	36 (14.6)	9 (3.6)	14 (5.6)	3 (1.2)	0
Other						
Pyrexia	91 (36.8)	0	0	23 (9.2)	0	0
Chills	28 (11.3)	0	0	10 (4.0)	0	0
Weight loss	27 (10.9)	1 (0.4)	0	13 (5.2)	1 (0.4)	0
Immune-related adverse events (irAEs)						
Any event	192 (77.7)	78 (31.6)	25 (10.1)	96 (38.2)	8 (3.2)	7 (2.8)
Dermatologic						
Pruritus	66 (26.7)	5 (2.0)	0	15 (6.0)	0	0
Rash	55 (22.3)	3 (1.2)	0	12 (4.8)	0	0
Gastrointestinal						
Diarrhoea	81 (32.8)	10 (4.0)	0	40 (15.9)	0	0
Colitis	11 (4.5)	4 (1.6)	1 (0.4)	0	0	0
Hepatic						
Increase in alanine aminotransferase	72 (29.1)	37 (15.0)	14 (5.7)	11 (4.4)	2 (0.8)	0
Increase in aspartate aminotransferase	66 (26.7)	34 (13.8)	9 (3.6)	8 (3.2)	1 (0.4)	0
Hepatitis	4 (1.6)	3 (1.2)	0	0	0	0

DTIC, dacarbazine

Of the grade 3 or 4 irAEs, the most commonly reported adverse reaction were hepatic in nature, with grade 3 or 4 elevations in liver-function values noted in 17.4 to 20.7% of patients. These reactions were generally reversible. Indeed, 91.3% of subjects who reported grade 3/4 liver irAEs had resolution, in a median of 3.4 weeks (95% CI: 3.0, 4.4). This transient nature was observed across all classes of irAEs with a median duration of 1.6 to 3.1 weeks and a median time to resolution of 1.4 to 4.7 weeks, depending on the event and grade as presented in Table 28. [7, 20]

Table 28: Duration and resolution of irAEs reported in CA184-024[7, 20]

irAE Category	Subjects with event, n (%)	Median duration, weeks	Median time to resolution, weeks
GI			
Grade 2-4	39 (15.8)	NR	2.0
Grade 3-4	14 (10.0)	2.0	2.1
Liver			
Grade 2-4	89 (36.0)	NR	3.4
Grade 3-4	69 (27.9)	3.1	3.4
Endocrine			
Grade 2-4	5 (2.0)	NR	NE
Grade 3-4	0	NA	NA
Skin			
Grade 2-4	46 (18.6)	NR	4.1
Grade 3-4	8 (3.2)	1.7	4.7
GI, gastrointestinal; irAE, immune-related adverse event; NE, not estimable; NR, not reported			

Subjects who survived more than 2 years from study entry and who had discontinued ipilimumab experienced few new onset irAEs (or repeat occurrence if the same toxicity was also reported on study) more than 70 days after last dose, most of which were low grade in severity. In subjects still receiving ipilimumab treatment beyond ≥ 2 years, the safety profile appears to be consistent with that of the induction period and medically manageable using established safety guidelines.[46]

MDX010-08

Ipilimumab in combination with DTIC as administered in CA184-024 resulted in numerically higher rates of AEs compared with ipilimumab monotherapy in trial MDX010-08; as we might expect for any adjunctive therapy.[47] It should however also be taken into account that the dose of ipilimumab at 3mg/kg was lower than used in CA184-024 Safety assessment in dosing trials has shown the frequency of irAEs of any grade rise with increasing dose of ipilimumab.[51]

The overall tolerability of ipilimumab for chemotherapy-naïve patients enrolled in MDX010-08, based on events observed in the initial cycle of therapy, is shown in Table 29 for the defined safety population of all treated patients.[47, 72]

Table 29: Summary of ipilimumab tolerability from MDX010-08[47, 72]

	Ipilimumab (N = 39)		Ipilimumab + DTIC (N = 35)	
	n	%	n	%
Subject with any AE				
No	0		0	
Yes	39	100.0	35	100.0
Subject with any severe AE[a]				
No	20	51.3	20	57.1
Yes	19	48.7	15	42.9
Subject with any serious adverse event				
No	28	71.8	22	62.9
Yes	11	28.2	13	37.1
Subject with any study drugs related AE[b]				
No	10	25.6	4	11.4
Yes	29	74.4	31	88.6
Death				
No	37	94.9	34	97.1
Yes	2	5.1	1	2.9
Withdraw due to AE				
No	38	97.4	32	91.4
Yes	1	2.6	3	8.6

[a] Any adverse event of severe grade 3 or 4 (severe or life threatening). [b] Any adverse event of relationship to study drug as suspected.
AE, adverse event; DTIC, dacarbazine

All patients experienced at least one AE and rates of severe AEs were similar between treatment groups. However, SAEs, drug-related AEs and AEs leading to drug discontinuation were more frequently reported in the ipilimumab monotherapy group compared with the ipilimumab + DTIC combination therapy group. All AEs were however generally manageable and reversible without known sequelae. One AE (pulmonary embolism/sepsis) with an outcome of death, suspected to be drug-related, was reported in the ipilimumab group.[47, 72]

IrAEs of any grade occurred in 65.7% of patients treated with ipilimumab in adjunction with DTIC compared with 53.8% of patients treated with ipilimumab monotherapy. Rash, commonly accompanied by pruritus, was the most frequent irAE in this study, noted in over 20% of subjects. Diarrhoea occurred in almost 20% of subjects and colitis was documented in 5.4% of subjects. With the exception of a single subject, diarrhoea and colitis were medically manageable and reversible. Total irAEs are reported in Table 30.[47]

Table 30: Total irAEs reported in MDX010-08[47]

irAE	Ipilimumab (n=39) n (%)	Ipilimumab + DTIC (n=35) n (%)
Any	21 (53.8)	23 (65.7)
Any severe	3 (7.7)	6 (17.1)
Any serious	4 (10.3)	5 (14.3)
Gastrointestinal disorder	8 (20.5)	10 (28.6)
Diarrhoea	8 (20.5)	9 (25.7)
Colitis	3 (7.7)	1 (2.9)
Skin and subcutaneous tissue disorder	19 (48.7)	15 (42.9)
Rash	11 (28.2)	8 (22.9)
Pruritus	9 (23.1)	7 (20.0)
Rash pruritic	2 (5.1)	2 (5.7)
Vitiligo	2 (5.1)	2 (5.7)
Alopecia	2 (5.1)	0
DTIC, dacarbazine. irAE, immune-related adverse event		

CA184-338

Of the non-RCT studies presented in section 6.8, safety data are available for one of the observational studies to date (CA184-338) and the pooled chemotherapy-naïve dataset. With a median follow-up time of ~12 months in both studies, a sufficiently long-term safety profile can be ascertained given that typically drug-related AEs occur during the initial four doses.[60, 61]

Tolerability of ipilimumab 3mg/kg monotherapy in clinical practice is observed in CA184-338 in which the majority (75.8%) of the 120 patients enrolled received all 4 doses of ipilimumab induction therapy. The incidence of drug-related AEs (54.2%) was lower than the incidence observed with ipilimumab + DTIC treatment in CA184-024 (89.5%). This may reflect increased experience with managing these types of AEs or under-reporting of mild AEs outside of a clinical trial setting.[20, 60]

The number of patients receiving ipilimumab therapy that reported irAEs in clinical practice also resulted in a lower rate of irAEs compared with that reported in a clinical trial setting. 52.5% of patients treated with ipilimumab 3mg/kg monotherapy experienced an irAE of any grade and in only 12.5% of patients was an irAE deemed severe (grade ≥3). Again, this may reflect increased experience with managing irAEs or under-reporting of mild irAEs outside of a clinical trial setting.[60]

There were no deaths due to drug-related AEs or irAEs observed with ipilimumab 3mg/kg first-line therapy in advanced melanoma patients treated in clinical practice.[60]

Pooled chemotherapy-naïve dataset

Pooled analysis of chemotherapy-naïve patients treated with ipilimumab 3mg/kg monotherapy across CA184-004, CA184-022, MDX010-08 and MDX010-022 showed similar rates of drug-related AE and irAEs to those observed in CA184-024 at 81.3% and 64.0%, further suggesting the increased reporting of mild AEs in a clinical trial setting.[61]

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Advanced melanoma is the most aggressive form of skin cancer and is fatal if undetected and untreated.[73] Its incidence is increasing and there are currently no approved first-line agents for both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients that have been shown to significantly improve long-term survival. This results in a high unmet medical need.

Ipilimumab has a well-characterised and manageable safety profile, mostly defined by mechanism of action driven irAEs often associated with immunotherapies. Dermatologic, gastrointestinal and hepatic irAEs were the most common across clinical trials of ipilimumab used as first-line therapy but all were transient in nature and rapidly resolved, often with the administration of corticosteroids and other immunosuppressants.[7, 20, 47, 60, 61] Such treatment of irAEs has been shown not to impact the development or maintenance of ipilimumab clinical activity in advanced melanoma.[40]

In subjects still receiving ipilimumab treatment beyond ≥ 2 years in CA184-024, the safety profile appears to be consistent with that of the induction period and medically manageable using established safety guidelines.[46] Ipilimumab 3mg/kg monotherapy used as a first-line agent demonstrated reduced rates of irAEs compared with ipilimumab 10mg/kg therapy used in combination with DTIC. [7, 20, 47, 60, 61, 74] This observation is further supported in the safety assessment of dosing trials which have shown the frequency of irAEs of any grade rise with increasing dose of ipilimumab.[51]

Serious complications associated with ipilimumab therapy are rare and are usually bowel perforations/colectomy and liver failure. Across all RCTs and non-RCTs investigating clinical efficacy of ipilimumab 3mg/kg first-line therapy, a single patient died from a pulmonary embolism/sepsis suspected to be drug-related.[7, 20, 47, 60, 61]

In conclusion, ipilimumab has a stable, medically manageable and usually reversible toxicity profile and is the only agent that offers a long-term safety profile in previously untreated patients with advanced melanoma.

6.10 Interpretation of clinical evidence

Summary

- Ipilimumab's efficacy and safety profile is consistent across a range of dosing regimens in previously untreated patients with advanced melanoma:
  - RCT evidence base: CA184-024, MDX010-08, CA184-004, CA184-022
  - Non-RCT evidence base: CA184-332, CA184-338 and pooled chemotherapy-naïve dataset
  - Ipilimumab shows equivalent efficacy across a number of dosing regimens (ipilimumab 10mg/kg + DTIC; ipilimumab 3mg/kg + DTIC and ipilimumab 3mg/kg monotherapy)
- Ipilimumab shows a durable biological effect and currently offers the only proven long-term survival profile in previously untreated patients with advanced melanoma:
  - 5-year data demonstrate a significant improvement in mean survival of 24.5 weeks compared with historical standard of care (DTIC)
- Ipilimumab is the only immunotherapeutic therapy for first-line treatment of advanced melanoma that is not restricted for use by BRAF V600 mutation status:
  - Ipilimumab provides an innovative mechanism of action that does not rely on molecular targeting of the BRAF pathway
  - Post-hoc analysis further demonstrates clinical activity of ipilimumab is not dependent on BRAF V600 mutation status
- Ipilimumab is the only therapeutic option for first-line treatment of advance melanoma that offers a long-term safety profile:
  - Ipilimumab has a well-characterised safety profile, mostly defined by transient immune-related adverse events
  - Medical management of adverse events does not affect the clinical activity of ipilimumab therapy
  - 2-year survival analysis confirms consistency of the ipilimumab adverse event profile throughout treatment
  - Frequency of immune-related adverse events rise with increasing dose, favouring the use of ipilimumab 3mg/kg
- Ipilimumab is the only therapeutic option for first-line treatment of advance melanoma that offers a long-term HRQL profile:
  - Longitudinal analysis of EORTC QLQ C-30 questionnaires demonstrates ipilimumab addition to therapy has no negative impact on HRQL
  - HRQL remains close to that of the age matched general population for patients who survive at least a further 6 months
- Ipilimumab's effect on survival is not influenced by prior therapy
- Ipilimumab should be considered a step change in first-line therapy of advanced melanoma

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Advanced melanoma is a deadly disease with increasing incidence. Historically, approved chemotherapy (DTIC) has not demonstrated a survival benefit, underscoring the need for new frontline therapies proven to prolong overall survival. Recent approval of vemurafenib provides an alternative first-line option for advanced melanoma patients with the BRAF V600 mutation; and has shown improved survival compared with DTIC, though available trial data do not allow assessment of its long-term survival profile. However, demographic studies show less than half of advanced melanoma patients presenting in clinical practice possess the BRAF V600 mutation. There is clearly still a continued unmet medical need for therapeutics that can demonstrate improvement in the long-term survival of patients with previously untreated, advanced melanoma regardless of BRAF mutation status, that do not have stringent restrictions on use.

Ipilimumab is the only therapeutic option for first-line treatment of advanced melanoma that offers a long-term survival profile in this population:

In primary analyses of the pivotal phase III trial, CA184-024, ipilimumab addition to DTIC therapy improved median OS by 2.1 months in previously untreated patients compared with DTIC monotherapy. Secondary analyses of 5-year data show an extended improvement in median OS of 24.5 weeks for ipilimumab 10mg/kg + DTIC therapy vs. DTIC monotherapy. Associated survival rates show at least a 10% increase with ipilimumab 10mg/kg + DTIC therapy vs. DTIC monotherapy at years 1-5.

Clinical equivalence of ipilimumab 10mg/kg + DTIC and ipilimumab 3mg/kg monotherapy is supported by qualitative synthesis of data across ipilimumab trials:

Ipilimumab dosing has been shown not to impact its clinical effectiveness in direct trial data from CA184-004 and CA184-022; both of which included at least a proportion of previously untreated, advanced melanoma patients. Furthermore, DTIC addition to therapy is shown not to significantly impact the clinical efficacy of ipilimumab, as we would expect, given that it has not demonstrated a survival benefit in clinical trials. This was shown directly in the phase II clinical trial, MDX010-08, where ipilimumab 3mg/kg + DTIC therapy resulted in comparative survival times to ipilimumab 3mg/kg monotherapy after a median follow-up of 20.9 and 16.4 months, respectively.

Survival profiling across RCTs show ipilimumab 10mg/kg + DTIC therapy (that has shown significant superiority in overall survival for previously untreated, advanced melanoma patients over DTIC monotherapy) and ipilimumab 3mg/kg monotherapy resulted in very similar median OS times of 11.2 vs. 11.4 months, respectively. In addition, pooled chemotherapy-naïve dataset analysis further supports the impressive survival profile associated to ipilimumab 3mg/kg monotherapy with a median OS of 13.5 months observed. Application of a Korn-model that adjusts for differences within datasets demonstrates this survival profile is significantly superior to standard of care for the treatment of previously untreated advanced melanoma patients.

Ipilimumab 3mg/kg monotherapy has been further investigated as a first-line treatment for advanced melanoma in the “real-world” setting. Preliminary analysis of ongoing observational studies shows median OS times of 11.5 - 14.3 months associated with

ipilimumab 3mg/kg first-line treatment in clinical practice. These closely reflect the ranges observed with ipilimumab use in RCTs, either as 3mg/kg monotherapy or in combination with DTIC at doses of 3mg/kg or 10mg/kg. Again, application of a Korn-model demonstrates a significant improvement in survival time with ipilimumab 3mg/kg monotherapy vs. DTIC monotherapy.

The clinical benefit of ipilimumab 3mg/kg monotherapy as a first-line therapy option for advanced melanoma patients is supported by the EMA who have approved a licence extension for ipilimumab use in previously untreated as well as pre-treated patients.

Ipilimumab is the only novel therapeutic option for first-line treatment of advanced melanoma that is not restricted for use by BRAF V600 mutation status:

Due to the fact that ipilimumab's novel mechanism of action stimulates the body's own immune system to fight cancer cells, its clinical activity is not affected by BRAF V600 mutation status. This is demonstrated for ipilimumab 3mg/kg monotherapy in a post-hoc analysis of CA184-004 that included both untreated and pre-treated advanced melanoma patients and in interim analysis of CA184-338 when used as first-line therapy in clinical practice. Ipilimumab therapy can therefore be used to treat both BRAF V600 mutation-positive and negative patients, the latter of which account for at least 50% of the total advanced melanoma population presenting for first-line therapy.

Ipilimumab is the only therapeutic option for first-line treatment of advanced melanoma that offers a long-term safety profile and associated HRQL data:

Ipilimumab has a well-characterised safety profile, mostly defined by mechanism of action-driven irAEs often associated with immunotherapies. The safety profile of ipilimumab 10mg/kg + DTIC combination in untreated subjects in CA184-024 was generally similar to the well-documented safety profile of 3 mg/kg ipilimumab monotherapy in that (1) the most frequent treatment-related AEs were inflammatory (e.g. irAEs), reflecting the mechanism of action of ipilimumab; (2) the type of irAEs seen corresponded closely to previous clinical experience involving most frequently gastrointestinal , skin, liver and endocrine organs; (3) most irAEs occurred during the treatment period; (4) irAEs were generally manageable and reversible using steroids and the guidance of the irAE management algorithms.

These results using a higher dose of ipilimumab in combination with a chemotherapeutic agent illustrate that the safety profile for untreated patients treated at a lower dose as monotherapy should be well tolerated. This assumption is further supported from the safety outcomes reported from the observational data collected for CA184-338, where 54% of individuals experienced an AE of any grade during induction compared with 98% of patients receiving 10mg/kg and DTIC. The pattern of toxicities reported in this observational study closely corresponded to previous experience across the ipilimumab trial programme and more recent use in the clinical setting in previously treated patients.

Long-term follow-up of surviving subjects from CA184-024 and observational studies demonstrate stability of this safety profile with consistency throughout induction and re-induction or maintenance phases. Common irAEs are transient in nature and medically manageable with systemic steroids that do not affect the clinical activity of ipilimumab therapy. Tolerability is further confirmed through HRQL analysis that showed ipilimumab 10mg/kg addition to DTIC therapy did not negatively impact HRQL

(measured using the EORTC QLQ C-30 questionnaire) of patients enrolled in CA184-024. In fact, post-hoc analysis demonstrates HRQL remains close to that of the age matched general population for patients who survive at least a further six months with ipilimumab therapy.

Preferred use of ipilimumab 3mg/kg is further supported from a safety perspective given that post-hoc analysis of safety data from CA184-022 shows the frequency of irAEs of any grade rise with increasing dose of ipilimumab.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The principal limitation of the clinical evidence base is that there are no direct comparative efficacy trials for ipilimumab 3mg/kg vs. DTIC therapy in previously untreated, advanced melanoma patients. The pivotal phase III trial that provides the main comparative evidence base for ipilimumab is provided by CA184-024 where ipilimumab 10mg/kg was administered in conjunction with DTIC therapy. Results from this trial are extrapolated to demonstrate the clinical superiority of ipilimumab 3mg/kg monotherapy over historical best supportive care (DTIC).

Conversely, a primary strength of the clinical evidence base is the extensive trial data available to support ipilimumab 3mg/kg monotherapy use in previously untreated, advanced melanoma patients. In addition to long-term RCT data from CA184-024 and MDX010-08, a pooled analysis of chemotherapy-naïve patients from 4 RCTs that included an ipilimumab 3mg/kg monotherapy treatment arm further supports its use. In addition, two observational studies of first-line use of ipilimumab 3mg/kg monotherapy in clinical practice allow assessment if its “real-world” effectiveness.

Strengths and limitations of individual trials that make up the clinical evidence base are outlined below:

CA184-024

CA184-024 is a large phase III, randomised, double-blind controlled study involving 502 patients; this ensures confidence in its robust set of results. All patients enrolled had previously untreated, advanced melanoma and therefore are directly relevant to the subject of this submission. It was a global study with a large proportion of European patients (351). Baseline characteristics and demographics were well balanced across the two treatment arms with randomisation stratified by baseline metastasis stage and ECOG performance status. The study also ran over a long period of time for this disease area, resulting in mature data that allows evaluation of the long-term survival profile of ipilimumab therapy. To ensure subject safety, an independent data monitoring committee monitored all safety information in accordance with the committee charter.

The main limitation of CA184-024 was the administration regime utilised in the ipilimumab treatment group where a 10mg/kg dose was used in conjunction with DTIC therapy. This is outside of the licence issued by the EMA. In addition, after induction dosing, maintenance style dosing was administered to patients who had not progressed. This later schedule is not specified in the UK licensed dose schedule.

Comparison of Kaplan–Meier curves across ipilimumab trials does however show such a maintenance phase of therapy does not significantly impact the survival profile of ipilimumab therapy.

MDX010-08

MDX010-08 is a phase II, randomised, open-label cross-over study involving 76 patients; significant for a phase II study. Its primary strength is that it included an ipilimumab 3mg/kg monotherapy treatment arm and is therefore directly relevant to this submission. In addition, the dosing regimen of 4 doses every 3 weeks is directly aligned with the UK licensed dose schedule. As it compares clinical efficacy of ipilimumab monotherapy to its use in conjunction with DTIC, it also allows assessment of the impact of DTIC addition to the clinical activity of ipilimumab therapy - thus providing means of extrapolation of comparative efficacy data from CA184-024. Baseline characteristics and demographics were well balanced across the two treatment arms. The study also ran over a reasonable period of time for this disease area.

The study was conducted in the US and thus one limitation in regard to this submission is that it did not involve any European patients. In terms of clinical efficacy, it was also not primarily designed to detect differences in survival between the two treatment arms. Though this was a pre-defined outcome of the companion study in which survival of patients enrolled in MDX010-08 was analysed; reported as MDX010-028.

Pooled chemotherapy-naïve dataset

The pooled analysis of chemotherapy-naïve patients from four RCTs presented breaks the randomised nature of patient enrolment from original trials. However, it does provide a means of assessing the impact of first-line ipilimumab 3mg/kg monotherapy on survival in patients with advanced melanoma from data captured in a clinical trial setting; and therefore is of direct relevance to this submission.

CA184-332 and CA184-338

CA184-332 and CA184-338 are retrospective observational studies that address “real-world” effectiveness of ipilimumab 3mg/kg monotherapy in previously untreated, advanced melanoma patients. Both studies are set in the US and thus dosing of ipilimumab was based on the US prescribing information. However, this is equivalent to the UK licensed dose schedule and thus is of direct relevance to this submission. Though retrospective studies have the potential to introduce biases due to different patient selection criteria compared with prospective clinical trials; CA184-332 and CA184-338 did not exclude patients on the basis of any factor that may be associated with worse outcomes (e.g. presence of brain metastases). In addition, patients enrolled in CA184-332 were identified programmatically without input from site or sponsor and CA184-338 enrolled sequentially treated patients.

CA184-004 and CA184-022

CA184-004 and CA184-022 are phase II, randomised, double-blind, dose-ranging studies of ipilimumab that enrolled both previously untreated and previously treated patients with advanced melanoma. Subset survival analyses of relevant patients to this submission were deemed inappropriate for use due to small patient numbers and thus these trials were removed from the main clinical evidence base. Outcomes from both studies do however demonstrate clinical equivalence between ipilimumab 3mg/kg and 10mg/kg doses and are used to support the extrapolation of CA184-024 results to ipilimumab 3mg/kg monotherapy.

Ipilimumab's effect on survival is not influenced by prior therapy

Several analyses show that ipilimumab's effect on survival is not influenced by prior therapy. This is a logical consequence of ipilimumab's mode-of-action:

- The mechanism of action of ipilimumab is blockade of CTLA-4 leading to T-cell activation. Ipilimumab 3 mg/kg induces a sustained increase from baseline in frequency of activated CD4 and CD8 T-cells for both the untreated and previously treated subjects.[61]
- The observation that ipilimumab's benefit is independent of line of treatment is consistent with its mechanism of action. Ipilimumab does not directly target the tumour but rather activates T-cells. Tumours are inherently unstable and undergo evolution during therapy. The immune system, which belongs to the host, is genetically stable during the course of the disease and therefore does not acquire genomic resistance to immune therapies (i.e. ipilimumab).[61]
- The immune profile of key T-cells is similar between previously treated and untreated advanced melanoma and, importantly, 3 mg/kg ipilimumab is biologically active in both populations, as shown by the sustained increases in the frequency of activated T-cells.[61]
- A meta-analysis of 42 Phase II advanced melanoma trials demonstrated that prior therapy status (yes vs. no) was not prognostic for OS (Korn et al.[1]). This observation is confirmed in the current Exposure-Response model where prior therapy (yes vs. no) was not a significant covariate for OS in subjects treated with ipilimumab. This means that the benefit of ipilimumab in advanced melanoma should be independent of line of therapy.[61]
- An exposure-survival analysis using a Cox Proportional Hazard model was conducted on [redacted]. The analysis included [redacted]. The model used actual exposure (trough concentration) rather than nominal dose. The data show that ipilimumab's efficacy is independent of line of therapy. The analysis was limited to subjects who received ipilimumab monotherapy to avoid potential bias of concomitant therapies.[61]
- The primary evidence of efficacy of 3 mg/kg ipilimumab monotherapy in previously treated advanced melanoma was based on a large Phase III study (MDX010-20) which demonstrated a statistically significant and clinically meaningful improvement in OS, regardless of prior therapy (as presented in the

submission for previously treated patients[9]). In subset analyses of OS from the MDX010-20 in previously treated, advanced melanoma, OS benefit was observed regardless of the number of (1 or ≥ 2) or type of prior anti-cancer systemic treatment (Figure 23).

- Specifically, OS benefit was observed for subjects regardless of prior DTIC (yes vs. no), non-DTIC chemotherapy (yes vs. no), prior immunotherapy (yes vs. no), and number of prior therapies (1 vs. ≥ 2).[61]

In summary, this means that ipilimumab's effect on survival is not influenced by prior therapy.

Figure 23: Forest Plot of Overall Survival by Prior Therapy Subgroup Analysis (MDX010-20) Ipilimumab versus gp100

[redacted]

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

All clinical evidence presented is for patients with advanced melanoma that are classed as previously untreated in the UK setting. In the case of CA184-024, CA184-332 and CA184-338, patients had not received any prior treatment for melanoma. In the case of MDX010-08 and the pooled chemotherapy-naïve dataset analysis, patients may have received prior immunotherapy treatment. Given that only DTIC was approved for first-line treatment of advanced melanoma prior to the recent approval of vemurafenib and

dabrafenib, chemotherapy-naïve patients are classed as eligible for first-line therapy in the UK setting. In addition, prior immunotherapy is shown not to impact the clinical activity of ipilimumab in a post-hoc analysis of MDX010-022.

Though some studies were solely conducted in the US, baseline characteristics and demographics of the patient populations across trials reflect typical advanced, melanoma patients who present in UK clinical practice. Of note, both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients were enrolled in all trials.

Intervention and comparator arms (where applicable) across studies presented are all relevant to this submission. Specifically, MDX010-08, CA184-322, CA184-338 and the pooled chemotherapy-naïve dataset analysis directly investigated the clinical efficacy of ipilimumab 3mg/kg monotherapy as first-line treatment in patients with advanced melanoma and thus are of direct relevance to this submission. Qualitative and quantitative synthesis of survival data across the ipilimumab trials shows superiority of ipilimumab 3mg/kg monotherapy over DTIC therapy: the historical standard of care in the UK.

Primary outcomes assessed in the clinical evidence base for ipilimumab are directly relevant to the decision problem and the clinical benefits experienced by patients in clinical practice. The fundamental aim of advanced, metastatic melanoma treatment is to prolong life without negatively impacting patient HRQL. Survival was a pre-defined primary endpoint in CA184-024, CA184-332, CA184-338 and the pooled dataset analysis and the primary endpoint of companion study MDX010-028 to MDX010-08 in which survival was assessed. Safety was a concomitant primary endpoint in CA184-332 and CA184-338 and was pre-defined as one of two primary outcomes of interest in MDX010-08. In addition, safety and HRQL were pre-specified secondary endpoints in CA184-024.

Consideration of the complete clinical evidence base thus allows a thorough assessment of the clinical efficacy and tolerability of ipilimumab 3mg/kg monotherapy in previously untreated patients with advanced, melanoma in the UK.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

When considering the evidence base for the clinical efficacy and safety of ipilimumab 3mg/kg monotherapy in previously untreated, advanced melanoma patients in full, robust conclusions can be made.

In total, 544 individual patients, representative of the UK population of relevance to this submission have been treated with ipilimumab therapy in prospective and retrospective clinical trials to date (CA184-024: n = 250; MDX010-08: n = 72; CA184-322: n = 61; CA184-338: n = 120; pooled chemotherapy-naïve dataset (minus MDX010-08

patients): n = 41). Of these patients, 259 were treated as per the UK licensed dose schedule for ipilimumab monotherapy: 3mg/kg monotherapy (MDX010-08: n = 37; CA184-322: n = 61; CA184-338: n = 120; pooled chemotherapy-naïve dataset (minus MDX010-08 patients): n = 41).

Median overall survival in the range of 11.2 to 14.3 months was observed across trials; this is significantly superior to the 9.1 months median survival experienced by patients treated with DTIC monotherapy in CA184-024. To put this into context: the ipilimumab benefit on survival for previously untreated, advanced, melanoma patients; previous meta-analysis of 42 trials (n=2,100) in metastatic melanoma patients showed a median survival time of only 6.2 months: this was not significantly affected by treatment history.

Furthermore, ipilimumab presents a consistent and medically manageable safety profile and RCT data show it does not negatively impact patients' HRQL. Given that the ultimate aim of treatment is to safely prolong life without negatively impacting patient HRQL, the outcomes assessed within this clinical evidence base are directly relevant to clinical practice.

The baseline characteristics and demographics of the patient populations across the clinical evidence base presented for ipilimumab reflect typical advanced, melanoma patients who present in UK clinical practice for first-line therapy.

In comparison with alternative trials of new therapeutics in this disease area, ipilimumab trials do not include/exclude patients based on BRAF V600 mutation status. This is due to the fact that ipilimumab's novel mode of action does not rely on BRAF V600 mutation. Demographic assessment of patients enrolled in CA184-332 and CA184-338 shows that at least half of the previously untreated, advanced melanoma patients presenting in clinical practice are BRAF mutation-negative. Hence, the clinical evidence bases presented for ipilimumab truly reflects the total population of advanced, melanoma patients and negates the need for BRAF screening prior to therapeutic prescription.

Observational studies, CA184-332 and CA184-338, provide a direct evidence base of first-line ipilimumab 3mg/kg monotherapy use in advanced, melanoma patients in clinical practice. As these are retrospective in design, no exclusion of patients is made on the basis of any factor that may be associated with worse outcomes.

A main consideration for assessing the suitability of patients for ipilimumab treatment is their current autoimmune disease status and history. Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation could be potentially life threatening. It should also be used with caution in patients with a history of autoimmune disease, after carefully considering the potential risk-benefit on an individual basis. For this reason, the ipilimumab clinical trials excluded patients with active autoimmune disease and those on long-term immunosuppressants.

The majority of the clinical evidence base (4/5 studies) presented for ipilimumab first-line treatment of advanced melanoma administered therapy as per the UK licensed dose schedule: ipilimumab 3mg/kg every 3 weeks for up to 4 doses.

The exception was the main comparative data for ipilimumab vs. historical standard of care (DTIC). In CA184-024, ipilimumab was administered at a 10mg/kg dose and in conjunction with DTIC therapy. Maintenance style dosing was also administered to

patients who had responded to induction therapy. As shown, neither the increased dose, nor the concomitant administration of DTIC, nor the maintenance phase of treatment significantly impacts upon the clinical activity of ipilimumab therapy.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic literature review was conducted on the 9th May 2013 to identify economic evaluations relevant to the decision problem. The following research question was posed in accordance with the decision problem:

"What is the cost-effectiveness of ipilimumab for treatment of people with previously untreated advanced (unresectable or metastatic) malignant melanoma compared with potential comparators (DTIC, dabrafenib and vemurafenib)?"

A precise search strategy was used, including terms for ipilimumab and potential comparators (DTIC, dabrafenib and vemurafenib), see appendix 10 for details.

In order to ensure the published literature was comprehensively reviewed, a wide range of databases were searched: Medline, Embase, Cochrane Library, NHS HEED, HTA database, DARE, CINAHL and Econlit. In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies identified were hand searches and scanned for additional publications of relevance to the research question.

Having identified studies from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. Table 31 shows the eligibility criteria for assessing the relevance of the different studies.

After a detailed review of the title and abstract, the papers that appeared to meet the inclusion criteria, were obtained for a secondary review. This secondary review involved the entire article being assessed according to the inclusion and exclusion criteria outlined in Table 31. The studies which, following a secondary review, were still assessed to have met the inclusion criteria are described in section 7.1.2.

Table 31: Eligibility criteria for economic evaluation publications and rationale for each criterion

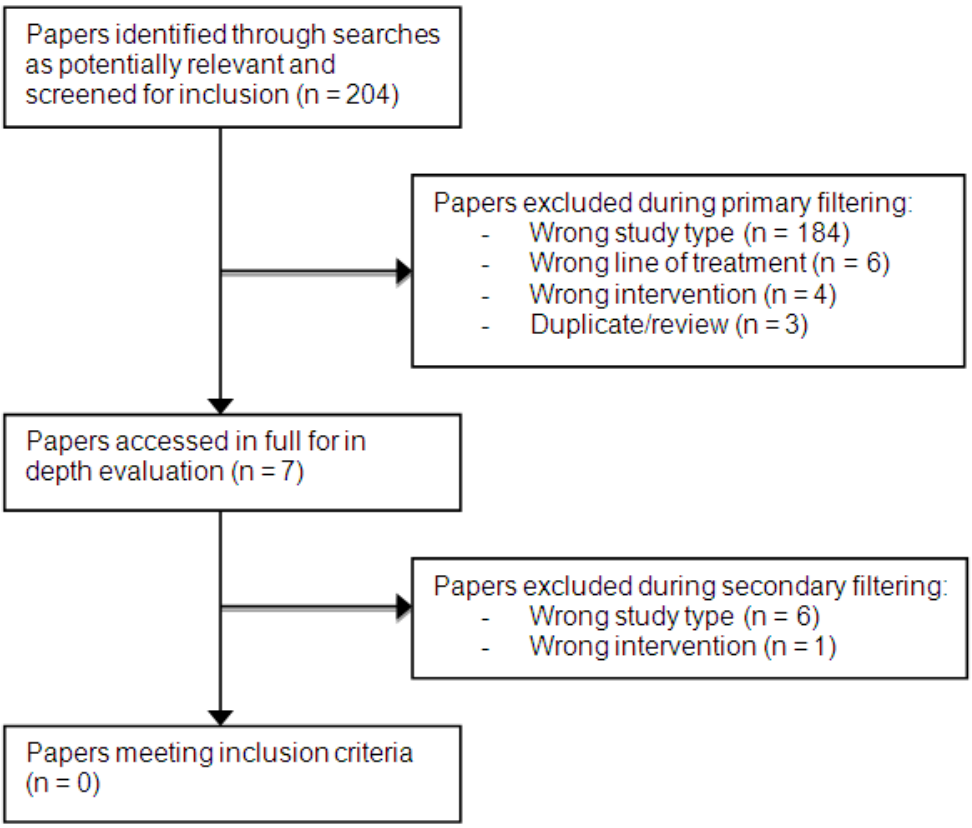
Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Full economic evaluation (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares ipilimumab to one or more of its comparators	The aim of the review was to identify relevant economic evaluations
Population	Adults with advanced (unresectable or metastatic) previously untreated melanoma	This is the relevant patient population
Interventions	The intervention of interest was ipilimumab	-
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which also reported costs
Comparators	The comparators included in the search are DTIC, dabrafenib and vemurafenib	The comparators for the literature search were selected in accordance with the NICE draft scope
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed, and the study's data and results must be extractable	Only studies which provided extractable data and results were usable
Exclusion Criteria		
Category	**Exclusion Criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of economic evaluations (although reference lists of these were hand-searched)	Primary study articles were required
DTIC, dacarbazine; QALY, quality-adjusted life year		

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

204 studies were initially identified. 197 of the 204 studies were excluded during primary filtering, as illustrated by Figure 24. Seven studies remained for secondary filtering. Six of these studies were the wrong study type, and one was using the wrong intervention. Consequently no studies were found that met all the inclusion criteria.

Figure 24: Identification of economic evaluations relevant to the decision problem



7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Not applicable.

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The current indication for ipilimumab in the EU is "for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy." It is anticipated that this will be extended to "for the treatment of advanced (unresectable or metastatic) melanoma in adults", to integrate its first-line therapeutic option (section 1.5).[8]

As a previous NICE STA (TA268) resulted in the recommendation of ipilimumab for previously treated patients, the population considered in this analysis is that of previously untreated patients.[9] The population considered within the relevant clinical trials in section 6.3.3 is previously untreated patients, which is in line with the decision problem.

Traditionally, first-line standard of care normally involved the administration of DTIC chemotherapy. But more recently, the majority of patients will undergo a molecular analysis of their tumour to determine the mutational status of the BRAF V600 gene, in order to identify those suitable for treatment with BRAF inhibitors (e.g. vemurafenib, approved for use in NICE TA269[32], and dabrafenib). Research carried out with 47 UK clinicians indicates that 96% of patients are now tested for BRAF mutation status.[75]

In the model, two sub-populations are therefore considered:

- **BRAF V600 mutation-positive patients**, eligible for first-line treatment with ipilimumab, DTIC, vemurafenib or dabrafenib. This is in line with the licensed indications of the treatments. Dabrafenib was considered as a potential comparator for this subpopulation. However, dabrafenib was eventually excluded from the analysis given it was not included in the final scope, has limited publically available data (including lack of overall survival data), and does not have a price in the UK.
- **BRAF V600 mutation-negative patients**, eligible for first-line treatment with ipilimumab or DTIC.

Model structure

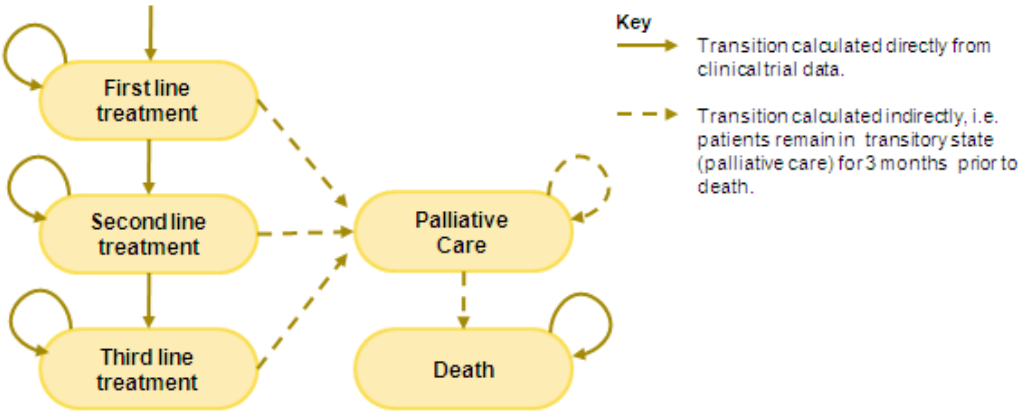
7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A de novo semi-Markov partitioned survival model was developed, in which health-states were used to represent the tiers of treatment. Patient movements between health states are derived using a two-stage indirect transition process. The two-stage indirect transition process is applied as follows (see section 7.3 for further details):

1. Movement between lines of treatments and the proportion of patients who die is calculated first;
2. The proportion of patients on each of the lines of treatment is then adjusted to account for the proportion of patients expected to be receiving palliative care (defined as 12 weeks prior to death).

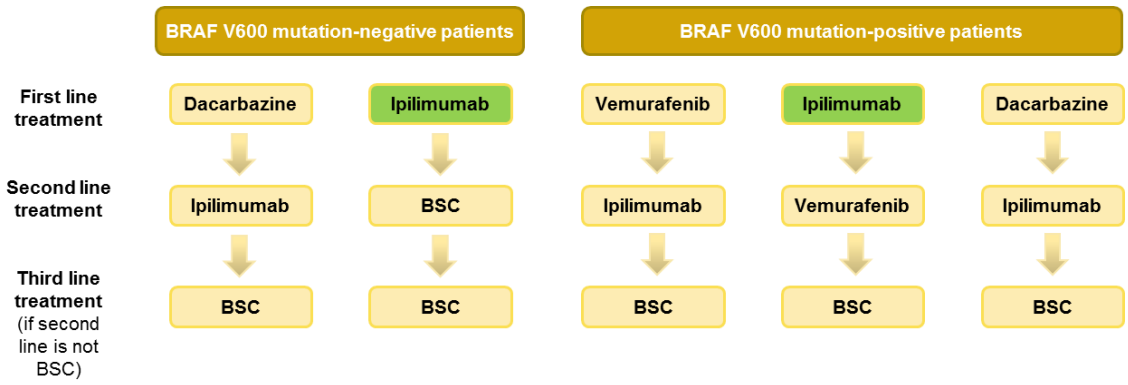
The structure of the model is shown diagrammatically in Figure 25.

Figure 25: Economic model structure (simplified)



The treatment pathway considered is dependent on patients' BRAF V600 mutation status, and the potential treatment patterns are shown in Figure 26, and explained in section 2.5.

Figure 26: Modelled treatment patterns[9, 22, 24, 25, 32]

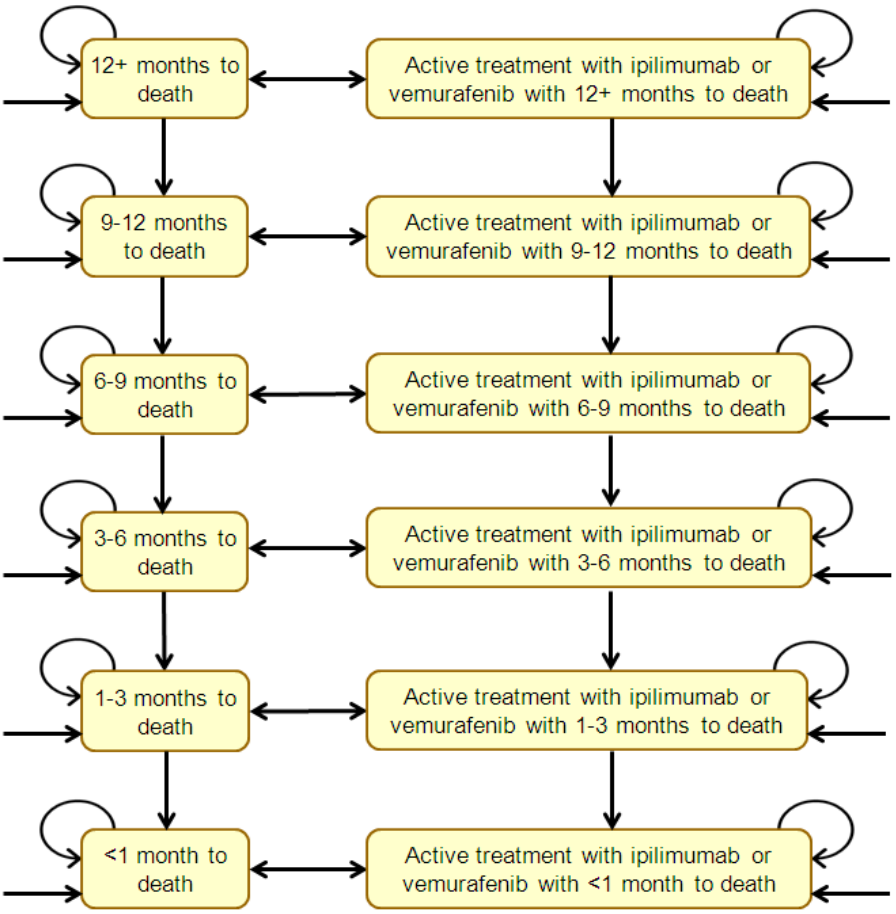


BSC (best supportive care): active treatment used off-license; In the final 3 months of life patients are assumed to receive palliative care.

In an analysis of directly-observed patient-level quality-of-life trial data (converted to utilities), the most meaningful correlation was identified to be between quality-of-life and time-to-death.

Additionally a utility decrement for active treatment with ipilimumab was derived based upon the patient level data, which was also applied to vemurafenib as the number of patients experiencing grade 3+ adverse events is similar. Based on this utility analysis (presented in section 7.4), time-to-death sub-health states are used to represent patients' health-related quality of life (HRQL) over the course of their treatment. These sub-health states are shown in Figure 27.

Figure 27: Sub-health states used to model HRQOL for ipilimumab and vemurafenib treatment



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model health states defined above are designed to represent the lines of treatment as presented in Figure 26 (as well as in section 2.5) to account for the costs and outcomes associated with each line of treatment. Consistent with the treatment pathway identified, the model reflects the pattern of care routinely provided by the NHS in a UK clinical context. The model structure outlined in section 7.2.2 allows estimating the cost and HRQL impact when ipilimumab was implemented as a first-line treatment option, and helps to inform the relevant decision problem.

The model structure is largely consistent with previous models used to represent the treatment of advance melanoma[9, 32] with palliative care modelled as a separate health state rather than solely indirectly as an additional cost as was the case in previous models.

In the majority of cases oncology models use health states defined solely as pre-progression and post-progression. This simple structure would not be appropriate in this case as:

- There is more than one line of active treatment given (Figure 26) – most oncology models only require one line of therapy to be modelled
- There is no link between quality of life and progression status (as demonstrated in section 7.4)

The health states in this model are therefore explicitly defined as treatment lines (i.e. first line, second line, third line) although disease progression is used as a proxy for movement between the lines of treatment (section 7.2.5).

7.2.4 Please define what the health states in the model are meant to capture.

The definition of the health states as lines of treatment is consistent with the treatment pathway and the treatment-dependent costs and outcomes that accompany each component. As patients progress through the lines of treatment included in the model, they incur treatment-specific drug, administration, resource use and adverse event costs.

The hereinafter described approach taken to estimate patients' quality of life was a result of the utility analyses presented in section 7.4. The time-to-death sub-health states (Figure 27), used to quantify HRQL outcomes, capture patient quality of life as a function of how much lifetime patients have left until they eventually decease. Based on the overall survival outcomes of the model, patients are distributed across six health states, each with an associated utility value. In the base case model, a utility decrement is additionally considered for patients on ipilimumab or vemurafenib therapy, to account for the negative impact of treatment-related adverse events on their quality of life.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

For patients treated with vemurafenib or DTIC, disease progression and associated movements of patients from one line of treatment to the next, are based on PFS as reported in the clinical trials (section 6.5.3), as this measure would be expected to be used by clinicians to determine the appropriate timing for a change of therapy.

For patients treated with ipilimumab, however, the situation is less clear as for some patients the usual definition of disease progression may not apply.

Ipilimumab is an immunostimulatory agent (i.e. through its mode-of-action it stops the immune response from being switched off), and therefore the clinical effects seen in ipilimumab patients are slightly different from those usually seen in cancer patients treated with conventional therapies. As the tumour is “stimulated” immunologically it appears to get larger for a short period of time, after which it begins to shrink. Thus, in conventional clinical trial assessment terms, the patient appears to have progressed. However, this is incorrect - the tumour is actually responding to the ipilimumab therapy. Thus, for some patients early assessments do not truly capture the clinical picture, because ipilimumab’s mode-of-action takes time to demonstrate clinical efficacy.[5] Patients on ipilimumab who ultimately achieve a positive clinical outcome may appear to have ‘progressed’ when assessed in the early stages of treatment. PFS is therefore may not be an accurate measure of the eventual response to ipilimumab.[6] For this reason, using PFS as a proxy for the ‘time to next line of treatment’ within the model overestimates the number of patients moving from first-line to second-line treatment, and overestimates costs on the ipilimumab arm. The reason for the latter is that the costs of first-line treatment with ipilimumab are almost static (ipilimumab’s induction dose being 3mg/kg every 3 weeks for a total of 4 doses; the average length of a course of treatment being 3 months), whereas the costs of second-line treatment depend on the time spent on treatment. Thus the earlier and the more patients that switch from first line to second line, the longer the time on second-line therapy and the higher the total costs. Other clinical measures that might have allowed determining more accurate determination of when patients change treatment were not included as a measure in the ipilimumab clinical trials. Therefore, despite the explained limitations of this approach, PFS was used in the model as a proxy for ‘time to next line of treatment’ for ipilimumab.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 32: Key features of the economic analysis

Factor	Chosen values	Justification	Reference
Time horizon	40 years	Lifetime horizon for the patient population defined (<0.001% of patients alive)	NICE Guide to the Methods of Technology Appraisals, 2013[76]
Cycle length	1 week (7 days)	Deemed sufficient resolution to model patterns of treatment administration, disease progression and OS and PFS transitions	N/A
Half-cycle correction	Yes	On advice of the ERG from TA268	NICE Guide to the Methods of Technology Appraisals, 2013[76]
Were health effects measured in QALYs?	Yes	-	
Discount of 3.5% for utilities and costs	Yes	-	
Perspective (NHS/PSS)	Yes	-	
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Ipilimumab's marketing authorisation *"for the treatment of advanced (unresectable or metastatic) melanoma in adults"* is expected in November 2013. The dosing regimen for ipilimumab used in the model matches the updated SPC.[8]

The dosing regimen applied for vemurafenib matches the SPC. The dosing of DTIC matches recommended dosing in the UK (850mg/m^2), based on published literature and the SPCs. DTIC is assumed to be dosed as stated within the CA184-024 clinical trial. Within this trial, treatment ended after the 8th dose. 12.2% of patients received this final dose.[7] Stopping treatment after 8 doses is not a requirement within DTIC's SPC.[77] As survival benefit with survival benefit over observation has never been demonstrated with DTIC it is unlikely that the lack of continuation of DTIC in the clinical trial beyond this point would have any impact on outcomes therefore the only impact will be a reduced cost for DTIC treatment within the model.[78]

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No clinical continuation rules have been assumed in the model. Patients treated with ipilimumab are assumed to receive treatment in accordance with the SPC.[8]

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

As displayed in Figure 26, patients in the model receive first-line treatment depending on their BRAF V600 mutation status (ipilimumab, DTIC or vemurafenib), before progressing onto second-line treatment (consisting of ipilimumab, vemurafenib or best supportive care).

If second-line treatment is ipilimumab or vemurafenib, patients may also progress on to third-line treatment with best supportive care (BSC). BSC is defined as either 'no treatment' or chemotherapy drugs commonly prescribed in the UK, a range of which are used. In the base case model, the breakdown of treatments comprising BSC was taken from the MELODY study (Table 33) as this study contained the largest number of patients (n=220) and additionally is presented as a proportion of patients receiving each treatment rather than a proportion of physicians prescribing each treatment.[37, 42]

Table 33: Breakdown of best supportive care (based upon the MELODY study) [38, 43]

Treatment	Proportion of patients
No treatment	69.5%
DTIC	18.8%
Carboplatin	3.6%
Interferon	3.6%
Vindesine	4.5%

The median duration of BSC (6.6 weeks) was also taken from the MELODY study (the mean was not reported), and patients were assumed to receive the component drugs for this period. After this time, patients were assumed to not receive any active therapy.[42]

Patients could die while in any health state in the model, and were assumed to spend the last 3 months (12 weeks) of life in palliative care to account for the additional costs expected to be incurred in providing end of life care. This is a slightly shorter time period than was used in the previously treated submission[9] of 4 months which was based upon expert clinical advice of a standard duration of 3-4 months. The duration of palliative care has been assumed to be 3 months based upon available data on patient quality of life which shows a large drop in quality of life in the last 3 months compared with the previous 3 months. There is no published literature available to quantify what standard practice is in relation to the provision of palliative care for melanoma in the UK, however, available literature for general palliative care indicates that 3 months may be appropriate.[79, 80 81]

In the two-stage indirect transition process (Figure 25), patient movements are calculated in two steps:

1. Movement between lines of treatments and the proportion of patients who die is calculated first, based on extrapolated trial data (see section 7.3.2).
2. The proportion of patients on each of the lines of treatment is then adjusted to account for the proportion of patients expected to be receiving palliative care.

It is necessary to calculate the patient movements in two steps as the proportion of patients entering palliative care in each cycle is dependent upon the transitions associated with the previous health states (as palliative care is defined as 3 months prior to death). The proportion of patients entering palliative care from each health state is assumed to be proportional to the distribution of patients across the three treatment lines.

Health-related quality of life (HRQL) outcomes were quantified using sub-health states in the model, based on the time to death, as explained in section 7.4. In order to do this, patients from all treatment health states of the main model are distributed across six time-to-death health states, each associated with a different utility value.

The following clinical trial data were used to populate and validate the model:

- CA184-024 pivotal phase III trial (hereinafter referred to as '024 study') in previously untreated advanced melanoma patients that investigates the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy (n=250, up to 5 years follow-up) compared with DTIC monotherapy (n=252, up to 5 years follow-up) → used to model efficacy, utilities and adverse events[20]
- Pooled chemotherapy-naïve dataset: Combined data from three phase II (CA184-004, MDX010-08, CA184-022) and one phase III (MDX010-020) trials in chemotherapy-naïve advanced melanoma patients that report the efficacy of ipilimumab 3mg/kg monotherapy (n=78, up to 5 years follow-up) which formed the basis of the submission to the EMA → used to model efficacy[61]
- Observational study data from study CA184-338 (n=120, up to 1.8 years follow-up) → used as a sensitivity analysis for adverse events and used to validate efficacy[60]

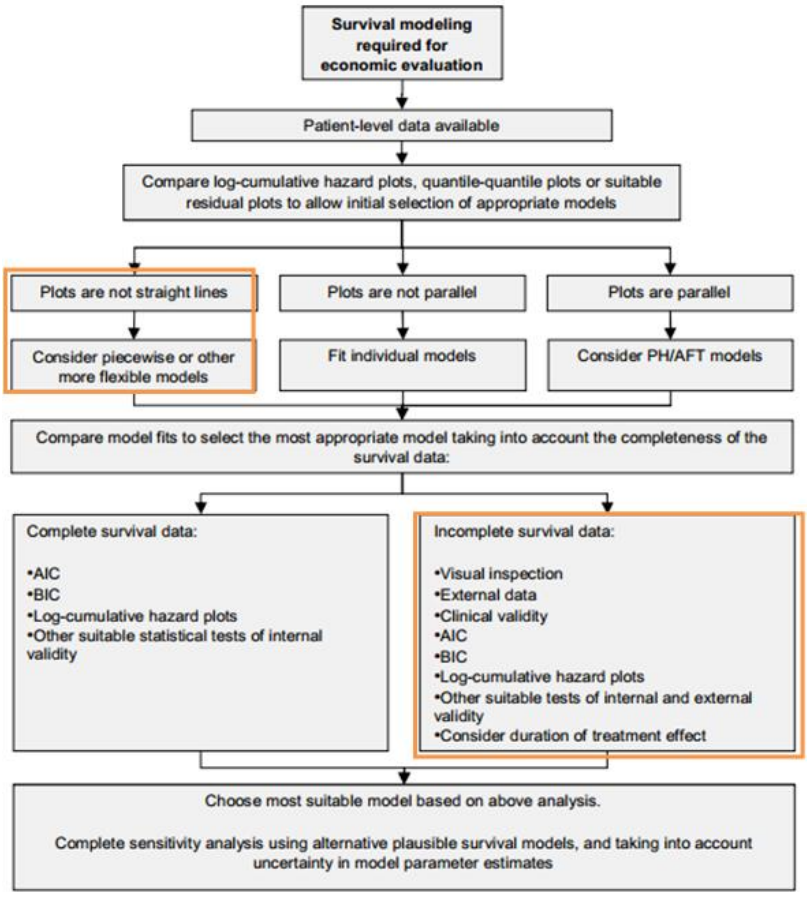
7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Overall survival for first-line ipilimumab and first-line DTIC

In the base case model, first-line ipilimumab and first-line DTIC were modelled using a 3 part curve fit, to account for the survival profile observed for participants of the CA184-024 trial and in the pooled chemotherapy-naïve dataset.

The NICE decision support unit model selection algorithm was used in order to select the most appropriate structure for modelling overall survival (Figure 28).

Figure 28 : Decision Support Unit guidelines for model selection[82]



The following process was used to determine the most appropriate curve fits for use in the model:

1. Inspection of the Nelson-Aalen plot to determine whether the plots are straight lines → Plots are not straight lines (Figure 30 and Figure 31)
2. Fitting of individual standard parametric curves for completeness and sensitivity analysis purposes only → not appropriate as poor fit of data and long-term survival is not accurately captured
3. Inspection of the Nelson-Aalen plot to determine at what point the hazard changes → the breaking point for the change in hazard was determined to be 24 months both for the CA184-024 trial and in the pooled chemotherapy-naïve dataset (Figure 30 and Figure 31)
4. Fitting of a 3 part curve using Kaplan Meier data up to the point at which the hazards change, a parametric curve fit up to 5 years (the extent of trial data available), and registry data thereafter → For graphical presentation see Figure 34
5. Fitting of a piecewise exponential curve for use in sensitivity analysis → presented in appendix D

The process and the findings are described in detail in the sections below.

Standard Parametric Curve Fits

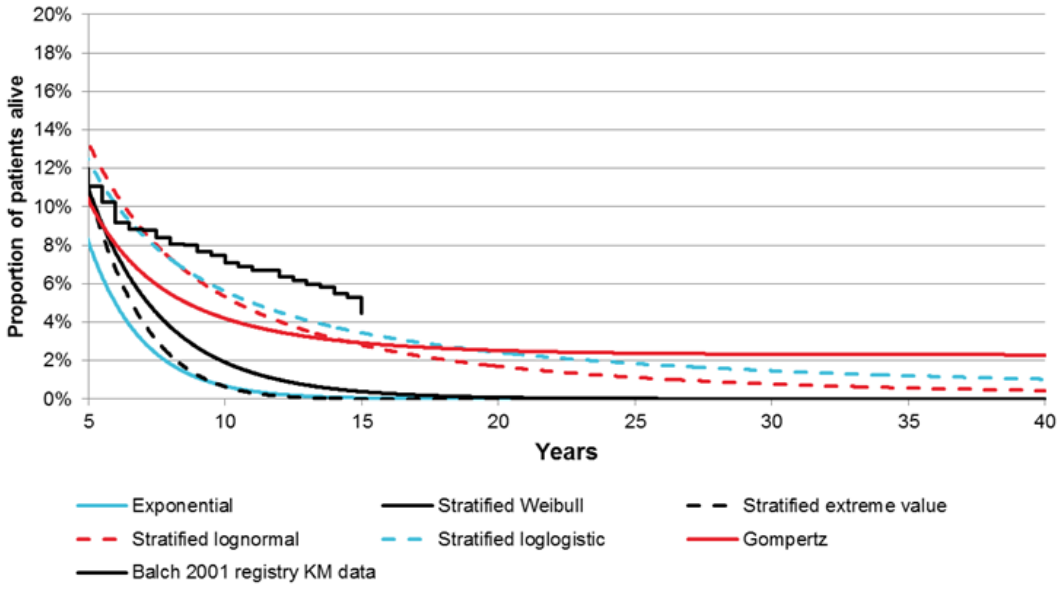
As shown in appendix D, single parametric curves were not sufficient to model the change in hazards over the duration of the trial period (in addition to not being recommended by decision support unit guidance in this case).

Hazards of death start high at the start of the observed period, but are much lower for those patients that survive past 3 to 4 years, and the single parametric curves consistently overestimated patient survival at the beginning of the observed period and underestimated patient survival by the end of the observed Kaplan–Meier data (see appendix D for full curve fits). Figure 29 shows the fit of the single parametric curves compared with registry evidence. There are two issues which are immediately evident:

- The fitted curves are considerably lower than registry evidence would suggest for long-term survival for non-active treatments.
- For 3 of the curve fits (Gompertz, Log-logistc and Lognormal) the curves asymptote to a value above 0 i.e. patients will never die.

This is consistent with the evidence from the submission for previously treated patients.[9]

Figure 29: Single curve fits using CA184-024 trial data for ipilimumab compared with registry data



As presented in appendix D, a 3-part curve fits the data well. This method was used within the submission for ipilimumab in previously treated melanoma patients where the situation was similar. The 3-part curve fit approach was recommended by clinicians as having higher external validity[9, 83], however the use of a piecewise exponential curve (presented as sensitivity analysis) was recommended by the ERG in TA268.[9]

Determination of the Point at which the Hazard Changes

In order to determine at what point the hazards for patients receiving ipilimumab changed the Nelson-Aalen plots were inspected (Figure 30 and Figure 31). The Nelson-Aalen plots show that the hazard is not constant over time (graph top-left). The graphs show a red separation-point at 24 months (year 2) and red fitted lined for below and above the separation-points (plots with alternative cut offs provided in appendix D).

The mean absolute error between the predicted lines and observed data is similar for 18 months (0.031) and 24 months (0.032), but worse for 30 months (0.040); however, a separation point at 24 months provides a better fit for the latter part of the dataset. The 24 month separation point was therefore selected for use within the modelling.

Figure 30 : Nelson-Aalen plot, CA184-024 trial OS data for ipilimumab

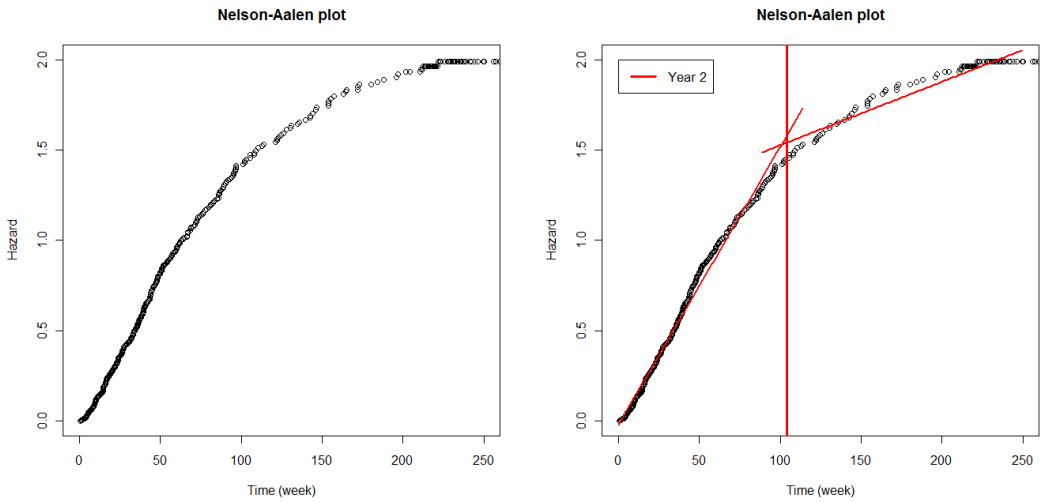
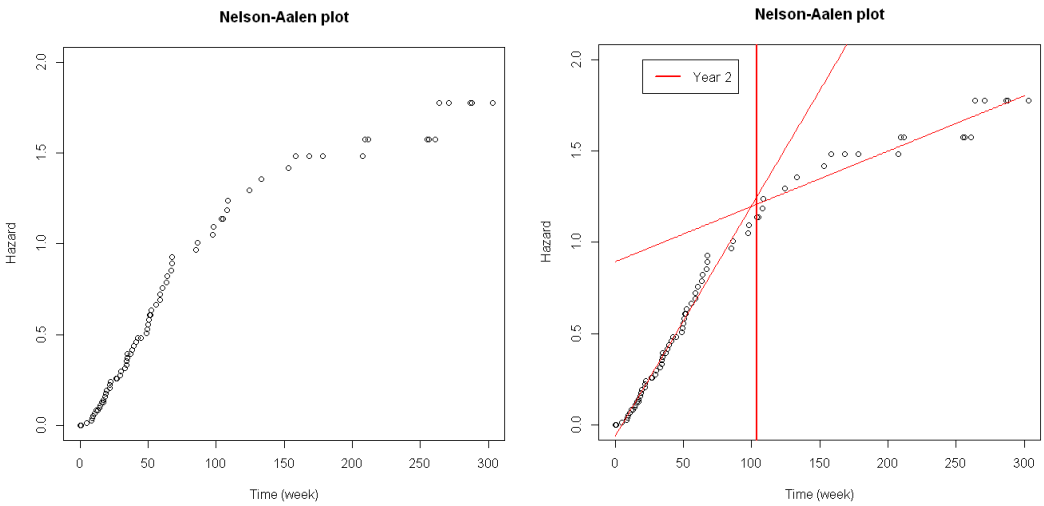


Figure 31: Nelson-Aalen plot, pooled chemotherapy-naïve OS data for ipilimumab



3 Part Curve Fit

Based upon '24 months' being the point at which the hazard changes, a 3 part curve fit was used within the model, in line with the model submitted as part of TA268.

The 3-part curve consisted of Kaplan–Meier data up to 2 years, a fitted parametric curve up to 5 years, from 5 years onwards a curve fitted to long-term registry data from the American Joint Committee on Cancer (AJCC).[84]

The base case curve is described in Table 34 and the parametric curve fits considered are shown in appendix D. The goodness of fit for each of the parametric curves is shown in Figure 32 and Figure 33 as the Akaike information criterion (AIC) and Bayesian information criterion (BIC) for each curve fit.

Based upon the AIC, the base case model uses the stratified lognormal curve fit for the CA184-024 clinical trial data and for consistency the lognormal curve fit for the pooled chemotherapy-naïve dataset, it is noted however that various curve fits may be appropriate therefore a variety of curve fits are tested in sensitivity analysis.

Figure 32: AIC and BIC goodness of fit statistics for first-line OS curve fits for ipilimumab and DTIC using the CA184-024 clinical trial

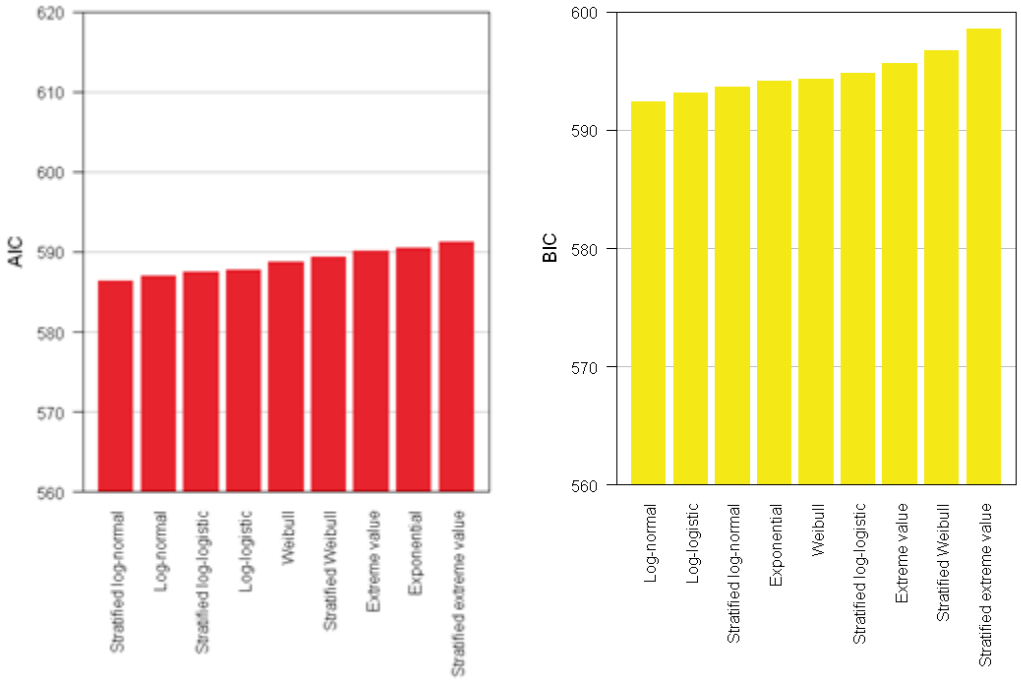
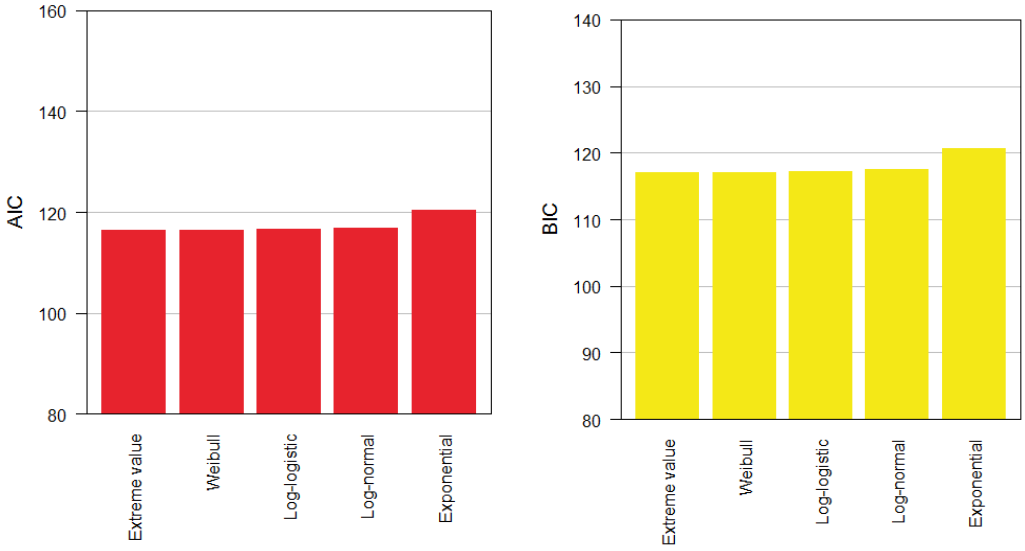


Figure 33: AIC and BIC goodness of fit statistics for first-line OS curve fits for ipilimumab in the pooled chemotherapy-naïve dataset



The AJCC registry data used for the final part of the base case OS curves was modelled using curves fit to digitised Kaplan–Meier data. Kaplan–Meier data are presented separately for stage IIIC and stage IV patient, and so curves were fitted to these datasets and combined using the breakdown by disease stage reported in the CA184-024 clinical trial.

Balch 2001 registry data[84] were selected for base case analysis as stage IV data are presented for 20 years within this analysis, whereas the more up to date analysis[15] presents only 15 years. The impact of using Balch 2009 is tested in sensitivity analysis.

Curves were fitted to patients alive at 5 years (i.e. to the Kaplan–Meier from this point onwards), as shown in appendix D. The goodness of fit statistics for these curves are shown in appendix D. Based on these (and the goodness of fit statistics based upon four years' worth of data, a Weibull curve fit was used for both stage IIIC and stage IV patients.

Using registry data after 5 years assumes that there is no further benefit from ipilimumab beyond the duration of the CA184-024 clinical trial evidence. This is considered to be highly conservative as evidence presented at ESMO indicates continuing benefit above the decline that would be expected using the registry out to 10 years.[85]

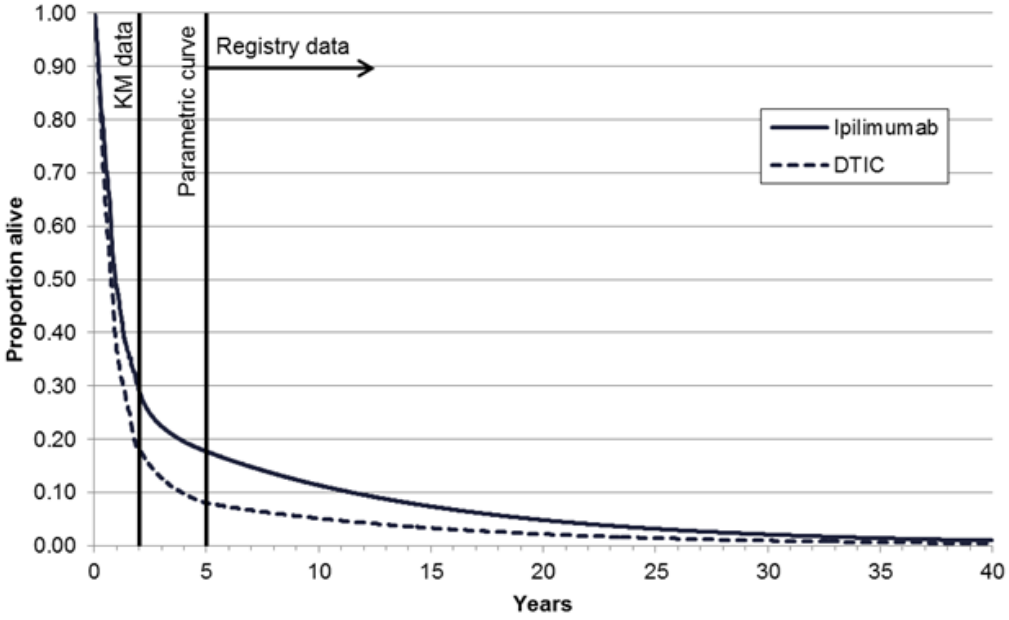
Table 34: First-line ipilimumab and DTIC OS 3 part curve fits

Curve Part	Duration	Curve fit and parameters	Source
CA184-024 analysis			
Kaplan Meier data	Cycles 0-104	N/A	CA184-024 clinical trial
Parametric curve	Cycles 105-260	Stratified Lognormal Ln scale: DTIC 4.8168 Ln shape: DTIC -0.4753 Ln scale: ipi 5.6738 Ln shape: ipi -0.8589	Curve fitted to survival of patients alive at 104 weeks
Registry data hazards	Cycles 261+	Weibull Stage IIIC: Constant -2.5134 ln(p) -0.2139 Stage IV: Constant -2.3854 ln(p) -0.0118	Balch et al. (2001)[Balch 2001]
Pooled chemotherapy-naïve dataset			
Kaplan Meier data	Cycles 0-104	N/A	Pooled chemotherapy-naïve data for ipilimumab, CA184-024 clinical trial for DTIC
Parametric curve	Cycles 105-260	Lognormal Ln scale: ipi 4.2065 Ln shape: ipi -0.1986	Curve fitted to survival of patients alive at 104 weeks, Pooled chemotherapy-naïve data for ipilimumab, CA184-024 clinical trial for DTIC
Registry data hazards	Cycles 261+	Weibull Stage IIIC: Constant -2.5134 ln(p) -0.2139 Stage IV: Constant -2.3854 ln(p) -0.0118	Balch et al. (2001)[Balch 2001]

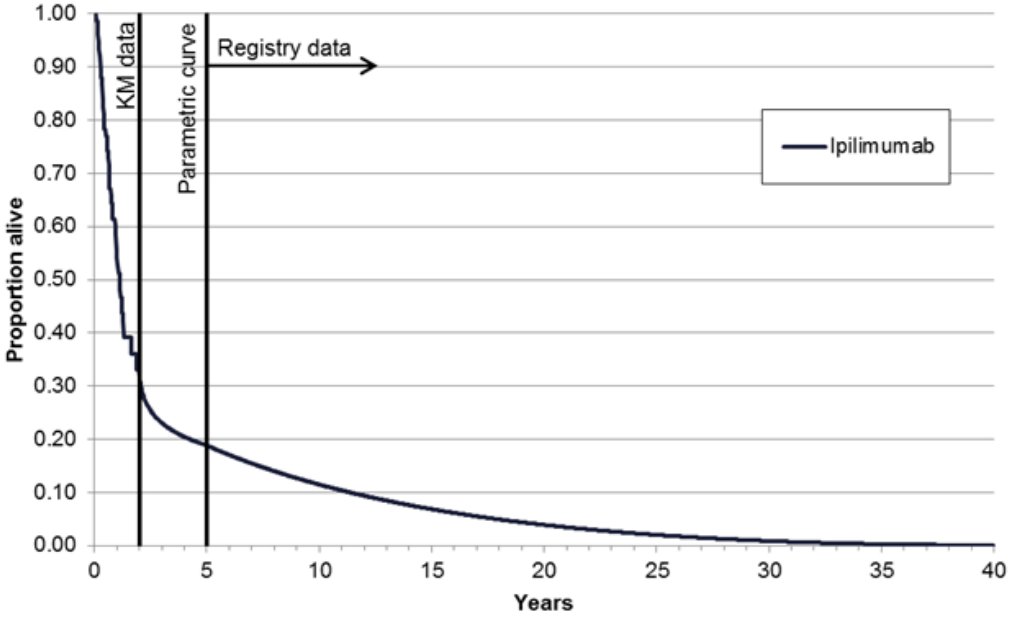
Figure 34 shows the final curve fits used within the model for ipilimumab and DTIC.

Figure 34: First-line ipilimumab and DTIC OS 3 part curve fits

CA184-024 clinical trial data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab

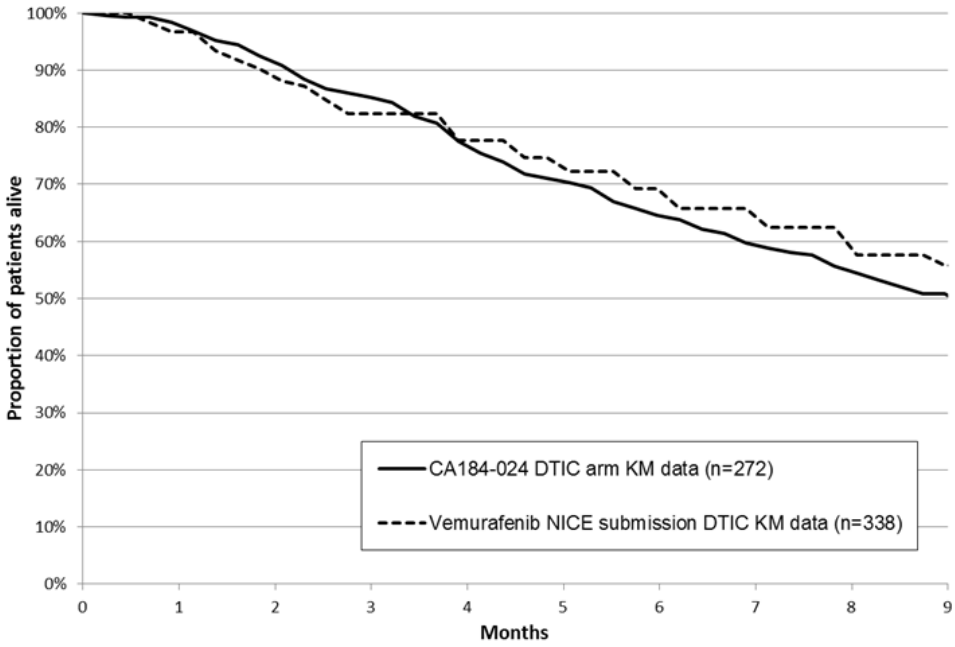


Impact of differences in clinical characteristics between the BRIM-3 trial and ipilimumab trials

No adjustment has been made within the model for differences in patient characteristics (notably BRAF V600 mutation status) between the BRIM-3 trial and the ipilimumab trials. This is based on a visual comparison of Kaplan Meier data on the OS of patients treated with DTIC from the CA184-024 clinical trial and the DTIC arm of the manufacturers submission from the NICE appraisal of vemurafenib, which includes only BRAF V600 mutation-positive patients.[32] This comparison is shown in Figure 35. The overall survival of patients treated with DTIC in both trials is similar suggesting that no adjustment is required.

Ipilimumab's innovative mechanism of action does not restrict use based on BRAF V600 mutation status. As reported in section 6.3.3, post-hoc analyses of 69 patients from study CA184-004 determined that rates of objective response and stable disease were comparable between patients with and without BRAF V600 mutations.[39]

Figure 35: Comparison of DTIC OS Kaplan–Meier data from the CA184-024 clinical trial and vemurafenib NICE appraisal



Modelling overall survival for vemurafenib

First-line vemurafenib is modelled as is reported in the previous NICE STA of vemurafenib.[32] This curve consisted of trial Kaplan–Meier data up to 14 months (60 cycles), followed by three different monthly risks of death between months 14 and 46 (cycles 61-200). At this point, the curve in the NICE appraisal switched to hazards from SEER registry data. Only short term observations are available from this source, so to better predict the hazards and to be consistent with the approach taken for ipilimumab and DTIC, the SEER data were replaced with curves fit to registry data from the AJCC [Balch 2001].[84] A separate curve was fit to registry data from 4 years and applied to cycles 201-261 of the vemurafenib curve, then the curve switched to

the 5 year fitted curves, meaning identical hazards are used for all of the treatment arms after this point.

Fitting AJCC rather than SEER data reduces overall survival on vemurafenib (and also on DTIC compared with the vemurafenib submission) as mortality rates are higher in the AJCC database. The ERG as part of the vemurafenib submission recommended the use of AJCC data rather than SEER data:

> Page 53, section 5.6.2: "In considering the long-term prognosis of patients with malignant melanoma, it is important to use the most complete and detailed registry analysis available. In this case the analysis reported by Balch, which formed the basis for the final 2009 AJCC melanoma staging and classification system, provides the results of sub-classifying metastatic melanoma on the basis of differential survival into four categories (M0, M1a, M1b, M1c in order of reducing expected survival). This study employed data from 7635 patients with metastatic disease at diagnosis and is therefore the most extensive source of relevant information for the population considered in this appraisal."

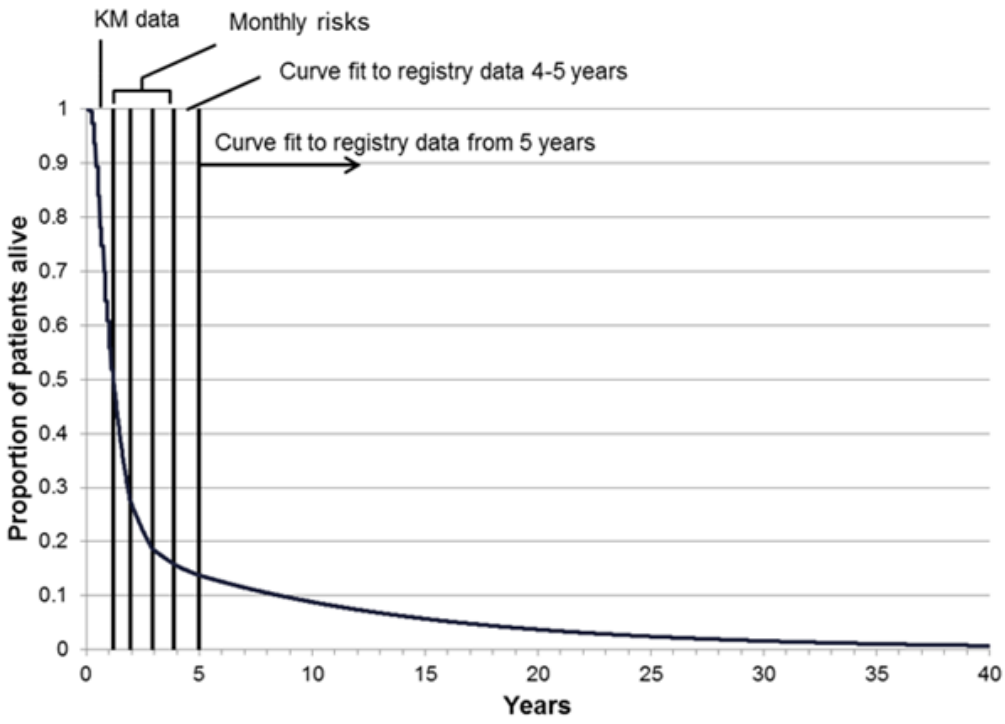
Kaplan–Meier data, curves fit for the registry data from 4 years and goodness of fit statistics are shown in appendix D. Based on these, Weibull distributions were applied to both BRAF V600 mutation-positive and -negative patients. Table 35 and Figure 36 show the curves fit for vemurafenib.

As an additional sensitivity analysis the curve fits considered by the ERG within the vemurafenib submission are also applied within the model (appendix D).

Table 35: First-line vemurafenib OS 3 part curve fit

Curve Part	Duration	Curve fit and parameters	Source
BRIM-3 trial Kaplan Meier data	Cycles 0-60	N/A	NICE TA269[32]
Monthly risk of death	Cycles 61-100	0.0658	
Monthly risk of death	Cycles 101-152	0.0328	
Monthly risk of death	Cycles 153-200	0.0141	
Registry data hazards	Cycles 201-260	Weibull Stage IIIC: Constant -2.2498 ln(p) -0.2517 Stage IV: Constant -2.0388 ln(p) -0.1069	Balch et al. (2001)[84]
Registry data hazards	Cycles 261+	Weibull Stage IIIC: Constant -2.5134 ln(p) -0.2139 Stage IV: Constant -2.3854 ln(p) -0.0118	Balch et al. (2001)

Figure 36: First-line vemurafenib OS 3 part curve fit



Background mortality

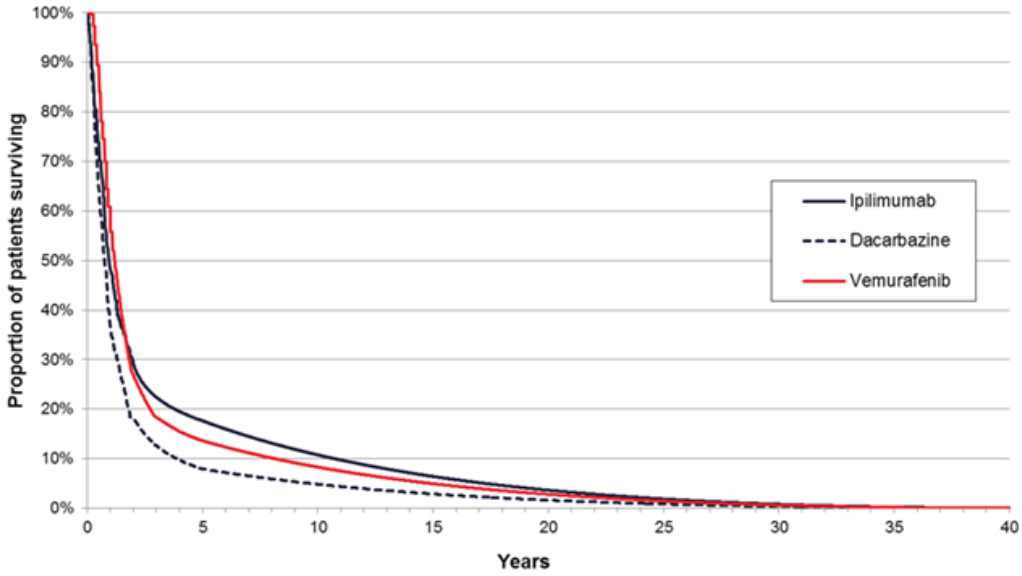
As the AJCC registry data records only melanoma-specific mortality rates, additional age-specific background survival rates were applied while registry data hazards are active. These were taken from Interim Life Tables for England and Wales (2009-2011)[86], as a weighted average of male and female mortality risks using the gender distribution of participants of the CA184-024 clinical trial.

Final overall survival predictions

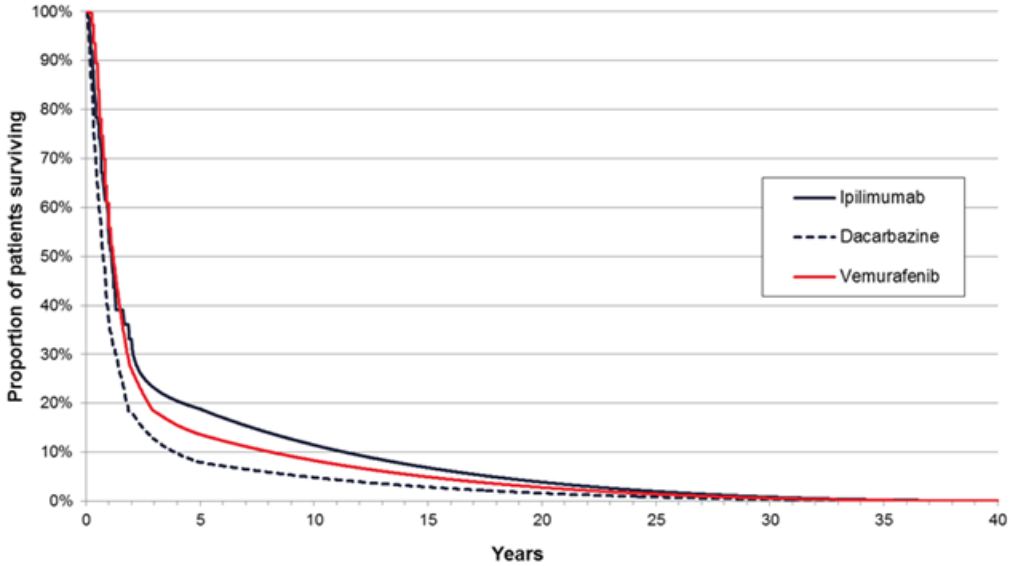
Figure 37 shows the final predictions for overall survival for the 3 treatments included in the model.

Figure 37: Comparative overall survival

CA184-024 data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab



Time on first-line treatment

For patients treated with DTIC and vemurafenib, clinical disease progression using PFS data was determined to be a suitable proxy for change of therapy. As no other information was available, this was also used as a proxy for change of therapy for ipilimumab; this is likely to bias against ipilimumab (see section 7.2.5).

The following process was used to determine the most appropriate curve fits for use in the model:

1. Fitting of standard parametric curves → not appropriate due to extremely poor fit caused by large numbers of patients assessed as progressed at the first assessment (12 weeks).
2. Inspection of the Nelson-Aalen plot to determine at what point the hazard changes → 12 weeks.
3. Fitting of a 2 part curve using Kaplan Meier data up to the point at which the hazard changes.

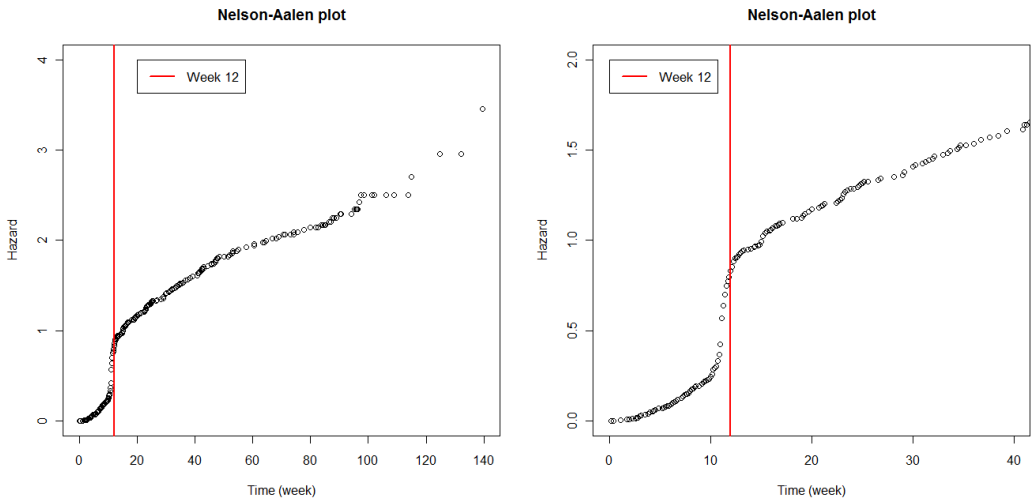
<u>Standard Parametric Curve Fits</u>

As shown in appendix D single parametric curves were not sufficient to model the change in hazards over the duration of the trial period. This is likely due to the time points used to assess progression - the first assessment was not scheduled until 12 weeks. At this point a large number of patients were assessed for the first time (who had likely progressed at some point before 12 weeks), resulting in a large amount of progression at this time.

<u>Determination of the Point at which the Hazard Changes</u>

In order to determine at what point the hazards for patients receiving ipilimumab changed the Nelson-Aalen plot was inspected (Figure 38), which was at 12 weeks, as expected from the a priori reasoning.

Figure 38: Nelson-Aalen Plot, CA184-024 trial ipilimumab PFS data



NB: scales are different

2 Part Curve Fit

Based upon 12 weeks being the point at which the hazard changes, a 2 part curve fit was used within the model, in line with the methodology applied for overall survival.

This consisted of using Kaplan–Meier data from the clinical trials up to week 12, followed by a parametric curve fitted to patients progression-free at week 12. The parameters used for the curve are shown in Table 36.

Parametric curves were fitted to the PFS data that were progression-free at 12 weeks starting from week 12 as shown in Appendix D. The AIC and BIC for each curve fits is shown in Figure 39. Based on both the AIC and BIC, the base case curve fit was a Weibull distribution. Alternative curve fits are tested in sensitivity analysis.

Figure 39: AIC and BIC goodness of fit statistics for first-line PFS curve fits for ipilimumab and DTIC

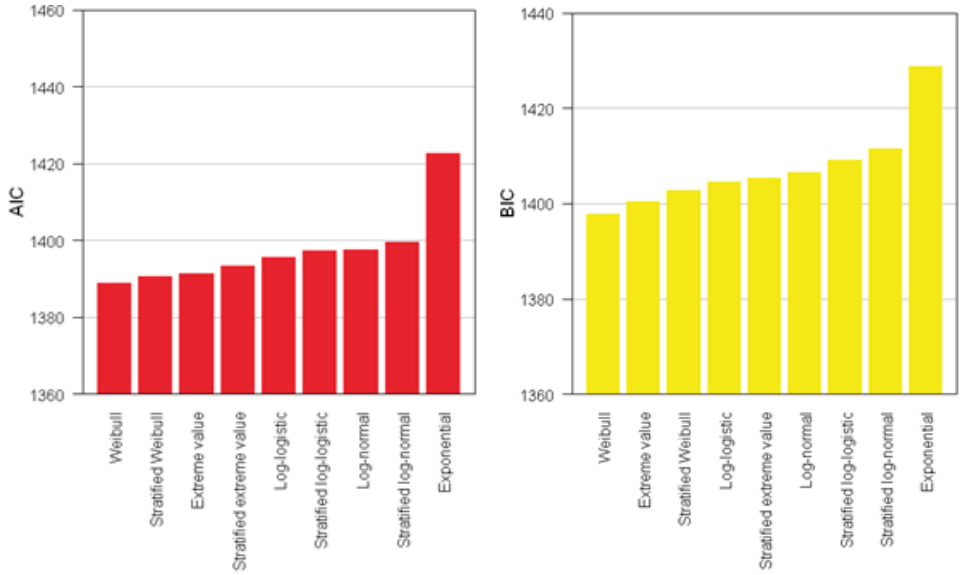


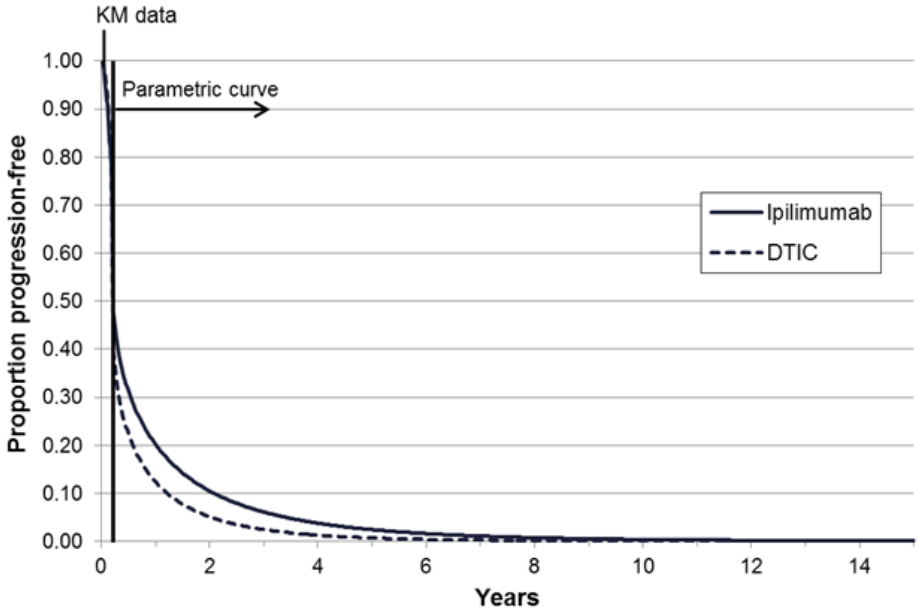
Table 36: First-line PFS two part curve fit: ipilimumab and DTIC

	Curve Part	Duration	Curve fit and parameters	Source
CA184-024 analysis	CA184-024 clinical trial Kaplan Meier data	Cycles 0-12	N/A	CA184-024 clinical trial
	Parametric curve	Cycles 13+	Weibull Treatment -0.441 Ln scale 3.475 Ln shape -0.382	Curve fitted to progression-free survival of patients progression free at 12 weeks
Pooled chemo-therapy-naïve data	Pooled chemotherapy-naïve Kaplan Meier data	Cycles 0-12	N/A	Pooled chemotherapy-naïve data & CA184-024 clinical trial for DTIC
	Parametric curve	Cycles 13+	Weibull Ln scale 3.195 Ln shape -0.635	Curve fitted to progression-free survival of patients progression free at 12 weeks CA184-024 clinical trial for DTIC

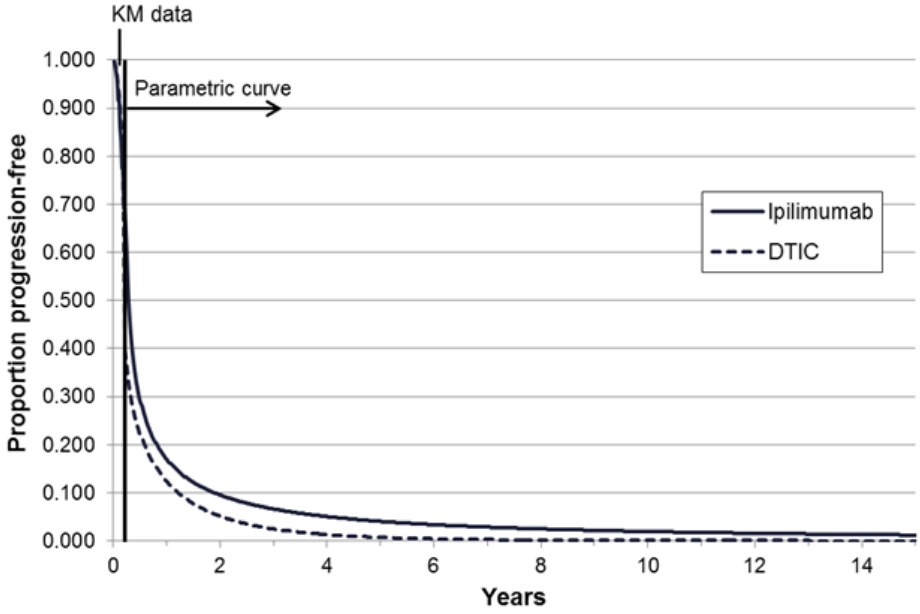
The final PFS curves for ipilimumab and DTIC are shown in Figure 40.

Figure 40: First-line ipilimumab and DTIC PFS two part curve fit

CA184-024 clinical trial data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab



Modelling Time on Treatment for Vemurafenib

Time on treatment for BRAF V600 mutation-positive patients receiving first-line vemurafenib is modelled using the two part curve reported in the NICE appraisal of vemurafenib[32], derived from analyses of the BRIM-3 trial. This consisted of Kaplan–Meier data up to month 9 (cycle 38), then a monthly risk of progression after that (cycle 39+). Table 37 shows the composition of the curve used to model vemurafenib PFS.

Table 37: First-line vemurafenib PFS two part curve fit

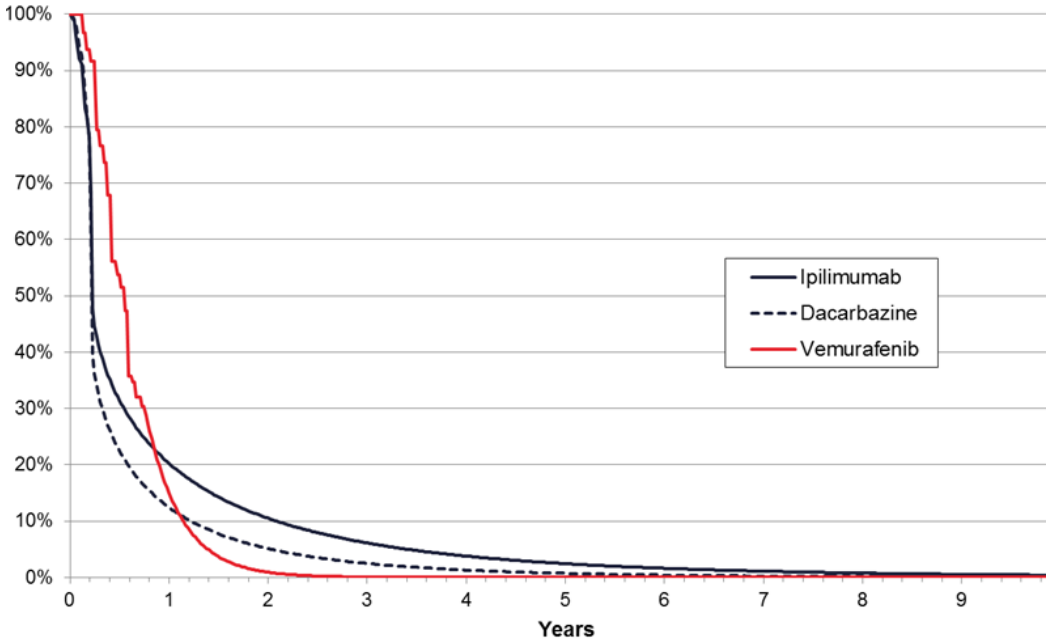
Curve Part	Duration	Curve fit and parameters	Source
Kaplan Meier data	Cycles 0-38	N/A	NICE appraisal of vemurafenib[32] [NICE TA269]
Monthly risk of progression	Cycles 39+	0.2087	

Final time on first treatment predictions

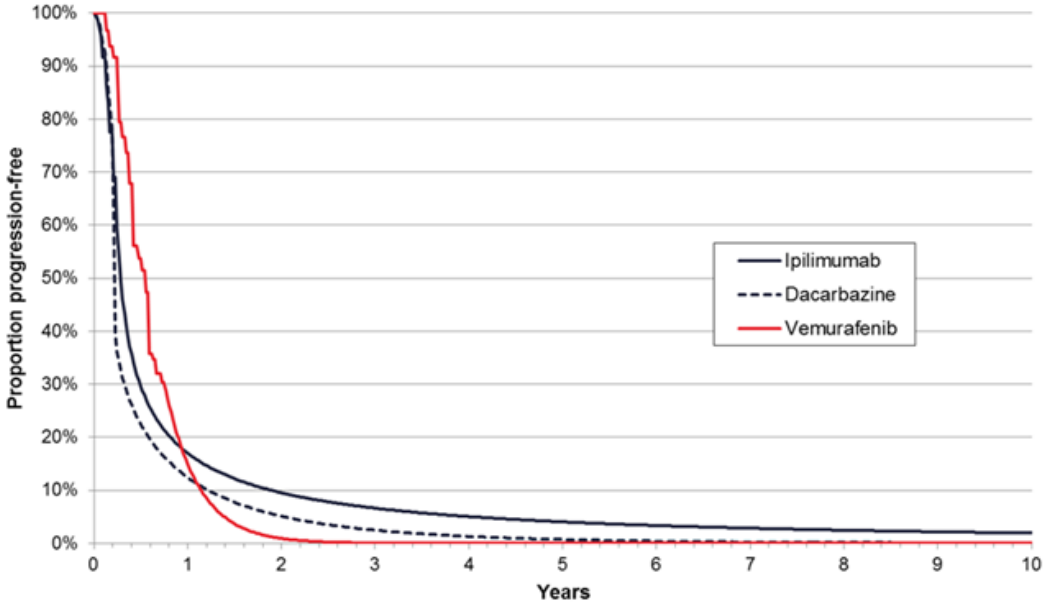
Figure 41 shows the final predictions of the time before moving to the next treatment line (modelled using PFS).

Figure 41: Comparison of PFS curves for ipilimumab, DTIC and vemurafenib

CA184-024 data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab



Second-line overall survival

The OS of patients on second-line treatments has been based on the first-line survival curves, however, was adjusted to account for poorer outcomes on second-line treatment using a hazard ratio (HR). This HR is derived from the expected life years achieved by patients from the second-line NICE appraisal for ipilimumab. The goal seek function in Microsoft Excel was used to calculate the HR that would produce the same number of second-line life years when applied to the first-line survival curves in the model. Using the upper and lower bounds for the second-line life years, upper and lower bound for the HR were generated, and these are shown in Table 38.

Table 38: Hazard ratio used to adjust for second-line overall survival

	Mean	Lower bound	Upper bound
CA184-024 data	1.211	1.121	1.332
Pooled chemotherapy-naïve dataset	1.262	1.163	1.389

Duration of response to second-line treatment

The duration of response to second-line treatments is derived from the number of pre-progression life years from the economic model evaluating second-line ipilimumab, used in the previous NICE appraisal.[9] The mean number of cycles spend pre-progression in the second-line model is used to generate a per-cycle risk of progression using the following formula,

$$P(prog) = 1 - e^{\left(-\frac{1}{D}\right)}$$

where P(prog) is the probability of progression from second-line treatment, and D is the mean duration of response in cycles.

As the duration of vemurafenib second-line is unknown, the median duration of response reported by Chapman et al.[55] (2011) is reduced by the same proportion as second-line ipilimumab. To do this, a multiplier is generated from the mean pre-progression life years from the second-line model, and the mean life years from the curve fit to first-line ipilimumab.

Adverse events

The incidences of adverse events for patients treated with ipilimumab were taken from the CA184-024 clinical trial. Event incidences for patients treated with vemurafenib were taken from Chapman et al.[55] Based on data from the patients treated with DTIC in the CA184-024 clinical trial, no events met the inclusion criteria. As a result, the incidence of all adverse events was set to 0% for these patients. For BSC, the source of the incidences for the component drugs can be found in appendix E. The inclusion criteria for adverse events in the model were any grade 3+ event, or grade 2+ for diarrhoea, with an incidence greater than or equal to 3%. In addition all endocrine disorders are included as these are known to be a serious event associated with treatment with ipilimumab.[8]

These inclusion criteria were produced with the help of clinical experts as part of the submission for previously treated patients for ipilimumab.[9]

For the base case model, the proportions of patients suffering each type of event on treatment with ipilimumab, vemurafenib and best supportive care are shown in Table 39.

Table 39: Adverse events risks associated with ipilimumab, vemurafenib and BSC treatment

Adverse Event	Ipilimumab[7]	Vemurafenib[55]	Best supportive care using MELODY definition[42]
Myalgia/Pain			0.18%
Skin Reaction		8.33%	
Fatigue			0.60%
Hypotension*			
Diarrhoea (not including colitis)	6.07%		1.64%
Colitis*			
Dyspnoea			0.37%
Resp. Distress/Pulm. Oedema*			
Anaemia			0.67%
Neutropenia			0.25%
Endocrine disorders	0.40%		
Arthralgia		3.27%	
* included within the definition of BSC for sensitivity analyses using either Collinson et al or Oxford Outcomes, see Appendix E			

Costs for adverse events are applied at the start of the model for first-line treatments, and in the first cycle of treatment for second and third lines. For ipilimumab, the costs for endocrine disorders are assumed to re-occur every 6 months based upon clinical expert advice from the previously treated submission.[9]

As utility decrements are already incorporated in the utility equations, which include a treatment effect of ipilimumab and vemurafenib that accounts for the HRQL impact of adverse events, there is no separate decrement to quality of life resulting from the above adverse events applied within the model (section 7.4).

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Patient movements between states each cycle are calculated in a manner that allows them to be time-dependent. The methods by which these patient movements have been derived are explained in section 7.3.1 and section 7.3.2.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Patient movements

For patients treated with ipilimumab, the time it took them to receive another therapy after stopping ipilimumab was used as a proxy for them moving to the next tier of treatment.

For patients treated with DTIC and vemurafenib, clinically defined disease progression was used as the intermediate outcome indicating that a patient would move onto subsequent therapy in line with UK clinical practice.

Quality of life

Patient HRQL was estimated from time to death as an intermediate outcome. In analyses presented in section 7.4, this was determined to be the most meaningful way of estimating HRQL, as disease progression, the typical outcome used to model patient utility, was deemed to be a poor predictor based on direct observations of patients participating in the CA184-024 clinical trial and experience from the MDX010-20 clinical trial.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Clinicians were not consulted specifically for this submission, however, clinicians were consulted regarding the following topics as part of the ipilimumab submission for previously treated patients:

- Time horizon
- Survival analysis
- Dosing
- Adverse events

Four leading clinical experts were approached in order to validate the economic model during individual face-to-face informal interviews. These experts were selected as key opinion leaders for melanoma practicing in the UK. The model was presented to the clinical experts during the interviews.

The clinical experts suggested that a life-time horizon should be used as it is observed in clinical practice that a few patients do live to near normal life expectancy. In addition, the reference case in NICE method guide requires a life-expectancy time horizon. This implies that if the average age of patient is around 50s (as reported by several clinical trials), the time horizon should be at least 30 years.

The clinicians commented that the unusual long-term survival observed in a group of patients at the end of MDX010-020 trial could be a unique phenomenon of immunotherapy such as ipilimumab, and this should be taken into account in the economic modelling. The Kaplan–Meier data for patients treated first line is similar in shape to the data from MDX010-020.

The clinicians commented that the ipilimumab re-induction observed in MDX010-020 is a reflection of real-life clinical practice; clinicians will not give more re-inductions than what have been observed in the trial and that the most relevant weight data to use when costing ipilimumab was from UK patients within the trial and patients within the compassionate use program.

The clinicians commented that the adverse events (AEs) associated with ipilimumab are different from other cancer treatments and need to be managed carefully. Serious (grade 3 and grade 4) AEs are associated with significant costs, but most grade 1 and 2 AEs can be managed at an earlier stage without expensive interventions. They recommended the inclusion of all grade 3+ adverse events experienced by 3% or more of patients, grade 2 diarrhoea as this can be expensive to treat and all endocrine adverse events as costs for these can be long-term.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

A list of parameters is provided in appendix F.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Both cost and clinical outcomes are extrapolated beyond observed follow-up periods. For clinical outcomes, the methods used to perform this extrapolation are presented in sections 7.3.1, 7.3.2. and 7.3.2 also contains the Kaplan–Meier data on which long-term extrapolations are based.

For OS, the application of registry and Office of National Statistics data to all treatment arms after 5 years means that it is assumed that there is no difference in the risk of death between ipilimumab, DTIC and vemurafenib after this point.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 40: List of model assumptions

Area	Assumption	Justification
Treatment pathway	The most relevant comparisons based upon current guidelines (Figure 26) are as follows: BRAF V600 mutation-positive • Ipilimumab -> Vemurafenib -> BSC • Vemurafenib -> Ipilimumab -> BSC • DTIC -> Ipilimumab -> BSC BRAF V600 mutation-negative • Ipilimumab -> BSC • DTIC -> Ipilimumab -> BSC	Based upon current national guidelines as presented in Figure 26 and section 2.4 and 2.5. Sensitivity analysis is also presented with no active 2nd line treatments
Time horizon	40 years	Lifetime time horizon (<0.001% of patients alive at this point) in line with the reference case[76]
Efficacy (OS and time to next line of treatment)	Equal efficacy of ipilimumab within the CA184-024 clinical trial at 10mg/kg and 3mg/kg	Analysis is presented both using the CA184-024 clinical trial which contains comparative information versus DTIC and using the pooled chemotherapy-naïve dataset analysis submitted to the EMA. Overall and PFS outcomes are similar using the two datasets (section 7.3.2).
	Equal efficacy of ipilimumab in BRAF V600 mutation-positive and -negative patients	Post-hoc analysis of a subgroup of 69 patients from the CA184-004 trial indicated that there was no difference in the rates of objective response and stable disease based on BRAF V600 mutation status.[39]
	No difference in efficacy for DTIC arms in the CA184-024 and BRIM-3 trials therefore it is possible to directly apply curves from the vemurafenib appraisal into the model	Visual comparison of the DTIC arms from the CA184-024 clinical trial and the vemurafenib NICE appraisal does not suggest that there is any difference (section 7.3.2).

Area	Assumption	Justification
	PFS can be used as a proxy for the time to next line of treatment	This is standard clinical practice for DTIC and vemurafenib. For ipilimumab using progression as a proxy will overestimate the number of patients moving to second-line treatment as it is possible for patients to initial progress and then become stable or respond to therapy due to its mode of action. The impact of this assumption within the model will be an overestimation of costs on the ipilimumab arm – as the costs of first-line treatment are fixed (ipilimumab is given as induction and re-induction therapy as demonstrated in the clinical trial) and the costs of second-line treatment are linked to the time spent on treatment (section 7.3.1).
	That the per-cycle risk of death is equal between ipilimumab, DTIC and vemurafenib after 5 years	Although there is evidence that ipilimumab may result in long-term survival, the risk of death after 5 years is conservatively assumed to be equal between arms (section 7.3.2).
HRQoL	The quality of life of patients is most accurately represented by the utilities derived from trial data dependent upon time to death and treatment received	As demonstrated in section 7.4 time to death shows the greatest correlation with utility additionally the utilities from the analysis of patient level data are similar to EQ-5D utilities presented within the literature.
Safety	Adverse event data taken from CA184-024 is assumed to be representative of the experience for patients receiving 3mg/kg	This assumption is tested in sensitivity analysis using data from CA184-338 (See appendix G)
Movement of patients within the model	Patients entering palliative care are distributed according to the proportion of patients within each line of treatment within that cycle	Simplifying assumption

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The burden of metastatic melanoma from the patient perspective has been evaluated in several clinical trials using a variety of health outcome questionnaires.[87] Studies indicate that there are three distinct periods of HRQL impact experienced by patients with melanoma: diagnosis, treatment and follow-up. The immediate period following diagnosis (acute survival phase) was often associated with high levels of HRQL impairment. Patients reported more pain, less energy and more interference of stressors (physical and emotional) on social activities. Acute survival is followed by extended survival, which is dominated more by fears of recurrence and less by the physical limitations the cancer or its associated therapies create.[87] The most common patient-reported, HRQL impairments are elevated pain and fatigue, with a concomitant decrement in physical and emotional functioning.[88]

Treatment related toxicities can also have an impact on quality of life with symptoms such as diarrhoea, nausea, stomatitis, hair loss and flu-like syndrome being associated with many treatments given for advanced melanoma.[89]

About one-third of patients with melanoma have reported clinically significant levels of distress, which is in accordance with findings in other cancers. Distress was highest around the time of diagnosis and immediately post-treatment, and decreased over time.[87]

Quality of life is widely recognised as a prognostic factor for survival in metastatic melanoma.[90-92] HRQL is often similar to the expected quality of life of members of the general population until the months immediately prior to end of life.[16-18, 93]

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

A patient's utility would be expected to increase or remain the same if the patient survives in the long-term due to clinical improvement.[16, 18, 87, 93] For patients who do not become long-term survivors quality of life has been shown to decrease with a large reduction in patient quality of life seen in the month prior to death.[16, 93] See Section 7.4.4 and 7.4.14 for how HRQL change over time is included in the model.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Method of elicitation, valuation and consistency with the reference case

HRQL data were collected in the CA184-024 trial using the EORTC QLQ-C30. 495 patients completed at least one questionnaire. Utilities have been derived from the EORTC QLQ-C30 using the valuation algorithm produced by Rowen et al.[94] These utilities are broadly consistent with the NICE reference case as the valuation algorithm uses an instrument valued by members of the general population using time trade off and are consistent with the utilities supplied within TA268.[9]

Method of valuation

Patient responses were converted to an eight-dimension preference-based measure, the EORTC-8D, using an algorithm published by Rowen et al.[94] Additional details regarding this algorithm are provided in appendix H.

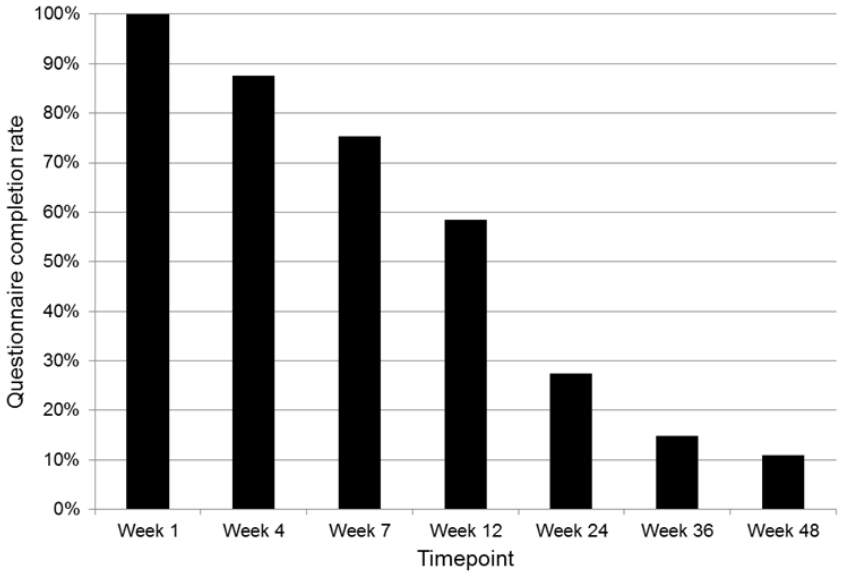
62 (2.38%) observations from the EORTC QLQ-C30 dataset could not be used to generate utility values due to missing data. This is lower than the dataset as a whole, as only 10 out of 30 EORTC QLQ-C30 questions are used in the EORTC-8D algorithm.

Points when measurement of EORTC QLQ-C30 was taken and completion rates

EORTC QLQ-C30 questionnaires in the CA184-024 trial were completed at weeks 1 (baseline), 4, 7 and 12 of the induction phase of treatment, weeks 24, 36 and 48 of the maintenance phase and subsequent weeks during follow-up. The number of questionnaires completed by each patient ranged from 1 to 20.

Complete HRQL profiles were available for 477 randomised patients. Data were missing for at least one variable in 164 (6.3%) of questionnaire observations. This was deemed to be low enough not to warrant imputation of missing values. Baseline questionnaires were completed by 477 patients; completion rates at subsequent time points are shown in Figure 42. Beyond Week 48 (n=52), observations continued up to Week 228 (n=1). A full list of the number of patients at each assessment can be found in appendix H.

Figure 42: EORTC QLQ-C30 questionnaire completion rates across weeks 1 to 48 in CA184-024



Summary of analyses performed

Three types of analyses were performed to determine the most appropriate structure to model utilities within the cost effectiveness analysis:

1. Assessment of the relationship between progression status and utility
2. Assessment of the relationship between utilities and time-dependent variables, including time to and from progression and time to death
3. Assessment of the interaction between treatment effect and the most appropriate time dependent variable for use in the modelling

Based upon this analysis, time to death was determined to be the best predictor of patient utility, as time to death showed the highest correlation with quality of life, and was hence used in the base case model.

The three analyses are described in the paragraphs below.

<u>Relationship between progression status and utility</u>

Each patient progression date was used to determine whether each quality of life observation was taken before or after they had clinically progressed. The mean and distribution of utility values for patients pre- and post-progression were calculated. For pre-progression patients, utility estimates ranged from 0.35 to 1, and for post-progression patients values ranged from 0.43 to 1.00. Pre- and post-progression utilities are shown in Table 41, split by treatment group. There was no statistically-significant difference between the EORTC-8D utilities of patients pre- and post-progression. Histograms of the distribution of utility values for patients' pre- and post-progression are presented in appendix H.

Table 41: EORTC-8D utilities by progression status and treatment group

	Pre-progression		Post-progression		p-value
	n	Mean Utility (SD)	n	Mean Utility (SD)	
Placebo + DTIC	843	0.8452 (0.1377)	160	0.8383 (0.1433)	0.5616
Ipilimumab + DTIC	694	0.8398 (0.1366)	168	0.8298 (0.1357)	0.3915
All patients	1537	0.8428 (0.1372)	328	0.8339 (0.1393)	**0.2895**
DTIC: dacarbazine; EORTC-8D: European Organization for Research and Treatment of Cancer – Eight dimensions					

Relationship between time to and from progression and time to death and utility

Analyses were performed to assess the relationships between changes in utility over time and different time-dependent outcomes. Utility was compared with time from baseline, time to death, time to progression and time from progression. Time from baseline was calculated from the date of assessments and the baseline observation.

Time to death was calculated from the date of assessments and the time of death, given as the date of the baseline observation plus the duration of the patient's overall survival in days. In these analyses, patients with censored overall survival were removed to ensure certainty in the death of death.

Time to progression was calculated from the date of assessments and the time of progression, given as the date of baseline observation plus the duration of the patient's PFS in days. In these analyses, patients with censored PFS were removed to ensure certainty in the date of progression.

Similarly, time from progression was determined for each observation as the number of days elapsed since a patient's progression date. Time to death, time to progression and time from progression were condensed into categorical variables in order to calculate mean utilities for different patient groups. The variables were grouped into categories of <1, 1-3, 3-6, 6-9, 9-12 and >12 months to/from the event.

Table 42 shows correlation coefficients between EORTC-8D utility estimates and four time variables: a) time from baseline, b) time to death, c) time to disease progression and d) time from disease progression.

Table 42: Correlation coefficients of time variables with respect to utility

Variable	Correlation coefficient
Time from baseline	0.16378
Time to death	0.31204
Time to disease progression	0.18741
Time from disease progression	0.18672

Utility estimates are plotted against each of these variables in appendix H. For time to death, time to progression and time from progression, logarithmic trend lines were fitted to determine the strength of the relationships.

Mean utility values were also summarised by time to death, time to progression and time from progression as categorical variables, and this is presented in Table 43.

Table 43: Average utilities by categorical time point

	N	Mean	SD
Time to death			
<1 month	49	0.633408	0.145942
Months 1-3	232	0.74131	0.153492
Months 3-6	336	0.807926	0.131085
Months 6-9	301	0.845007	0.130789
Months 9-12	221	0.867973	0.115384
Months 12+	676	0.885777	0.112202
Time to progression			
<1 month	347	0.781251	0.157128
Months 1-3	713	0.838923	0.132092
Months 3-6	190	0.891895	0.105457
Months 6-9	113	0.912681	0.086657
Months 9-12	64	0.893156	0.101154
Months 12+	110	0.876345	0.125926
Time from progression			
<1 month	72	0.822264	0.150439
Months 1-3	108	0.795898	0.149452
Months 3-6	57	0.863211	0.130273
Months 6-9	29	0.854966	0.114751
Months 9-12	21	0.842476	0.126464
Months 12+	41	0.894756	0.090923

SD: standard deviation

Based upon this analysis time to death was determined to be the best predictor of patient utility as time to death showed the highest correlation with quality of life and results were internally consistent (the lower the time to death the lower the utility).

Relationship between time to death, treatment and utility

In order to assess the effect of time to death and treatment on patient utility, as well as the random variation in individual utility values, a mixed effects regression model was built. The model consisted of two components:

- A fixed effect component which models the impact of each categorical time to death and whether or not the patient was treated with ipilimumab.
- A random effects component which describes the patient variation within each of the groups defined by time to death and treatment.

By including treatment group in the regression, the impact of treatment related adverse events on quality of life was incorporated into utility estimates. The fit of the models was examined by plotting predicted values against those observed in the trial. The results of the fixed elements of the models were also presented, for each time to death category and treatment arm. Figure 43 shows the model used to predict the utility values for patients based the EORTC-8D utility scores generated from the trial observations.

Figure 43: Mixed effects regression model fit to EORTC-8D utilities

EORTC_UTILITY	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_ICAT_TIME__2	.1084549	.0147604	7.35	0.000	.0795251	.1373848
_ICAT_TIME__3	.1793933	.0154161	11.64	0.000	.1491783	.2096084
_ICAT_TIME__4	.2233947	.0160104	13.95	0.000	.1920148	.2547746
_ICAT_TIME__5	.248883	.0165405	15.05	0.000	.2164643	.2813017
_ICAT_TIME__6	.2544198	.0162519	15.65	0.000	.2225666	.286273
_ITx_1	-.0205837	.0110921	-1.86	0.063	-.0423238	.0011564
_cons	.6307192	.0157866	39.95	0.000	.599778	.6616604

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
PID: Identity				
sd(_cons)	.1027197	.0042197	.0947734	.1113322
sd(Residual)	.076234	.0014346	.0734734	.0790983

EQ-5D: European quality of life-5 dimensions questionnaire

Treatment with ipilimumab was not a significant predictor of utility (p=0.063), although there was a trend towards a slight reduction in utility with ipilimumab treatment (-0.02). This is expected to be a result of the adverse event profile of ipilimumab compared with DTIC.

The graphs in appendix H show the predicted utility values against those generated from trial observations and the residuals of the predicted values. Both of these graphs give an idea as to the degree of patient variation there is in each patient group. A weak positive correlation can be seen in the first graph, with observed values increasing with health states that are expected to be better (further from death and not treated with ipilimumab).

As there is no trend in the distribution of residuals across the health states, this suggests that the random patient effect is constant across the defined health states.

Table 44 shows the expected utilities from the fixed component of the regression model, giving an average estimate for each time to death and treatment group. The impact of ipilimumab on utility is included within this analysis in order to be conservative, despite the non-significant p value. Utilities are similar to those seen in the analysis without the inclusion of treatment effect (Table 43).

Table 44: EORTC-8D regression utility estimates

Time to death	DTIC	Ipilimumab	Vemurafenib
<1 month	0.6307192	0.610136	0.610136
Months 1-3	0.7391741	0.71859	0.71859
Months 3-6	0.8101125	0.789529	0.789529
Months 6-9	0.8541139	0.83353	0.83353
Months 9-12	0.8796022	0.859019	0.859019
Months 12+	0.885139	0.864555	0.864555

* assumed the same as ipilimumab (see section 7.4.8)

Goodness of fit

The AIC was generated for the mixed effects regression fit to the data. For comparison, an identical regression model was built without the treatment effect included, to assess the goodness of fit of the model with and without the treatment effect.

Table 45: AICs for mixed effects regressions with and without treatment effect

Model	AIC
Time to death only	-3338
Time to death and treatment effect	-3339

The AICs show that the addition of treatment effect results in a slight improvement of model fit, but that the two models are roughly equal in terms of goodness of fit, hence for the base case model time to death with treatment effect was considered as the most conservative option.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic review was conducted in May 2013 to identify utility and HRQL studies for advanced (unresectable or metastatic) melanoma. A precise search strategy was used including terms for HRQL and advanced (unresectable or metastatic) melanoma, see appendix 12 for details.

In order to ensure the published literature was comprehensively reviewed, a wide range of databases were searched in the week commencing 20th May 2013. These included: Medline, Embase, NHS HEED, HTA database, DARE, CINAHL, and

Econlit. In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies identified were hand searched and scanned for additional publications of relevance to the research question.

Having identified studies from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. Table 46 shows the inclusion criteria for assessing the relevance of the different studies.

The papers that, after a detailed review of the title and abstract, appeared to meet the inclusion criteria, were obtained for a secondary review. This involved the entire article being assessed according to the criteria outlined in Table 46.

Table 46: Eligibility criteria for utility and HRQL studies and rationale for each criterion

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Studies reporting utilities or HRQL data	The aim of the review was to identify relevant utility data
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To allow all relevant papers to be identified
Outcomes	Any reported measurement in the form of utilities was included. Also utility values mapped from a measure of HRQL.	The aim of the review was to identify relevant utility studies
Exclusion Criteria		
Category	**Exclusion criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were being hand-searched)	Primary study articles were required

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.

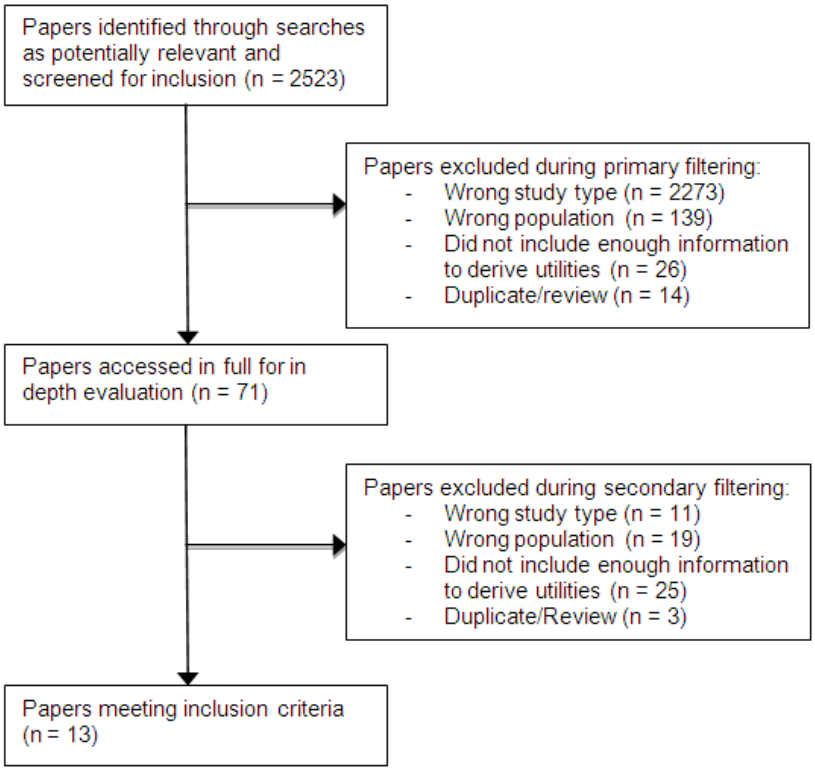
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Identification of relevant studies

As illustrated by Figure 44, a large proportion of the initially identified papers failed to meet the inclusion criteria as given in Table 46. The main reason for exclusion during primary filtering, excluding 2,273 of 2,523 papers, was because they were the wrong study type. Other papers were excluded because they were measuring in the wrong population or had quality of life outcomes which were not utilities and could not be mapped to utilities with the available information. In addition, duplicates and reviews were excluded.

During secondary filtering, most papers were excluded because they had HRQL outcomes that could not be mapped into utility values. Other papers were excluded for the same reasons as during primary filtering. One paper could not be accessed. This left thirteen studies that met all the inclusion criteria both after primary and secondary filtering. These studies are described below.

Figure 44: Identification of utility and HRQL studies relevant to the decision problem



Overview of the Relevant Studies

Thirteen studies are included that report relevant HRQL data. Seven of the studies directly measure quality of life. Beusterien et al (2009)[89] and Hogg et al (2010)[95] measure utilities and utility decrement for 8 toxicity states in members of the general public. Dixon et al (2006)[18] and King et al (2011)[96] measure utilities in the melanoma

population. Askew et al (2011)[17] are validating a technique for mapping FACT-Melanoma to EQ-5D utilities and both studies by Batty et al[16, 97] are comparing several mapping techniques. The six remaining studies are cost-effectiveness studies using utilities from published articles.

Results

Appendix I presents the results of the fifteen included studies as well as information on the methods used.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Table 47 provides a summary of the utilities found within the relevant literature. The utilities derived from the trial are similar to those found in the previously treated ipilimumab trials[16] with an average utility of 0.84 across all patients. This is consistent as it is expected that quality of life would be slightly higher for first-line patients compared with previously treated patients.

The utilities are also similar to those found in other trial based studies – Askew et al[17] found an average utility of 0.86 for stage IV patients and Dixon et al[18] found an average utility of 0.77 at 3 months rising to 0.87 at 48 months of follow-up.

Utilities are higher than those found in the King et al study,[96] however, this study is based upon a small sample size (n=11 for new diagnoses of stage IV and n=24 for established diagnoses) and the method of valuation does not meet the NICE reference case.

Utilities from the two vignette studies[89, 95] predict a high utility for patients in partial response with a large drop for patients in progressive disease. This is not reflected within actual trial data, however, with the drop predicted in the vignettes instead reflected within the trial data in the month prior to death.

Table 47: Summary of literature utilities from primary utility studies

Publication	Utilities	n	Source
Askew 2011[17]	0.85 stage III 0.86 stage IV	100 102	EQ-5D
Batty 2011[97] (previously treated ipilimumab)	0.80 pre-progression 0.76 post progression	971	EORTC-8D
Batty 2012[16] (previously treated ipilimumab)	0.80 pre-progression 0.76 post progression 0.64 pre-progression 0.62 post progression	971 963	EORTC-8D SF-6D
Beusterien 2009[89]	0.85 PR, 0.77 SD, 0.59 PD & BSC	140, 63 UK	SG Vignettes (UK)
Dixon 2006[18]	0.77 (3 months) to 0.87 (48 months)	80 to 10	EQ-5D

Publication	Utilities	n	Source
Hogg 2010[95]	0.84 PR, 0.79 SD, 0.55 PD, 0.54 BSC	87	SG Vignettes (Canada)
King 2011[96]	0.53 stage III new diagnosis 0.91 stage III established diagnosis 0.69 stage IV new diagnosis 0.53 stage IV established diagnosis	8 10 11 24	Time trade-off by patients

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

The majority of serious adverse events experienced by patients receiving ipilimumab, vemurafenib or DTIC are short term in nature (ipilimumab-related main adverse events: diarrhea, colitis, fatigue vs. vemurafenib arthralgia and skin reaction).

Management of gastrointestinal adverse events has improved with increased use of ipilimumab following the production of adverse event management guidelines as part of the MDX program with rates of colectomy dropping following full implementation of guidelines despite an increase in the rates of events due to the use of higher dosing of ipilimumab.

Table 48: Summary of GI related AEs and outcomes following implementation of guidelines

	Partial Implementation of Guidelines MDX Program (mostly 3 mg/kg)	Full Implementation of Guidelines BMS Program (10 mg/kg)
Perforation/Colectomy	0.9%	0.5%
Drug-related diarrhoea	22%	32%
GI serious irAEs (Majority diarrhea/ colitis)	9%	13%

Source: Adapted from Chin K et al.[98]
Key: MDX = Ipilimumab (MDX-010, Yervoy®; Bristol-Myers Squibb) ; BMS= Bristol-Myers Squibb ; GI=gastrointestinal ; irAEs=immune-related adverse events

Ipilimumab treatment is, however, associated with endocrine disorders which can result in permanent impacts on HRQL for a very small proportion of patients. Detection and management of these adverse events is improving with the implementation of guidelines.

The impact of adverse events has been taken into account within the model through the use of a treatment related utility decrement which is applied to all patients receiving either ipilimumab or vemurafenib either first or second line for the entire time they receive these treatments. This approach is likely highly conservative as the majority of adverse events happen while patients are actually receiving treatment (induction or re-induction) and there are long periods of time where patients do not receive treatment but have not yet progressed to alternative treatment.

It has been assumed that the same utility decrement would apply to patients treated with vemurafenib, based upon the fact that similar proportions of patients experiencing grade 3+ events (50% for vemurafenib vs. 56% for ipilimumab, see section 6.9.2, Table 26)[32] compared with DTIC rates of approximately 30% and the fact that patients receive vemurafenib continuously until progression. It should be noted that for some patients adverse events such as sun sensitivity continue after treatment with vemurafenib is stopped, this is not accounted for within the model.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

The typical structure of cost-effectiveness models in oncology is made up of pre- and post-progression health states, with patient transitions driven by progression-based efficacy outcomes from clinical trials. However, data from both the CA184-024 and MDX010-20 trials suggest that progression-based methods may not be sufficiently predictive of utility to accurately account for patient quality of life for this indication (Batty et al. 2011; Batty et al. 2012, Hatswell et al, submitted).[16, 93, 97]

As a result, disease progression may not be the best basis on which to define health states in an economic model. The decrease in utility in the 12 months prior to death observed in trial patients is consistent with previous analyses in second-line melanoma patients treated with ipilimumab (Batty 2012; Hatswell et al, submitted), and suggest a potential alternative to progression-based outcomes. Time to death showed the greatest correlation with utility in tests of the impact of time dependent variables upon utility using data from CA184-024 (section 7.4.3) and MDX010-20.[93]

The mixed effects regression models build on the relationship with time to death, by incorporating the quality of life decrement expected to accompany the adverse event profile of ipilimumab. The patient utilities collected in the trial will include the impact of adverse events; however, introducing the treatment effect would allow the economic model to differentiate between the utility profiles by treatment, accounting for the impact of adverse events. Whether this difference in utility would be sustained in the long-term is not certain, given the short duration of ipilimumab induction protocols. Based on the AIC, goodness of fit of the models does not appear to be substantially altered by the inclusion of treatment effect.

The analyses presented here suggest that modelling patient utility by time to death health states might provide the most meaningful estimates of their quality of life. This approach is further validated by its inclusion in the previous NICE appraisal of second-line ipilimumab.[9] The additional regressions incorporating the treatment effect of ipilimumab offer an alternative approach, noting limitations in determining the length of time for which these treatment effects should be applied.

The regression model including both time to death and treatment effect was used as the model base case. Although treatment effect was not significant within the

analysis conducted this allows adverse events to be accounted for as accurately as possible using trial data. Using these data will overestimate the impact of adverse events as it is likely most events would occur during the induction period of the trial. Sensitivity analysis is presented without the use of this decrement.

Table 49: Summary of utility values for the cost-effectiveness analysis

Time to death	Utility value (95% CI)	Reference in this submission	Justification
<1 month	0.631 (0.600 – 0.668)	7.4.3	Best fit to trial data
Months 1-3	0.739 (0.710 – 0.768)	7.4.3	Best fit to trial data
Months 3-6	0.810 (0.780 – 0.840)	7.4.3	Best fit to trial data
Months 6-9	0.854 (0.823 – 0.885)	7.4.3	Best fit to trial data
Months 9-12	0.880 (0.847 – 0.912)	7.4.3	Best fit to trial data
Months 12+	0.885 (0.853 – 0.917)	7.4.3	Best fit to trial data
Treatment effect of ipilimumab	-0.021 (-0.042 – 0.001)	7.4.3 and 7.4.8	Best fit to trial data
Treatment effect of vemurafenib	-0.021 (-0.042 – 0.001)	7.4.8	Assumed the same based upon grade 3+ event rates

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinicians were not consulted with regards to utilities for this submission, however, clinicians were consulted regarding HRQL estimates for the second-line ipilimumab model (including following initial submission, the potential for use of time to death rather than progression based utilities).

Four leading clinical experts were approached in order to validate the economic model during individual face-to-face informal interviews. These experts were selected as key opinion leaders for melanoma, practicing in the UK. The model was presented to the clinical experts during the interviews including the data available for quality of life for second-line patients (EORTC-8D, SF-6D and Beusterein et al) and their opinions were asked as to what source would best reflect quality of life in the UK patients, no background evidence was given to the experts prior to the interviews.

The clinicians commented that the trial-based utility data (specifically that collected by the EORTC) was more reliable as these data were collected using a disease-specific utility measurement and was based upon patient assessment of their health rather than a clinician-described vignette as in Beusterien et al. Clinicians also commented that it is clinically plausible to expect only a small utility decrement when patients are within progressive disease when treated with immunotherapy such as ipilimumab. Clinical experts thought that this small decrement may be due to the unique kinetics of response associated with treatment with ipilimumab. Saenger et al.[6] state that patients treated with ipilimumab have a significantly different kinetics of response from those of chemotherapy and other immunotherapy with responses observed weeks to months after therapy initiation which may be preceded by apparent early disease progression, or may occur simultaneously with different progressing lesions within the same patient (a 'mixed' response).

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQL is based upon time to death and the treatment. HRQL decreases over time as more patients progress closer to death. Treatment effect is assumed to be constant until the patient receives an alternative treatment. This represents a conservative approach when estimating the impact of adverse events from ipilimumab as treatment is not dosed continuously.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects were excluded. HRQL in the model is based upon time to death rather than progression as this had both a better goodness of fit to trial data and was more clinically plausible given the evidence for a positive relationship between quality-of-life measures and the survival duration of both melanoma and other cancer patients.[90-92, 99]

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

See section 7.4.11.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Values have not been amended. Age adjustment is taken into account indirectly as patients age, they become closer to death within the model.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

There are no HRG and PbR codes specific to ipilimumab. Ipilimumab is administered as a 90 minute intravenous infusion and will be administered in the hospital setting, usually as a day case in outpatient chemotherapy suites. Most hospitals have established oncology units which already provide the staffing and infrastructure for administration of cancer treatments. Because of the infusion time, it was assumed that ipilimumab would be administered on a day case basis. Chemotherapy delivery is costed using the HRGs listed in Table 50. Delivery of ipilimumab would be costed under HRGs SB13Z and SB15Z.

Table 50: HRGs for Chemotherapy Delivery[100]

HRG code	Description
SB11Z	Deliver Exclusively Oral Chemotherapy
SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance
SB13Z	**Deliver more Complex Parenteral Chemotherapy at First Attendance**
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
SB15Z	**Deliver Subsequent Elements of a Chemotherapy Cycle**
SB17Z	Deliver Chemotherapy for Regimens not on the National List

Chemotherapy procurement HRGs are provided for the procurement of drugs for regimens in 10 bands (Table 51). The 2012/13 Department of Health Payment by Results Tariff Spreadsheet shows that there is no mandatory PbR Tariff for "Procure Chemotherapy" drugs, in any band, any tariff is agreed locally.

Table 51: HRGs for Chemotherapy Procurement[101]

HRG code	Description
SB01Z	Procure Chemotherapy drugs for regimens in Band 1
SB02Z	Procure Chemotherapy drugs for regimens in Band 2
SB03Z	Procure Chemotherapy drugs for regimens in Band 3
SB04Z	Procure Chemotherapy drugs for regimens in Band 4
SB05Z	Procure Chemotherapy drugs for regimens in Band 5
SB06Z	Procure Chemotherapy drugs for regimens in Band 6

HRG code	Description
SB07Z	Procure Chemotherapy drugs for regimens in Band 7
SB08Z	Procure Chemotherapy drugs for regimens in Band 8
SB09Z	Procure Chemotherapy drugs for regimens in Band 9
SB10Z	Procure Chemotherapy drugs for regimens in Band 10

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The HRGs for delivery of chemotherapy have been used to cost administration in the model. As the HRG for procurement covers many different drugs (and their associated side effects), drug costs have been taken instead from eMIT[102] and the BNF[103] and side effects have been costed individually to allow differentiation between treatments. Where possible, NHS reference costs or information from PSSRU[104] has been used to cost adverse events and monitoring and other resource use associated with treatment.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic literature review was conducted in May 2013 to identify cost and resource use studies for advanced (unresectable or metastatic) melanoma. A precise search strategy was used which included terms for costs and resource use and for advanced (unresectable or metastatic) melanoma, see appendix 13 for details.

In order to ensure the published literature was comprehensively reviewed, a wide range of databases were searched in the week commencing 20th May 2013. These included: Medline, Embase, NHS HEED, HTA database, DARE, CINAHL, and Econlit. In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies identified were hand searched and scanned for additional publications of relevance to the research question.

Having identified studies from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. Table 52 shows the inclusion criteria for assessing the relevance of the different studies.

Table 52: Eligibility criteria for cost and resource use studies and rationale for each criterion

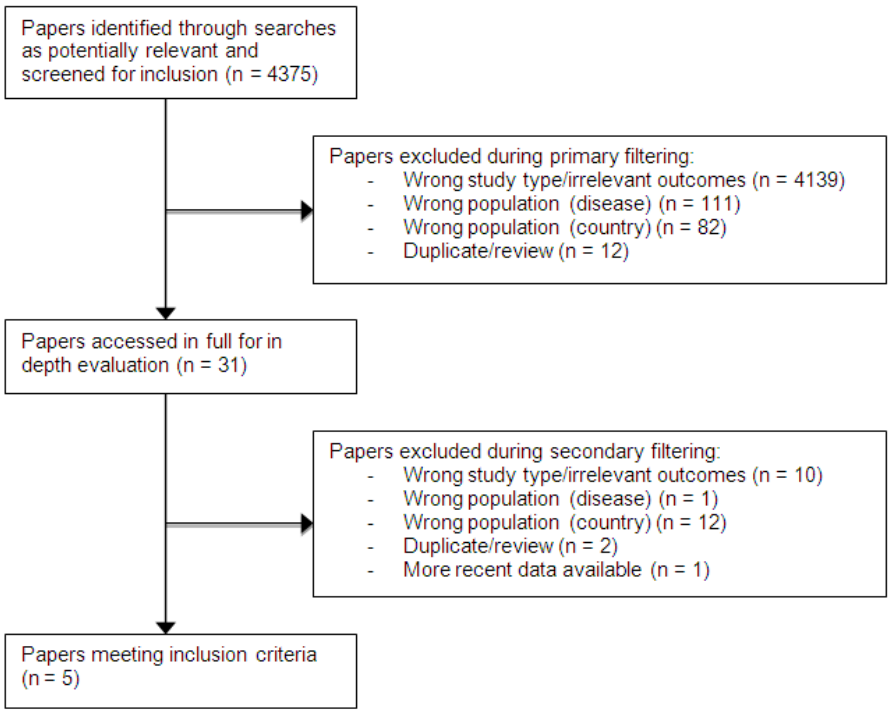
Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To allow all relevant evidence to be identified
Outcomes	Studies reporting the resource use and costs associated with the treatment and ongoing management of advanced melanoma	The aim of the review was to identify relevant costs and data about resource use
Country of Study	UK	Costs and use of resources from a K perspective were required
Exclusion Criteria		
Category	**Exclusion criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were being hand-searched)	Primary study articles were required

Identification of Relevant Studies

The papers that appeared to meet the inclusion criteria after a detailed review of the title and abstract were obtained for a secondary review. In this secondary review the entire article was assessed according to the criteria outlined in Table 52.

Figure 45 shows that the majority of papers initially identified, failed to meet the inclusion criteria. 4,139 of 4,375 papers were excluded for being the wrong study type or having irrelevant outcomes. Other papers were excluded for measuring in the wrong population, either based on disease or country. Duplicates and reviews were also excluded. During secondary filtering most studies were excluded because they were measured in the wrong country, they had irrelevant outcomes, or the wrong study type. And again, some duplicates and reviews were excluded. For one study more recent data were available. This left five studies that met all the inclusion criteria both after primary and secondary filtering.

Figure 45: Identification of cost and resource use studies relevant to the decision problem



Results

Table 53 presents the key characteristics of the studies included. Appendix I provides the full results of the five studies as well as information on methods used.

Table 53: Characteristics of the costs and resource use studies identified

Reference	Country	Population	Study Type	Resource use and costs included
Dixon, 2006[18]	UK	Malignant melanoma	Cost-effectiveness analysis	Inpatient costs, outpatient costs, GP, costs, nurse visit costs and interferon costs for two groups (observation and interferon)
Johnston, 2012[105]	UK, Italy and France	Advanced melanoma	Economic impact	Hospitalisation and outpatient costs, use of hospital and hospice
Lee, 2012[83]	UK	Previously treated metastatic melanoma	Cost-effectiveness analysis	Costs for drugs, treatment, palliative and terminal care
Lorigan, 2010[106]	UK	Advanced melanoma	Health-care resource utilisation study	Hospitalisation rates and duration of hospitalisation
Morris, 2009[107]	UK	Malignant melanoma	Cost analysis	Costs of GP consultations, inpatient care, day cases, and outpatient attendances. NHS costs, patient costs and indirect costs

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Resource use data are taken from the Oxford Outcomes study reported by Lorigan et al.[41, 42] (details below):

- the criteria for selecting the experts: 6 clinical experts in the UK, experienced in the treatment of advanced melanoma patients, were asked to complete the resource use survey. Participating physicians were experienced with ipilimumab through compassionate use or through involvement in clinical trials.
- the number of experts approached: 10
- the number of experts who participated: 5
- declaration of potential conflict(s) of interest from each expert or medical specialty whose opinion was sought: Yes
- the background information provided and its consistency with the totality of the evidence provided in the submission: Yes. Details of the background information can be found in the Questionnaire in appendix 16
- the method used to collect the opinions:
- Questionnaire validation (1 physician per country)
- Telephone interview (1 hour)
- Physicians will be provided with the draft questionnaire & interview guide to review, prior to the interview (1 hour)
- Questionnaire completion (5 physicians in the UK)
- Self-administered questionnaire (1 hour)

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- To be completed as paper copy or electronically in document editor (i.e. Microsoft® Word)
- Telephone interview can be conducted, if physician prefers
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?): self-administered questionnaire
- the questions asked: please refer to the Questionnaire in appendix 16
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique): No

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Drug costs

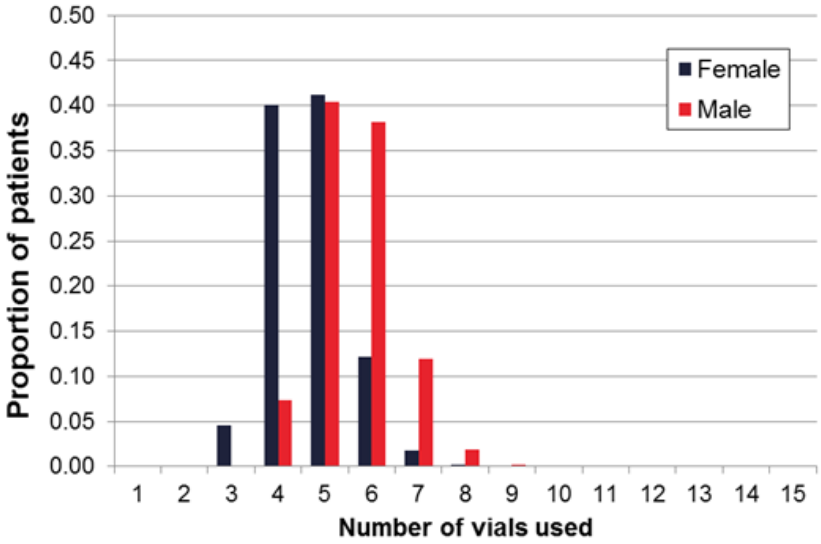
The drug costs of the treatments included in the model are presented in Table 55. The total dose required was calculated for each drug, and this was used to generate a drug cost per administration (as reported in section 7.3.6).

Dose of ipilimumab per administration

In the base case, this was done for ipilimumab using a method of moments calculation, in which individual patient level data for the weights of UK patients from the CA184-024 clinical trial (n=40) and the ipilimumab compassionate use program (n=258) were used to estimate the average number of vials that would be required for treatment. Method of moments assumes a lognormal distribution for body weight and calculates the proportion of patients requiring each possible number of vials based upon the lognormal distribution derived from the individual patient weights. This calculation is the most accurate method of accounting for wastage assuming that no vial sharing occurs.

The distributions around the number of vials required by male and female patients calculated using the method of moments are shown in Figure 46. The mean number of vials per patients used for each dose of ipilimumab based upon this method is 5.23. This is similar to the mean number of vials predicted using the same method in the submission for previously treated patients (5.21).[9]

Figure 46: Distribution around number of vials needed for male and female patients based upon individual patient level data from UK patients in CA184-024 and the UK compassionate use programme



Number of ipilimumab administrations

Due to adverse events in the induction period, not all will patients receive all 4 induction doses of ipilimumab. The proportion of patients receiving each dose during the induction phase of the CA184-024 clinical trial was used within the model to predict how many patients, eligible for treatment within the protocol (alive and not progressed), receive each dose. As only one induction was included in the CA184-024, the number of patients subsequent re-inductions was estimated using the proportion of patients receiving re-induction from the MDX010-20 clinical trial. The proportion receiving each of the 4 possible doses within the re-induction is assumed to be the same as the proportion of patients receiving each of the 4 possible doses during initial induction. The proportion of patients receiving each dose is presented in the full list of parameters in appendix F.

Costs of vemurafenib

Patients were assumed to be dispensed with 4 packs of vemurafenib tablets every 4 cycles, in line with the dispensing routine presented in the vemurafenib NICE appraisal. [NICE TA269] This calculation includes the costs of wastage with vemurafenib if patients do not take all doses within the packs they are dispensed.

Cost of DTIC & BSC component drugs

The BSC component drugs are detailed in Table 54, along with the total dose required for each administration. Dosing schedules were taken from product SPCs (information presented in appendix F). An average height and weight for patients of 170cm and 78.65kg were assumed based upon the patients in the CA184-024 clinical trial.

In the base case, the number of vials required to provide the dose of each drug was rounded up to the nearest full vial. In sensitivity analysis, the costing of BSC component drugs was changed to be applied as the cost per mg (section 7.7.9).

Table 54: Drug dosages required and drug cost per administration

Drug	Total dose required	Method used	Total drug cost per administration
Ipilimumab	5.23 vials	Method of moments	5.23 * £[redacted] = £[redacted]
Vemurafenib*	4 packs	4 packs dispensed every 4 cycles	4 * £[redacted] = £[redacted]
DTIC	2 x 1000mg vials	Round up to nearest full vials	2 * £26.94 = £53.88
Best supportive care			
DTIC	2 x 1000mg vials	Round up to nearest full vials	2 * £26.94 = £53.88
Paclitaxel	1 x 300mg vial + 2 x 30mg vials	Round up to nearest full vials	£22 + 2*£4 = £30.00
Carboplatin	1 x 150mg vial + 2 x 50mg vials	Round up to nearest full vials	£10 + 2*£5 = £20.00
Paclitaxel and carboplatin	As above for the separate components	Round up to nearest full vials	£30 + £20 = £50.00
Cisplatin	1 x 100mg vial + 1 x 50mg vial	Round up to nearest full vials	£14 + £7 = £21.00
Interferon alfa-2b	1 x 10MU vial	Round up to nearest full vials	£42.35
Cisplatin and interferon	1 x 50mg cisplatin vial + 1 x 10MU interferon vial	-	£7 + £42.35 = £49.35
Vindesine	2 x 5mg vials	Round up to nearest full vials	2 x £78.30 = £156.60
Treosulfan	1 x 5000mg vial + 1 x 1000mg vial	Round up to nearest full vials	£39.44 + £152.41 = £191.85

*vemurafenib costs are provided per dispensation

The calculation of the rounded number of vials required for each drug accounted for multiple vial sizes (where there was more than one size available). It was assumed that vials would be selected in such a way as to minimise costs (i.e. one larger vial selected rather than two smaller vials if possible).This provides an estimate of the most efficient way to provide the full dose given the vial sizes available, minimising the amount of wasted drug.

The dosage and costing of first-line DTIC is assumed to be equal to DTIC given as part of BSC.

Patient Access Schemes

A patient access scheme (PAS) is in place for both ipilimumab and vemurafenib. The costs presented in Table 55 include these patient access schemes.

Table 55: Drug costs (including PAS for ipilimumab and vemurafenib)

Drug	Tablet dose/ vial concentration	Pack size/ Vial volume	Cost per vial/ pack	Source
Ipilimumab	5mg/ml	10ml (50mg)	£[redacted]	BNF September 2013[103]
		40ml (200mg)	£[redacted]	BNF September 2013
Vemurafenib	240mg	56 tablets	£[redacted]	BNF September 2013

Drug	Tablet dose/ vial concentration	Pack size/ Vial volume	Cost per vial/ pack	Source
DTIC		100mg	£3	eMIT October 2013 - £31.04 for pack of 10
		200mg	£4	eMIT October 2013 - £41.32 for pack of 10
		500mg	£15	eMIT October 2013
		600mg	£23	BNF September 2013
		1000mg	£27	eMIT October 2013
Best supportive care				
Paclitaxel	6ml/ml	5ml	£4	eMIT October 2013
		16.7ml	£9	eMIT October 2013
		25ml	£11	eMIT October 2013
		50ml	£22	eMIT October 2013
Carboplatin	10mg/ml	5ml	£5	eMIT October 2013
		15ml	£10	eMIT October 2013
		45ml	£25	eMIT October 2013
		60ml	£34	eMIT October 2013
Cisplatin	1mg/ml	10ml	£2	eMIT October 2013
		50ml	£7	eMIT October 2013
		100ml	£14	eMIT October 2013
Interferon alfa-2b	10million/ml	1ml	£42	BNF September 2013
		2.5ml	£106	BNF September 2013
Vindesine	-	5mg	£78	BNF September 2013
Treosulfan		1000mg	£39	BNF September 2013
		5000mg	£152	BNF September 2013

Drug administration costs

The administration costs associated with each type of treatment are shown in Table 56 and the NHS reference cost for each type of administration is shown in Table 57. As there are two potential costs for parenteral chemotherapy (first attendance and subsequent), the maximum cost was taken and applied to each administration, to simplify their application for all parenteral drugs (ipilimumab, DTIC and the majority of the drugs which make up BSC). For all drugs requiring parenteral administration this was assumed to be carried out as a day case appointment.

Table 56: Administration type and costs associated with each treatment in the model

Drug	Type of administration		Administration cost per administration
	Complexity	In/outpatient	
Ipilimumab	Complex	Inpatient	£285 per administration
Vemurafenib	Oral chemo.	Outpatient	£138 on initiation only
DTIC	Complex	Inpatient	£284 per administration
Best supportive care			
Paclitaxel	Complex	Inpatient	£284 per administration
Paclitaxel with Carboplatin	Complex	Inpatient	£284 per administration
Carboplatin with Paclitaxel	Complex	Inpatient	£284 per administration
Carboplatin	Complex	Inpatient	£284 per administration
Cisplatin	Complex	Inpatient	£284 per administration

Drug	Type of administration		Administration cost per administration
	Complexity	In/outpatient	
Cisplatin with Interferon alfa-2b	Complex	Inpatient	£284 per administration
Interferon alfa-2b with Cisplatin	Complex	Inpatient	£284 per administration
Interferon alfa-2b	Complex	Inpatient	£284 per administration
Vindesine	Complex	Inpatient	£284 per administration
Treosulfan	Complex	Inpatient	£284 per administration

The administration costs of vemurafenib were applied for the first cycle only as an outpatient appointment, as subsequent doses are assumed to be taken orally at home.

The SPC for ipilimumab indicates that liver and thyroid function tests should be performed prior to each dose being administered. To account for this additional cost, the cost of a single complete metabolic panel is added to the administration cost of ipilimumab (£1.23).

Table 57: Unit cost for each type of administration

Type of administration	Unit cost	Source
Complex Parenteral Chemotherapy - first attendance	£248	NHS Reference costs 2011/2012[100]: SB13Z Inpatient: Day case and day/night
Subsequent elements of a Parenteral Chemotherapy cycle	£284	NHS Reference costs 2011/2012: SB15Z Inpatient: Day case and day/night
Exclusively Oral Chemotherapy	£138	NHS Reference costs 2011/2012: SB11Z Outpatient
Complete metabolic panel (CMP)	£1.23	NHS Reference costs 2011/2012: Total DAP841

Resource use costs

Five studies containing resource use costs were identified in the literature review (section 7.5.3). The Dixon et al[18], Morris et al[107] and Johnston et al[105] papers do not present the level of detail required to link the costs of treatment with changes in disease (such as progression) although the Johnston et al study does show substantial increases in hospitalisation costs where progression is a more frequent cause of hospitalisation (€ 13875 for BSC where progression was the cause of 80% of hospitalisations vs. € 4872 for systematic therapy where progression was the cause of 30% of hospitalisations.

The Lorigan et al abstract[106] identified has since been published[42] and the Lee et al poster[83] used the same original source material. Based upon this review of the available information the resource use and methodology for applying costs were taken from the MELODY study.[41, 42]

Two types of resource use costs were included within the model:

- One off costs – treatment initiation, progression to a new line of therapy, terminal care which was applied on death.
- Per cycle costs – on treatment, receiving palliative care.

Table 58 shows the cost of each of the resource use unit costs associated with these resource types.

Table 58: Resource use unit costs

Resource use element	Unit cost	Source
Outpatient		
Medical oncologist outpatient visit	£125.67	NHS Reference costs 2011/2012[100] Total OPATT 370
Radiation oncologist outpatient visit	£114.84	NHS Reference costs 2011/2012 Total OPATT 800
General practitioner visit	£32.00	PSSRU 2012[104]: pp183 without qual. with indirect costs
Palliative care physician outpatient visit	£136.16	NHS Reference costs 2011/2012 Ave of total for SD04A and SD05A
Psychologist outpatient visit	£136.00	PSSRU 2012: pp171 per hour of client contact. 1 hour visit assumed
Plastic surgeon outpatient visit	£85.89	NHS Reference costs 2011/2012 Total OPATT 160
Inpatient		
Oncology/general ward - inpatient	£1,455.83	NHS Reference costs 2011/2012 Ave of JD03A/JD03B/JD03C/JD04A/JD04B/JD04C. Weighted by activity.
Palliative care unit - inpatient	£226.27	NHS Reference costs 2011/2012 Ave of total for SD01A and SD03A
Terminal care		
Hospice stay	£6,177.20	Improving Choice at End of Life, Addicott and Dewer, the Kings Fund, 2008. PSSRU 2012
Home care		
Palliative care physician - home care	£65.00	PSSRU 2012: pp109 Outpatient medical specialist palliative care attendance
Palliative care nurse - home care	£85.70	NHS Reference costs 2011/2012 Other currencies: CN202AF
Home aide visits	£157.00	PSSRU 2012: pp109 Outpatient non-medical specialist palliative care attendance
Laboratory tests		
Complete blood count (CBC)	£3.09	NHS Reference costs 2011/2012 Total DAP823
Complete metabolic panel (CMP)	£1.23	NHS Reference costs 2011/2012 Total DAP841
Lactate dehydrogenase (LDH)	£1.23	
Radiological examinations		
CT scan of abdomen/pelvis	£100.98	NHS Reference costs 2011/2012 Ave of total for RA08Z/RA09Z/RA10Z
CT scan of chest	£100.98	
MRI of brain	£168.47	NHS Reference costs 2011/2012 Ave of total for RA01Z/RA02Z/RA03Z
CT scan of brain	£100.98	NHS Reference costs 2011/2012 Ave of total for RA08Z/RA09Z/RA10Z
PET/CT scan	£168.47	NHS Reference costs 2011/2012 Ave of total for RA01Z/RA02Z/RA03Z
Bone scintigraphy	£136.54	NHS Reference costs 2011/2012 Total RA35Z
Echography	£80.14	NHS Reference costs 2011/2012 Ave of total for RA23Z/RA24Z/RA25Z/RA26Z/RA27Z
Chest x-ray	£118.50	NHS Reference costs 2011/2012 Total RA16Z

Resource use element	Unit cost	Source
Pain control		
Morphine - Oral	£10.60	Oxford outcomes Melanoma Resource Use report[41] adjusted for inflation using PSSRU 2012[104]
Morphine - IV	£115.02	
Morphine - Transdermal patch	£39.29	
NSAIDs (Ibuprofen)	£0.73	
Other: Paracetamol	£4.48	

Table 59 presents the expected use of each resource for each of the cost types, together with the total cost of the aggregated resource use.

Table 59: Resource use by health state and patient movement

Resource use element (Frequency per month)	First-line treatment initiation		While receiving treatment (first or second line)		Initiation of subsequent treatment line		While patients are not receiving treatment		While receiving palliative care		Terminal care – applied on death	
	% patients	Resource use	% patients	Resource use	% patients	Resource use	% patients	Resource use	% patients	Resource use	% patients	Resource use
Outpatient												
Medical oncologist outpatient visit	81%	3.6			75%	2.4	89%	1.9	63%	0.9		
Radiation oncologist outpatient visit	6%	2.3			6%	1.5	6%	1	6%	1.5		
General practitioner visit	4%	2	4%	2	3%	2	4%	2	78%	1.9		
Palliative care physician outpatient visit					15%	1			29%	1.2		
Psychologist outpatient visit									4%	3		
Plastic surgeon outpatient visit	2%	1.5	2%	1.5	2%	1.5	2%	1.5				
Inpatient												
Oncology/general ward - inpatient	6%	2.8	5%	1.3	17%	3.4	5%	1.3	14%	3.6		
Palliative care unit - inpatient									26%	4		
Terminal care												
Hospice stay											100%	1
Home care												
Palliative care physician - home care									24%	1		
Palliative care nurse - home care									58%	1.4		
Home aide visits									22%	7.3		

Resource use element (Frequency per month)	First-line treatment initiation		While receiving treatment (first or second line)		Initiation of subsequent treatment line		While patients are not receiving treatment		While receiving palliative care		Terminal care – applied on death	
	% patients	Resource use	% patients	Resource use	% patients	Resource use	% patients	Resource use	% patients	Resource use	% patients	Resource use
Laboratory tests												
Complete blood count (CBC)	100%	1.2	100%	1.3	90%	1.8	100%	1.3				
Complete metabolic panel (CMP)	100%	1.2	95%	1.3	90%	1.8	95%	1.3				
Lactate dehydrogenase (LDH)	100%	1.2	95%	1.3	90%	1.8	95%	1.3				
Radiological examinations												
CT scan of abdomen/pelvis	100%	1	96%	0.4	76%	1.1	96%	0.4				
CT scan of chest	100%	1	96%	0.4	76%	1.1	96%	0.4				
MRI of brain	6%	1	21%	0.3	22%	0.7	21%	0.3				
CT scan of brain	41%	1	11%	0.2	29%	1.1	11%	0.2				
PET/CT scan	5%	1	2%	0.4	2%	0.7	2%	0.4				
Bone scintigraphy	19%	1	1%	0.3	2%	0.7	1%	0.3				
Echography	6%	1	12%	0.3	12%	0.3	12%	0.3				
Chest x-ray	20%	1	30%	1.1	10%	0.7	30%	1.1				
Pain control												
Morphine - Oral									51%	1		
Morphine - IV									22%	1		
Morphine - Transdermal patch									15%	1		
NSAIDs (Ibuprofen)									55%	1		
Other: Paracetamol									18%	1		
Total aggregate cost per week	**£955.03**		**£60.24**		**£1,354.38**		**£115.09**		**£384.23**		**£6,177.20**	

Costs of second and third-line treatment

The costs of second-line treatment with ipilimumab were taken from the second-line submission including the PAS.[9] The average administration cost per cycle from the second-line evaluation was £32.84. The average drug cost per cycle was £[redacted], which was adjusted proportionately to the difference in average weight between the CA184-024 clinical trial and the second-line evaluation, using a multiplier of 0.9977. This generated a per cycle drug cost of £[redacted] for second-line ipilimumab.

For second-line vemurafenib, the administration cost on initiation was assumed to be equal to the cost applied first-line. The drug costs were applied using the cost per mg including the PAS. To account for the wastage incorporated in the "cost per dispensation" cost used for first-line vemurafenib, an additional 5.78% was added to the drugs costs, calculated as the percentage increase generated for first-line vemurafenib using the cost per dispensation, compared with cost per mg. The total drug cost per cycle for second-line vemurafenib was £[redacted].

The drug and administration costs of BSC are shown in Tables 25 and 27, respectively, and were applied only to patients in the first 7 cycles of BSC (whether this is at second or third line). This was based on the median duration of 6.6 weeks for treatment from the MELODY study (MELODY).[42]

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table 60: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
First-line treatment	Technology	**Ipilimumab:** £[redacted] per administration (£[redacted] per cycle before next therapy is initiated) **DTIC:** £44 per administration (£10 per cycle before the next therapy is initiated) **Vemurafenib:** £[redacted] per dispensation (£[redacted] per cycle)	7.5.5
	Administration	**Ipilimumab:** £285 per administration (£24 per cycle before next therapy is initiated) **DTIC:** £284 per administration (£53 per cycle before the next therapy is initiated) **Vemurafenib:** £138 on treatment initiation	7.5.5
	Resource use	**All treatments:** £955 on treatment initiation; £60.24 per cycle	7.5.5
	Adverse events	**Ipilimumab:** £43 on treatment initiation; £1.92 every 6 months **Vemurafenib:** £25 on treatment initiation	7.5.7
Second-line treatment	Technology	**Ipilimumab:** £[redacted] per cycle before the next line of therapy is initiated **Vemurafenib:** £[redacted] per cycle **BSC:** £26.30 over 7 cycles	7.5.5
	Administration	**Ipilimumab:** £33 per cycle **Vemurafenib:** £138 on treatment initiation **BSC:** £318 over 7 cycles	7.5.5
	Resource use	**All treatments:** £1,354 on treatment initiation All patients receiving treatment: £60 per cycle Patients not receiving treatment: £115 per cycle	7.5.5
	Adverse events	**Ipilimumab:** £43 on treatment initiation; £2 every 6 months **Vemurafenib:** £21 on treatment initiation **BSC:** £17 on treatment initiation	7.5.7
Third-line treatment	Technology	£26 over 7 cycles	7.5.5
	Administration	£318 over 7 cycles	7.5.5
	Resource use	All patients receiving treatment: £60 per cycle Patients not receiving treatment: £115 per cycle	7.5.5
	Adverse events	£17 on treatment initiation	7.5.7
Palliative care	Technology	£0	7.5.5
	Administration	£0	7.5.5
	Resource use	£384 per cycle; £6,177 upon death	7.5.5
	Adverse events	£0	7.5.7

Costs presented to zero decimal places

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The methodology for costing adverse events was taken from the most appropriate source identified in the literature review which is also used for resource use costs (Sections 7.5.3 and 7.5.5)[41, 42], with additional cost data taken from NHS reference costs.[100]

The incidence of adverse events for patients treated with ipilimumab, vemurafenib and BSC used in the base case model have been presented previously in section 7.3.2. A breakdown of adverse events incidence for each of the BSC components drugs can be found in appendix E, together with alternative incidences for ipilimumab-treated patients based upon observational study data, which are used in sensitivity analysis.

The costs of adverse events, associated with ipilimumab, are presented in Table 61 as a per patient per event cost.

Table 61: AE unit costs for patients treated with ipilimumab

Adverse events	Inpatient		Outpatient		Total per AE
	% Treated	Average cost	% Treated	Average cost	
Diarrhea (not including colitis)	47.6%	£815.37	52.4%	£564.80	£684.01
Endocrine disorders	33.2%	£563.91	66.8%	£428.94	£473.72

The cost of adverse events for vemurafenib and BSC are shown below in Table 62 as per patient per event cost. The source of the unit costs is presented in Table 63. For costs that were sourced from the Oxford Outcomes report, these were inflated to 2012 prices using PSSRU inflation indices.[104]

The costs of endocrine disorders were assumed to be incurred once every 6 months, as this is an ongoing condition. The costs for all other events were applied once at treatment initiation.

Table 62: AE unit costs for patients treated with vemurafenib, DTIC and BSC

Adverse events	Inpatient		Outpatient		Total per AE
	% Treated	Average cost	% Treated	Average cost	
Myalgia/Pain			100.0%	£146.00	£146.00
Skin Reaction	5.2%	£1,198.44	94.8%	£193.61	£245.99
Fatigue	5.0%	£579.96	95.0%	£152.52	£173.89
Hypotension*					£0.00
Diarrhea (not including colitis)	55.0%	£815.37	45.0%	£140.08	£511.49
Colitis	100.0%	£983.36			£983.36

Adverse events	Inpatient		Outpatient		Total per AE
	% Treated	Average cost	% Treated	Average cost	
Dyspnoea*					£0.00
Resp. Distress/Pulm. Edema	100.0%	£1,950.00			£1,950.00
Anaemia	43.5%	£573.54	56.5%	£960.23	£792.10
Neutropenia	30.0%	£1,575.10	70.0%	£199.36	£612.08
Arthralgia			100.0%	£146.00	£146.00

* These adverse events were not included in the Oxford Outcomes Report because physicians indicated that they would not be common and/or costly. Costs for these have therefore been set to zero.

Table 63: List of adverse events and summary of costs included in the economic model[100, 108]

Adverse events	Average cost		Reference
	Ipilimumab	Vemurafenib and BSC	
Myalgia/Pain	£146.00	£146.00	HRG service code: 191, Pain management, multi-professional non-admitted face-to-face
Skin Reaction	£245.99	£245.99	Oxford Outcomes: Average of Rash and Pruritus
Fatigue	£173.89	£173.89	Oxford Outcomes: Fatigue
Hypotension	£0.00	£0.00	*
Diarrhea (not including colitis)	£684.01	£511.49	Oxford Outcomes: Diarrhoea
Colitis	£853.10	£983.36	Oxford Outcomes: Colitis
Dyspnoea	£0.00	£0.00	*
Resp. Distress/ Pulm. Edema	£1,950.00	£1,950.00	DZ20Z, Pulmonary Oedema, NHS Trusts Non-Elective Inpatient (Long Stay) HRG Data
Anaemia	£728.62	£792.10	Oxford Outcomes: Anaemia
Neutropenia	£920.13	£612.08	Oxford Outcomes: Neutropenia
Endocrine disorders	£473.72	£563.91	Oxford Outcomes: Hypopituitarism - every 6 months
Arthralgia	£146.00	£146.00	HRG service code: 191, Pain management, multi-professional non-admitted face-to-face

*The following adverse events were not included in the Oxford Outcomes Report because physicians indicated that they would not be common and/or costly: headache, pain, injection site reaction, leucopoenia, hypotension, hypertension, dyspnoea, stomatitis, urticaria, vitiligo, anuria, oliguria, and peripheral neuropathy. Costs for these have therefore been set to zero.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

There are no additional costs included in the model other than those outlined in the previous sections.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainty around the following structural assumptions has been included within the model:

- **Treatment pathway:** Results are presented in the base case for the treatment pathway with active second-line treatments as this is the most clinically relevant treatment pathway. Additional results are presented with no active second-line treatments. Results are also presented using alternative sources for the mix of best supportive care treatments from research carried out by Collinson et al[108] and Oxford Outcomes.[41]
- **Time horizon:** Results are presented for shorter time horizons 10, 20 and 30 years.
- **Source of adverse events data:** Results are presented taking adverse events data for ipilimumab from observational study CA184-338.
- **Dosing:** Scenarios are presented using different datasets for patient weights and using alternative methods to model dosing (cost per mg and rounding up to the nearest full vial).
- **Utilities:** Within the base-case analysis, patients receiving either ipilimumab or vemurafenib have reduced utility due to adverse events. As the utility decrement for treatment effect was not significant in CA184-024, alternative analysis is presented assuming that treatment does not negatively impact utility. Alternative utility analysis is also presented using time to death utilities based upon data from MDX010-20.

- **Modelling overall survival:** Within the base-case analysis, a 3 part curve fit is used to model survival. Alternative curve fits are presented including a piecewise exponential curve fit (as was recommended by the ERG in TA268), alternative parametric curves for the second part (2 to 5 years) of the 3 part curve fit and single parametric curves. Curves presented are those which the AIC and BIC represent a valid fit. The impact of using the ERG analysis for OS for vemurafenib is also investigated.
- **Modelling progression free survival:** Within the base-case analysis, a 2 part curve fit is used to model progression free survival. Alternative curve fits are presented including alternative parametric curves for the second part (12 weeks) of the 2 part curve fit and single parametric curves. Curves presented are those which the AIC and BIC represent a valid fit.
- **Source and modelling of registry data:** The impact of using registry data from Balch 2009[15] rather than Balch 2001[84] is investigated along with the impact of using alternative parametric curve fits to the data. Curves presented are those which the AIC and BIC represent a valid fit.

Results are presented using both the data from CA184-024 and the data from the pooled chemotherapy-naïve dataset to model outcomes of a therapy with ipilimumab.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The following variables were included in sensitivity analysis:

Table 64: List of variables included in sensitivity analysis

Parameter	Distribution	Rationale
Height and weight	Height: Normal distribution: 95% CI, based on trial data Weight: Lognormal distribution: 95% CI, based on trial data	Based upon available trial data
First-line overall survival and PFS for ipilimumab and DTIC	Multivariate normal distribution: 95% CI, based on trial data	Based upon available trial data
First-line overall survival and PFS for ipilimumab and vemurafenib)	±10% to the hazard rates	As per manufacturer submission[32][NICE TA269]
Second-line overall survival for ipilimumab and vemurafenib	95% CI of the hazard ratio derived using the 95% CI of second-line life years, calculated using What-If solver analysis	Based upon the confidence intervals of the data submitted for TA268[9]
Second-line time on treatment for ipilimumab and vemurafenib	95% CI of second-line ipilimumab pre-progression life years	Based upon the confidence intervals of the data submitted for TA268

Parameter	Distribution	Rationale
Proportion of patients experiencing adverse events for ipilimumab and vemurafenib	Beta distribution: 95% CI, based on trial data	Based upon available trial data
The proportion of patients receiving each dose of ipilimumab	Beta distribution: 95% CI, based on trial data	Based upon available trial data
The breakdown of patients representing BSC	Beta tree: 95% CI, based upon published data[42]	Based upon most appropriate source for BSC (largest number of patients and presented as a proportion of patients receiving each treatment rather than a proportion of physicians prescribing each treatment)
The cost of administration	Normal distribution: 95% CI, SE assumed 20% of the mean	Assumption
The resource use	Normal distribution: 95% CI, SE assumed 20% of the mean	Assumption
The cost of adverse events	Normal distribution: 95% CI, SE assumed 20% of the mean	Assumption
The utility regression coefficients	Normal distribution: 95% CI, based on trial data	Based upon available trial data

Deterministic sensitivity analysis was undertaken through the production of a tornado diagram (testing the sensitivity of the model to all parameters and ordering them by impact on the incremental net benefit).

Drug costs were not included within the sensitivity analysis, as the majority of these are taken from the BNF and, therefore, were considered not being subject to uncertainty.

The proportion of patients experiencing adverse events for BSC was not included in sensitivity analysis as only a small proportion of patients experience adverse events and their impact is very limited within the model.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis was undertaken with all parameters included as described in section 7.6.2, distributions are presented in section 7.3.6.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

As shown in Table 65, the results in the model are similar to those of the clinical trials. The results which are the furthest from the clinical trials are the OS and PFS for vemurafenib which were taken from the manufacturer submission for vemurafenib (TA269).[32] It should be noted that the ERG in the appraisal of TA269 had concerns that the manufacturer survival estimates may be overestimating the benefits of vemurafenib. The ERG state that they are “concerned that resultant extrapolation (of overall survival) appears to lack a coherent underlying and compelling logic connecting the natural history of the disease, the mode of action of the interventions, and the accumulated experience of clinicians and patients.”

The ERG developed an alternate model to address this weakness which is applied in scenario analysis (section 7.7.9).

Table 65: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result (no active second-line treatments)
Median OS ipilimumab	CA184-024: 10.5 months Pooled chemotherapy-naïve dataset: 13.5 months	CA184-024: 11.5 months Pooled chemotherapy-naïve dataset: 13.6 months
Median OS DTIC	024: 8.9 months	9.2 months
Median OS vemurafenib	Chapman 9.2 months	14.5 months
Restricted mean OS (5 years) ipilimumab	21.0 months	22.3 months
Restricted mean OS (5 years) DTIC	15.3 months	15.4 months
Median PFS ipilimumab	CA184-024 and pooled chemotherapy-naïve dataset: 2.8 months	CA184-024: 2.8 months Pooled chemotherapy-naïve dataset: 3.4 months
Median PFS DTIC	CA184-024: 2.6 months	2.8 months
Median PFS vemurafenib	Chapman: 5.3 months	6.7 months

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

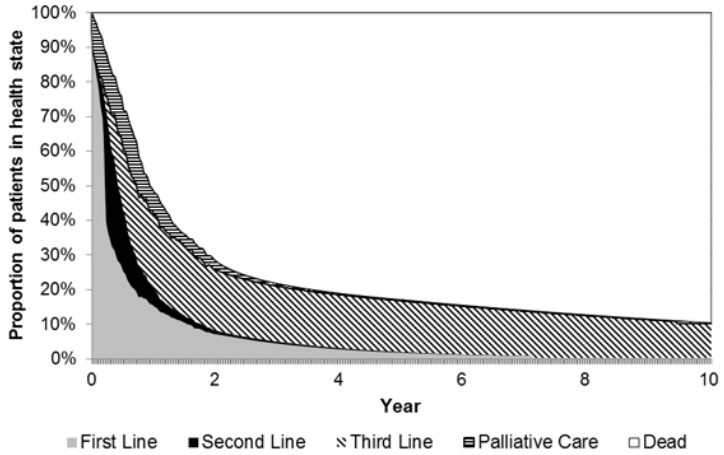
Figure 47 and Figure 48 illustrate how patients move through the model states over time when treated with ipilimumab, DTIC or vemurafenib. The diagrams show that the proportion of patients alive in the longer term (2+ years) is higher for ipilimumab than either of the comparator treatments. Appendix J shows Markov traces for the full 40 years time horizon of the model.

The proportion of patients who are alive and therefore eligible to receive second-line treatments within the model is:

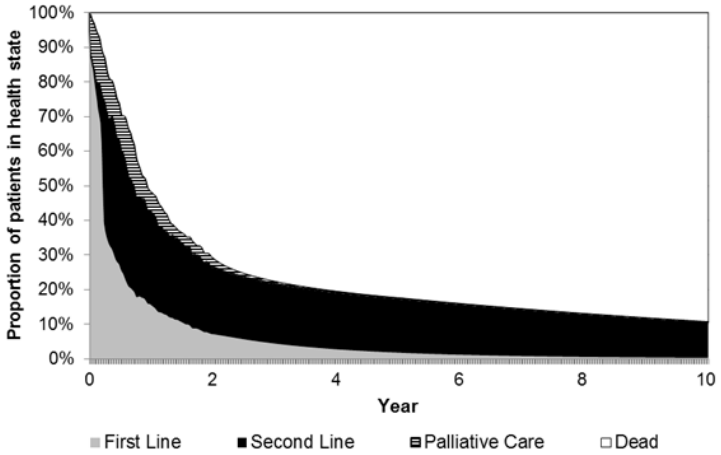
- 62% following treatment with ipilimumab
- 55% following treatment with vemurafenib
- 51% following treatment with DTIC

Figure 47: Markov trace diagram (proportion of patients in health state by year), CA184-024 clinical trial data for ipilimumab

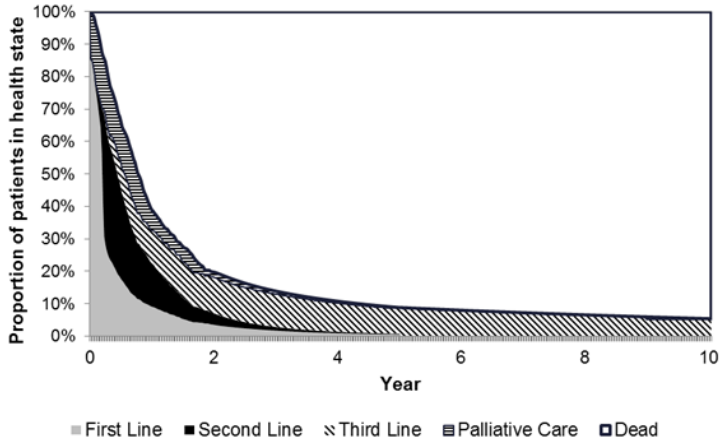
Ipilimumab followed by vemurafenib, BRAF mutation-positive patients



Ipilimumab followed by BSC, BRAF mutation-negative patients



DTIC followed by ipilimumab, BRAF mutation-positive and -negative patients



Vemurafenib followed by ipilimumab, BRAF mutation-positive patients

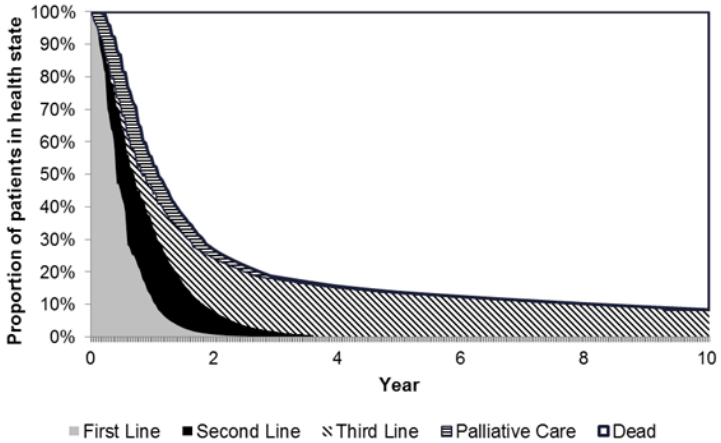
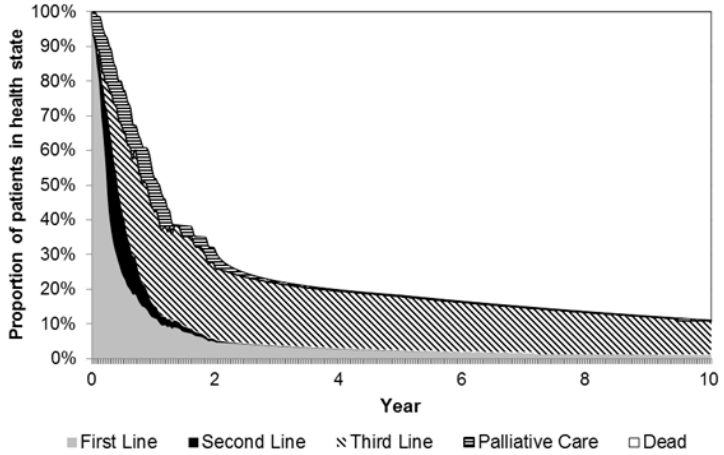
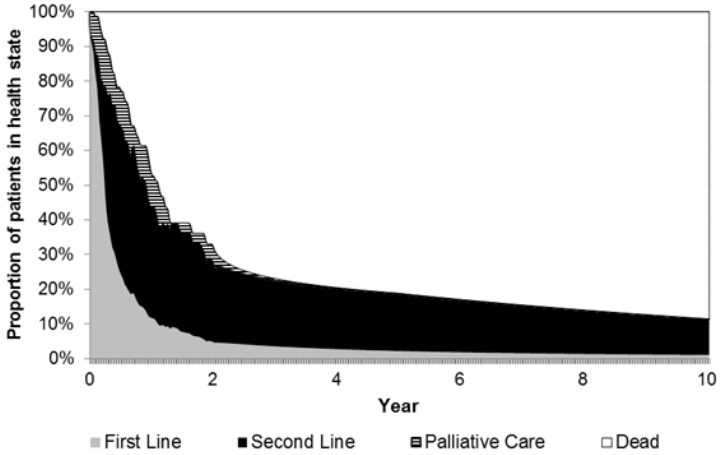


Figure 48: Markov trace diagram (proportion of patients in health state by year), pooled chemotherapy-naïve data for ipilimumab

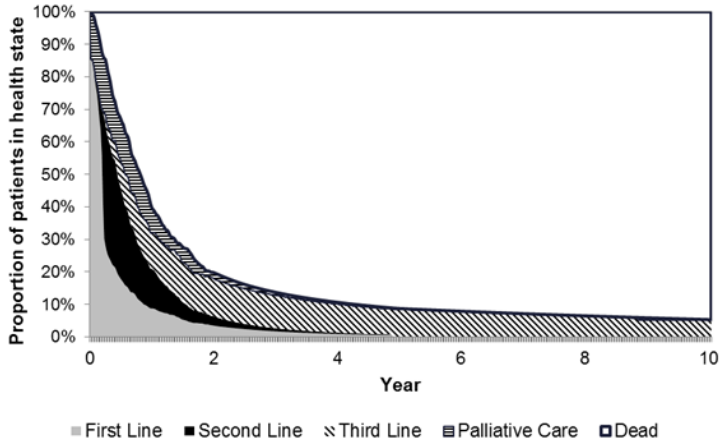
Ipilimumab followed by vemurafenib, BRAF mutation-positive patients



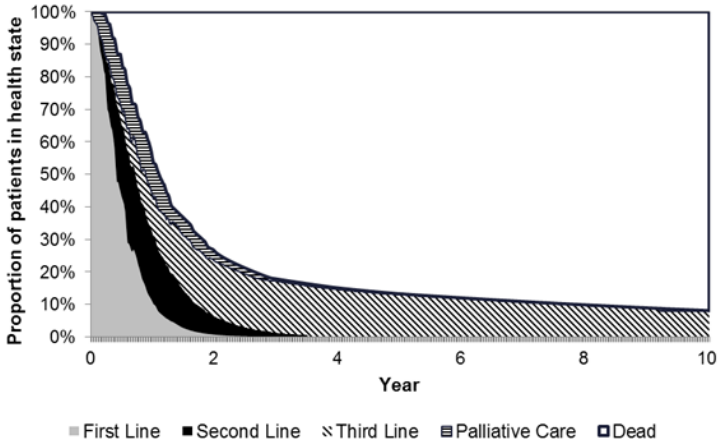
Ipilimumab followed by BSC, BRAF mutation-negative patients



DTIC followed by ipilimumab, BRAF mutation-positive and -negative patients



Vemurafenib followed by ipilimumab, BRAF mutation-positive patients



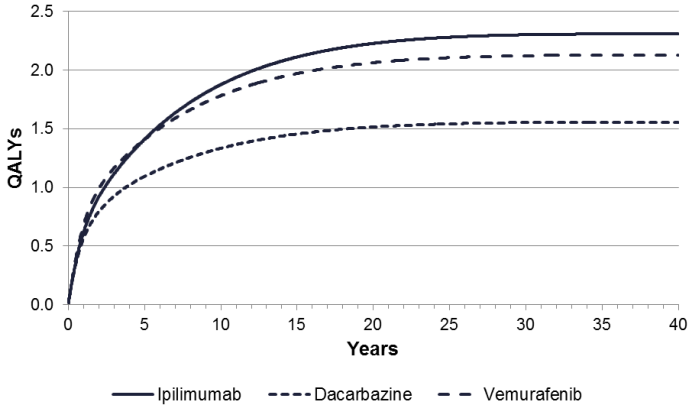
7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure 49 illustrates how QALYs are accumulated over time. QALYs are initially higher for vemurafenib as vemurafenib has a faster mechanism of action compared with ipilimumab.

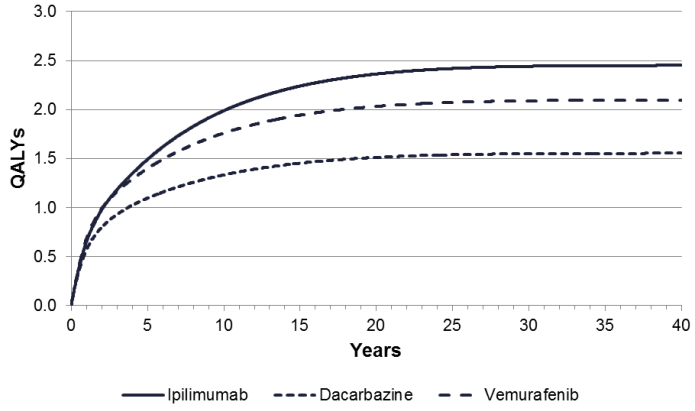
However, as responses to vemurafenib may not be durable and the majority of people who receive it develop resistance and tumour relapse[3], but stabilise on ipilimumab, the QALY gain for ipilimumab overtakes the gain for vemurafenib.

Figure 49: QALY accumulation over time

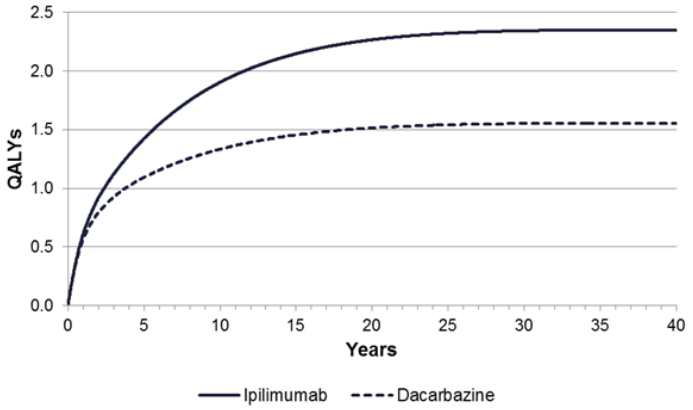
CA184-024 data, BRAF mutation-positive



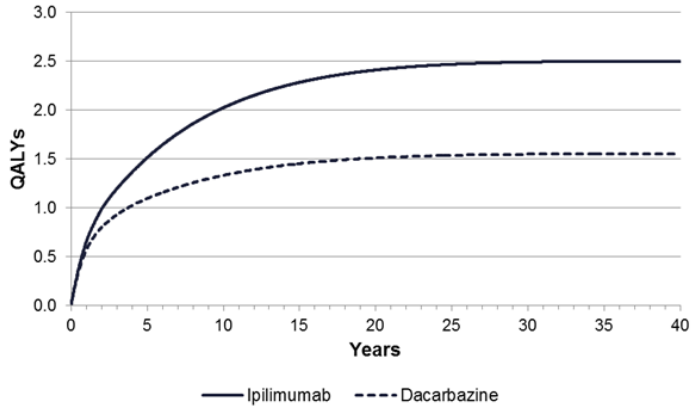
Pooled chemotherapy-naïve data for ipilimumab, BRAF mutation-positive



CA184-024 data, BRAF mutation-negative



Pooled chemotherapy-naïve data for ipilimumab, BRAF mutation-negative



NB: Scale is different.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 66 to Table 69 illustrate the life years by clinical outcome. The tables illustrate that compared with patients on DTIC or vemurafenib, patients treated with ipilimumab:

- Spend longer on first-line treatment, accumulating more life years in this state,
- Spend longer on third-line treatment – as patients who have stabilised on ipilimumab and are experiencing long-term survival are often classed as progressed due to the unique mode of action of ipilimumab.

Table 66: Model outputs by clinical outcomes, CA184-024 data for ipilimumab – BRAF V600 mutation-positive

Life years	Ipilimumab	DTIC	Vemurafenib
First-line life years	0.63	0.40	0.54
Second-line life years	0.18	0.31	0.37
Third-line life years (BSC)	2.26	1.22	1.85
Palliative care life years	0.22	0.22	0.23
Total life years	**3.29**	**2.15**	**2.98**

Table 67: Model outputs by clinical outcomes, pooled chemotherapy-naïve data for ipilimumab – BRAF V600 mutation-positive

Life years	Ipilimumab	DTIC	Vemurafenib
First-line life years	0.69	0.40	0.54
Second-line life years	0.15	0.29	0.34
Third-line life years (BSC)	2.42	1.22	1.82
Palliative care life years	0.22	0.22	0.23
Total life years	**3.49**	**2.14**	**2.93**

Table 68: Model outputs by clinical outcomes, CA184-024 data for ipilimumab – BRAF V600 mutation-negative

Life years	Ipilimumab	DTIC
First-line life years	0.63	0.40
Second-line life years	2.51	0.31
Third-line life years (BSC)	0.00	1.22
Palliative care life years	0.22	0.22
Total life years	**3.35**	**2.15**

Table 69: Model outputs by clinical outcomes, pooled chemotherapy-naïve data for ipilimumab – BRAF V600 mutation-negative

Life years	Ipilimumab	DTIC
First-line life years	0.69	0.40
Second-line life years	2.64	0.29
Third-line life years (BSC)	0.00	1.22
Palliative care life years	0.22	0.22
Total life years	**3.56**	**2.14**

It is not possible to present disaggregated results for QALYs due to how utilities were valued (by time to death rather than by line of treatment).

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 70 illustrates the disaggregated costs and shows that, in total and over a patient's lifetime, treatment with ipilimumab is expected to cost approximately £23,766 more than treatment with DTIC but £12,625 less than treatment with vemurafenib.

While the costs accumulated in the first-line treatment are higher when treated with ipilimumab, the majority of patients treated with vemurafenib are likely to go on to receive ipilimumab at second line as, although patients respond initially to vemurafenib, the majority of patients who receive it develop resistance and tumour relapse. This means that the majority of patients treated with vemurafenib at first line incur both the cost of vemurafenib and the cost of ipilimumab in second line.

Second-line costs are lower for DTIC due to the substantially poorer outcomes of patients, i.e. due to lower survival less patients will be alive and therefore not be able to receive second-line treatment.

Table 70: Disaggregated costs, CA184-024 data for ipilimumab – BRAF V600 mutation-positive

Health state	Cost ipilimumab	Cost DTIC	Cost vemurafenib	Absolute increment vs. DTIC	Absolute increment vs. vemurafenib
First-line drug costs	£[redacted]	£[redacted]	£[redacted]	£34,709	£4,953
First-line administration costs	£774	£1,112	£138	-£337	£636
Second-line drug costs	£[redacted]	£[redacted]	£[redacted]	-£13,607	-£18,418
Second-line administration costs	£74	£520	£626	-£446	-£551
Third-line drug costs	£29	£11	£13	£18	£16
Third-line administration costs	£144	£43	£49	£101	£94
Resource use costs	£12,159	£8,632	£11,363	£3,527	£795
Palliative care costs	£9,718	£10,037	£9,958	-£319	-£240
Adverse events costs	£147	£27	£58	£121	£89
Total costs	**£68,033**	**£44,267**	**£80,658**	**£23,766**	**-£12,625**

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

Table 71: Disaggregated costs, pooled chemotherapy-naïve data for ipilimumab – BRAF V600 mutation-positive

Health state	Cost ipilimumab	Cost DTIC	Cost vemurafenib	Absolute increment vs. DTIC	Absolute increment vs. vemurafenib
First-line drug costs	£[redacted]	£[redacted]	£[redacted]	£35,823	£6,002
First-line administration costs	£799	£1,115	£138	-£316	£661
Second-line drug costs	£[redacted]	£[redacted]	£[redacted]	-£13,826	-£17,666

Health state	Cost ipilimumab	Cost DTIC	Cost vemurafenib	Absolute increment vs. DTIC	Absolute increment vs. vemurafenib
Second-line administration costs	£84	£491	£575	-£407	-£491
Third-line drug costs	£34	£12	£13	£23	£21
Third-line administration costs	£173	£46	£51	£128	£122
Resource use costs	£12,868	£8,622	£11,224	£4,246	£1,644
Palliative care costs	£9,763	£10,033	£9,963	-£270	-£199
Adverse events costs	£150	£27	£58	£123	£92
Total costs	**£68,416**	**£42,891**	**£78,230**	**£25,525**	**-£9,814**

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

Table 72: Disaggregated costs, CA184-024 data for ipilimumab – BRAF V600 mutation-negative

Health state	Cost ipilimumab	Cost DTIC	Absolute increment vs. DTIC
First-line drug costs	£[redacted]	£[redacted]	£34,221
First-line administration costs	£764	£1,112	-£348
Second-line drug costs	£[redacted]	£[redacted]	-£23,632
Second-line administration costs	£218	£520	-£302
Third-line drug costs	£0	£11	-£11
Third-line administration costs	£0	£43	-£43
Resource use costs	£12,464	£8,632	£3,832
Palliative care costs	£9,703	£10,037	-£334
Adverse events costs	£136	£27	£109
Total costs	**£57,760**	**£44,267**	**£13,492**

Table 73: Disaggregated costs, pooled chemotherapy-naïve data for ipilimumab – BRAF V600 mutation-negative

Health state	Cost ipilimumab	Cost DTIC	Absolute increment vs. DTIC
First-line drug costs	£[redacted]	£[redacted]	£35,481
First-line administration costs	£792	£1,115	-£323
Second-line drug costs	£[redacted]	£[redacted]	-£22,287
Second-line administration costs	£241	£491	-£249
Third-line drug costs	£0	£12	-£12
Third-line administration costs	£0	£46	-£46
Resource use costs	£13,198	£8,622	£4,576
Palliative care costs	£9,731	£10,033	-£302
Adverse events costs	£137	£27	£110
Total costs	**£59,839**	**£42,891**	**£16,948**

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 74 to Table 77 illustrate the base case model results. Results are presented allowing patients to receive an active second-line treatment in line with available guidance as presented in Figure 26. Results are presented both versus individual comparators and as incremental analysis.

As stated in section 4, consideration of the evidence base shows ipilimumab for first-line therapy of advanced melanoma meets NICE's End of Life criteria when compared with treatment with DTIC:

- advanced melanoma patients have a short life expectancy with a median survival of 6-9 months[19]; this was previously assessed as true in TA269.
- ipilimumab offers an extension to life, normally of at least an additional 3 months compared with standard of care: restricted mean analysis shows a survival gain of 5.7 months over the 5 year trial (see section 6.5.1);
- estimated advance melanoma patient population eligible for first-line therapy is small: expected patient numbers of ~338 in 2014; this was previously assessed as true in TA269.

Regardless of BRAF V600 mutation status, the treatment with ipilimumab is highly cost-effective compared with treatment with DTIC when the willingness to pay threshold of £50,000 for end of life therapies is applied. For BRAF V600 mutation-positive patients the ICER is £31,559 using CA184-024 results and £28,465 using pooled chemotherapy-naïve data for ipilimumab. For BRAF V600 mutation-negative patients the ICER is £16,958 using CA184-024 results and £17,866 using pooled chemotherapy-naïve data for ipilimumab.

Due to improved overall survival and a reduced cost of for treatment, when both first and second-line costs are considered, treatment with ipilimumab dominates treatment with vemurafenib in BRAF V600 mutation-positive patients.

Both analyses, i.e. using CA184-024 data or pooled chemotherapy-naïve data for ipilimumab, produce alike results. Meaning that the different dose (ipilimumab 10mg/kg + DTIC) in CA184-024 has not affected results.

Table 74: Base case results, CA184-024 data for ipilimumab – BRAF V600 mutation-positive

Comparison vs. ipilimumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Ipi vs. comparator
Ipilimumab	£68,033	3.2901	2.3101				
DTIC	£44,267	2.1476	1.5570	£23,766	1.1425	0.7531	**£31,559**
Vemurafenib	£80,658	2.9815	2.1298	-£12,625	0.3086	0.1803	**Dominant**

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Incremental analysis – comparison vs. baseline (DTIC)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. baseline (A)	Incremental analysis
DTIC	£44,267	1.56				
Ipilimumab	£68,033	2.31	£23,766	0.75	£31,559	**£31,559**
Vemurafenib	£80,658	2.13	£12,625	-0.18	£63,534	**Dominated**

Table 75: Base case results, pooled chemotherapy-naïve data for ipilimumab – BRAF V600 mutation-positive

Comparison vs. ipilimumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Ipi vs. comparator
Ipilimumab	£68,416	3.4884	2.4499				
DTIC	£42,891	2.1388	1.5532	£25,525	1.3496	0.8967	**£28,465**
Vemurafenib	£78,230	2.9266	2.0955	-£9,814	0.5618	0.3544	**Dominant**

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Incremental analysis – comparison vs. baseline (DTIC)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. baseline (A)	Incremental analysis
DTIC	£42,891	1.55				
Ipilimumab	£68,416	2.45	£25,525	0.90	**£28,465**	**£28,465**
Vemurafenib	£78,230	2.10	£9,814	-0.35	**£,65,157**	**Dominated**

Table 76: Base case results, CA184-024 data for ipilimumab – BRAF V600 mutation-negative

Comparison vs. ipilimumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Ipi vs. comparator
Ipilimumab	£57,760	3.3522	2.3527				
DTIC	£44,267	2.1476	1.5570	£13,492	1.2046	0.7956	**£16,958**

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Table 77: Base case results, pooled chemotherapy-naïve data for ipilimumab – BRAF V600 mutation-negative

Comparison vs. ipilimumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Ipi vs. comparator
Ipilimumab	£59,839	3.5621	2.5018				
DTIC	£42,891	2.1388	1.5532	£16,948	1.4233	0.9486	**£17,866**

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

As the ICER when comparing to DTIC for the BRAF V600 mutation-negative population is lower than when comparing for the BRAF V600 mutation-positive population (as there are no costs for use of vemurafenib at second line) comparisons for all sensitivity analyses are presented only for a BRAF V600 mutation-positive population which represents a worst case scenario.

Figure 50 and Figure 51 present tornado diagrams, illustrating the effect on the incremental net benefit per patient of treatment with ipilimumab of varying the 20 most influential parameters between their upper and lower bounds. Net benefit has been chosen as the results are easier to interpret in cases where one drug dominates another.[109]

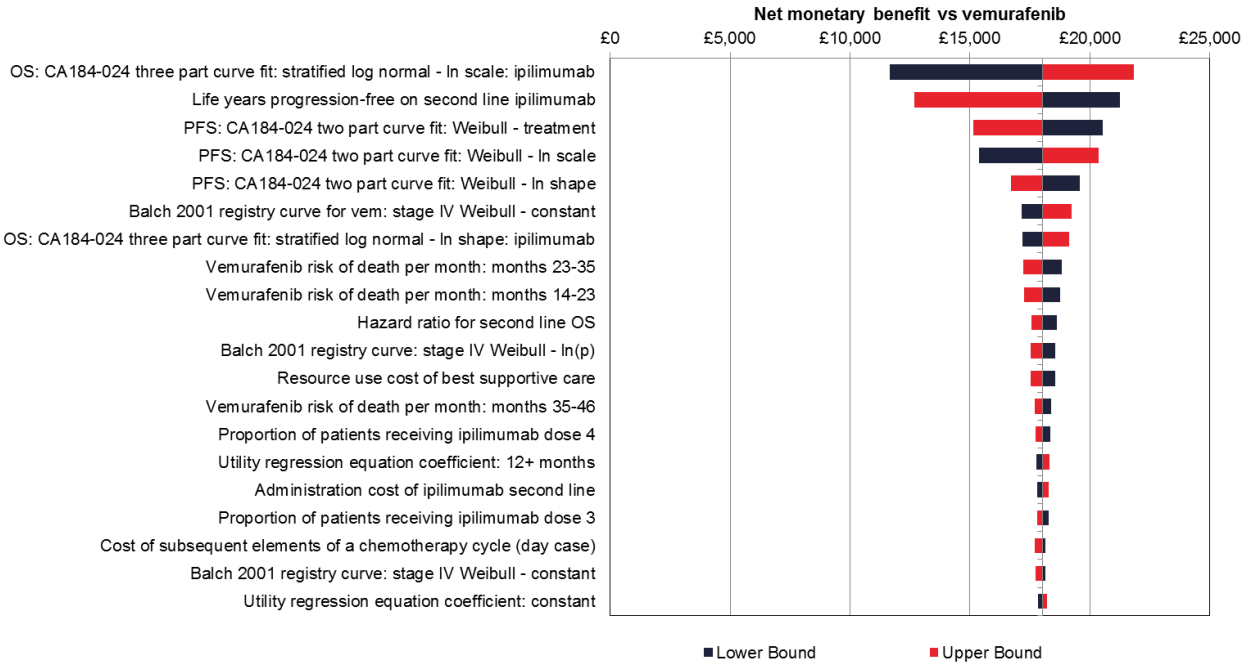
The assumed willingness to pay for a QALY used in the net benefit calculation is £30,000 compared with vemurafenib and £50,000 compared with DTIC.

The model is most sensitive to parameters used to model overall survival of ipilimumab and DTIC, the time spent on second-line treatment and the time spent on first-line treatment with ipilimumab relative to DTIC.

In all cases, the net benefit remains positive when using data from the CA184-024 clinical study, which means that for all one-way variation in parameters, ipilimumab remains cost-effective. When using data from the pooled chemotherapy-naïve analysis at the lower bound of the overall survival data for ipilimumab the net benefit is -£7,221 versus DTIC. Uncertainty has more impact when using the pooled chemotherapy-naïve dataset as analysis is based upon fewer patients (n=78 compared with n=250).

Figure 50: Tornado diagram containing 20 most influential parameters vs. vemurafenib

CA184-024 data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab

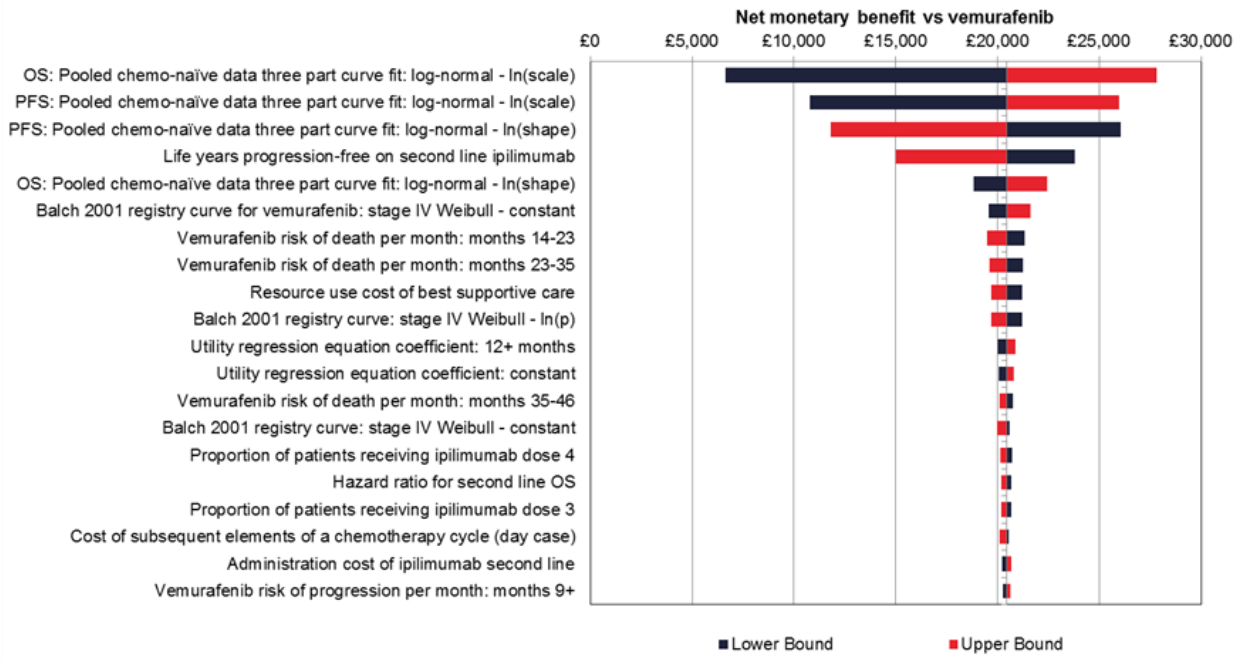
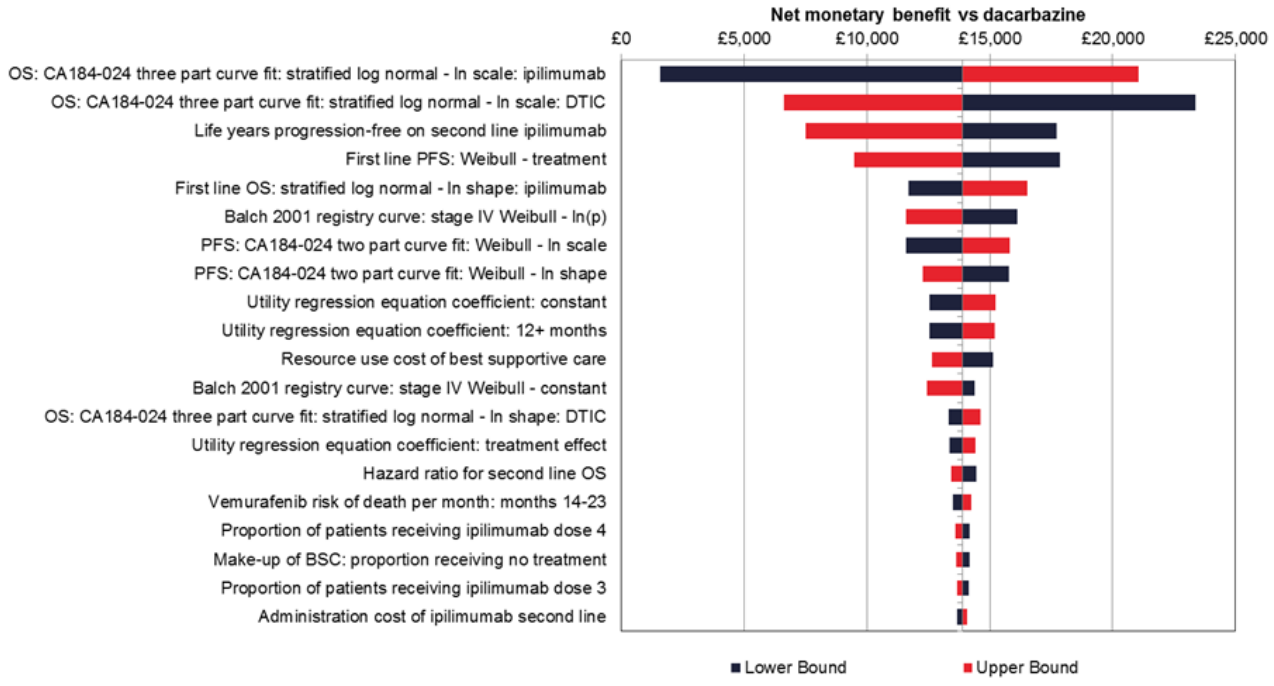
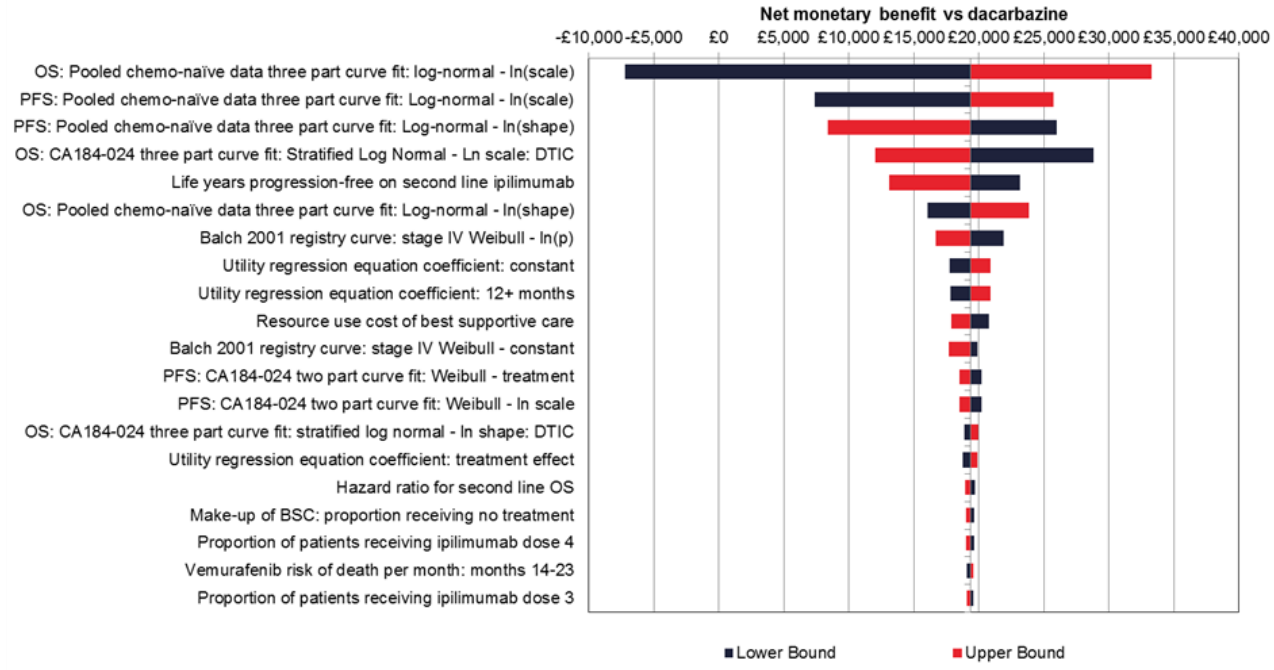


Figure 51: Tornado diagram containing 20 most influential parameters vs. DTIC

CA184-024 data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab

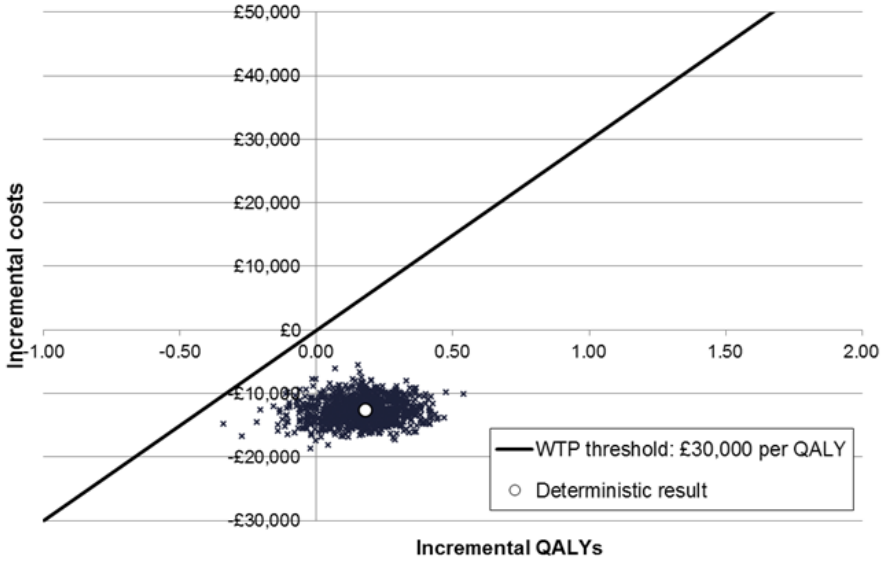


7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 52 and Figure 53 present ICER scatter plots containing the result of 1,000 runs of the probabilistic sensitivity analysis. As it can be seen, for both ipilimumab data sources the majority of the 1,000 simulation points are substantially below the line representing the £30,000 threshold vs. vemurafenib and the £50,000 threshold vs. DTIC.

Figure 52: PSA scatter plots vs. vemurafenib

CA184-024 data for ipilimumab – Ipi. vs. vemurafenib



Pooled chemotherapy-naïve data for ipilimumab – Ipi. vs. vemurafenib

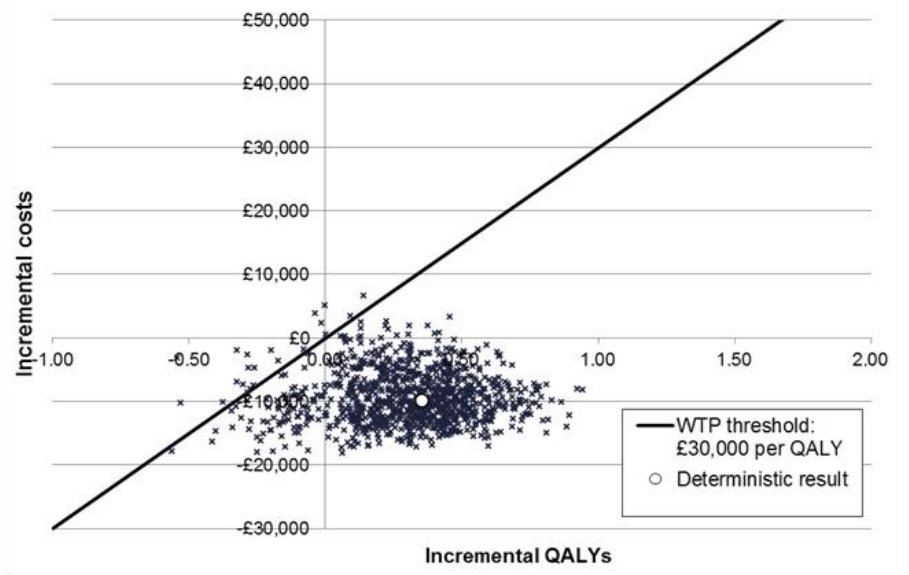
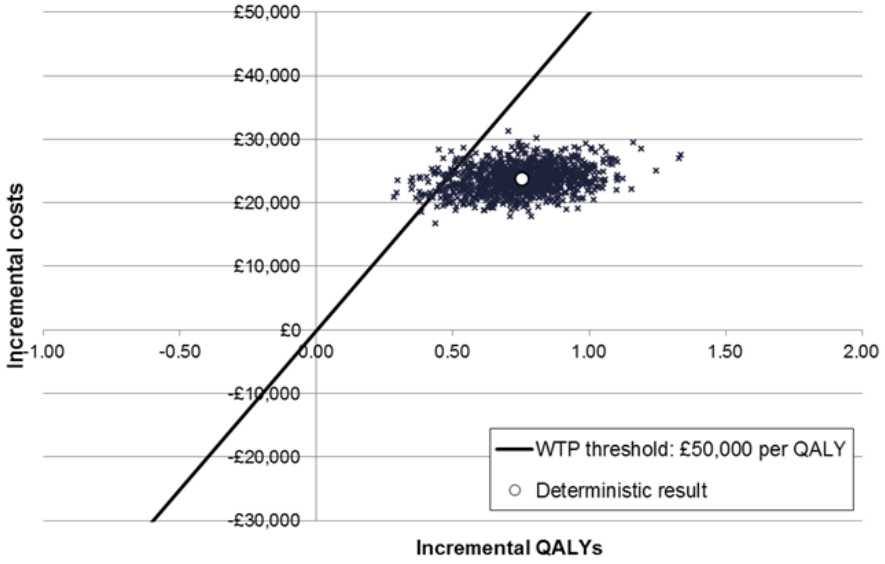


Figure 53: PSA scatter plots vs. DTIC

CA184-024 data for ipilimumab - Ipi. vs. DTIC



Pooled chemotherapy-naïve data for ipilimumab - Ipi. vs. DTIC

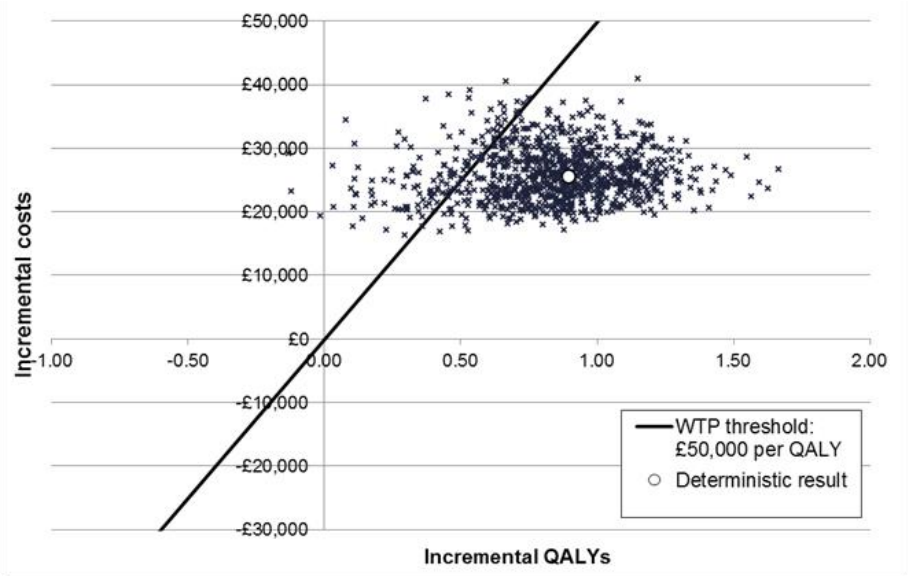
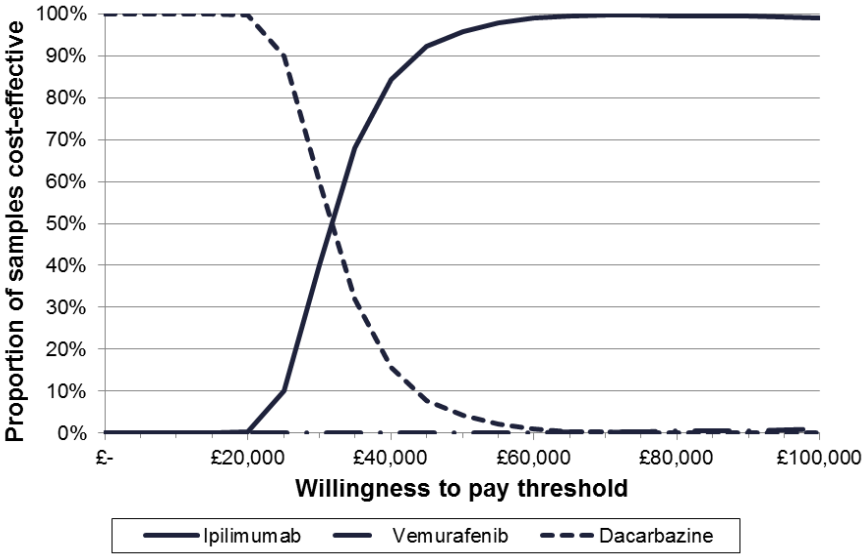


Figure 54 below shows the cost-effectiveness acceptability curves for treatment with ipilimumab: The probability of ipilimumab being the most cost-effective treatment vs. DTIC and vemurafenib is 96% at a willingness to pay threshold of £50,000 when using CA184-024 trial data; when pooled chemotherapy-naïve data are used for ipilimumab the probability of ipilimumab being the most cost-effective treatment is 87%.

Figure 54: Cost-effectiveness acceptability curves

CA184-024 data for ipilimumab



Pooled chemotherapy-naïve data for ipilimumab

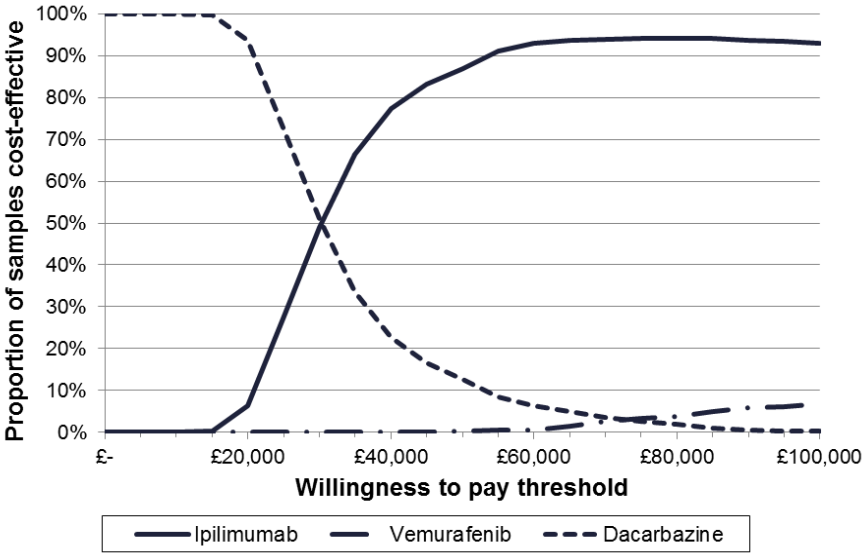


Table 78 shows that the results of the probabilistic analysis are similar to those of the deterministic analysis indicating no bias in the deterministic results deriving from skew in the distributions of the parameters.

Table 78: Results of PSA (mean over 1,000 runs)

Ipi data source	Ipilimumab		Vemurafenib		DTIC		ICER vs. vem	ICER vs. DTIC
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
CA184-024	£67,938	2.29	£80,629	2.12	£44,298	1.54	**Dominated**	**£31,619**
Pooled chemo-therapy-naïve	£68,736	2.38	£78,156	2.08	£42,898	1.54	**Dominated**	**£30,756**

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 79 reports the results of the scenario analyses (which are detailed in section 7.6.3). As can be seen from the results of the scenario analyses, the cost-effectiveness of ipilimumab is relatively insensitive to changes in the structural assumptions including the source of clinical data and assumptions regarding the modelling of survival.

The least favourable ICER produced is £49,579 vs. DTIC when CA184-024 trial data are used together with a single lognormal parametric curve fit and proportional hazards are assumed. As the single parametric curve fits are shown earlier to be a poor fit to the data and proportional hazards is not present between ipilimumab and DTIC this does not represent a realistic scenario.

In all scenarios ipilimumab remains dominant compared with vemurafenib with an incremental net benefit per patient ranging between £10,001 and £25,731 (based on CA184-024 clinical trial data).

The use of pooled chemotherapy-naïve data for ipilimumab improves the cost-effectiveness of ipilimumab and reduces the ICER compared with DTIC by approximately £3,000.

Table 79: Results of the scenario analyses (BRAF mutation-positive population)

Parameter	Base Case	Sensitivity Analysis	CA184-024 Clinical Trial data for ipilimumab				Pooled chemotherapy-naïve data for ipilimumab			
			DTIC		Vemurafenib		DTIC		Vemurafenib	
			ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*
Base case	N/A	N/A	£31,559	£13,887	Dominant	£18,034	£28,465	£19,311	Dominant	£20,445
Varying the time horizon										
Time horizon	40 Years	10 Years	£41,354	£4,690	Dominant	£16,041	£36,743	£8,682	Dominant	£17,441
		20 Years	£32,924	£12,178	Dominant	£17,677	£29,624	£17,338	Dominant	£19,904
		30 Years	£31,671	£13,730	Dominant	£18,008	£28,559	£19,129	Dominant	£20,402
Treatment Pathway										
Active second-line treatments	All patients receive either ipilimumab or vemurafenib second line	No patients receive either ipilimumab or vemurafenib second line	£42,449	£6,732	£28,980	£191	£38,364	£12,109	£22,305	£2,585
Source of best supportive care definition	MELODY study	Leeds survey	£29,620	£15,347	Dominant	£18,551	£26,603	£20,981	Dominant	£21,218
		Oxford Outcomes report	£31,185	£14,169	Dominant	£18,086	£28,113	£19,626	Dominant	£20,542
Source of adverse event incidence data	CA184-024 clinical trial	338 Observational study	£32,396	£13,257	Dominant	£17,411	£29,168	£18,681	Dominant	£19,822
Varying the approach to modelling dosing										
Patient weight data used	Weighted average	Named patient programme	£31,428	£13,986	Dominant	£18,132	£28,351	£19,413	Dominant	£20,546
		UK trial participants	£32,636	£13,076	Dominant	£17,223	£29,398	£18,475	Dominant	£19,608
Dosing calculation	Method of moments	Cost per mg	£26,359	£17,803	Dominant	£20,365	£24,068	£23,254	Dominant	£22,810
		Round up to nearest full vial	£29,486	£15,448	Dominant	£19,595	£26,668	£20,922	Dominant	£22,056

Parameter	Base Case	Sensitivity Analysis		CA184-024 Clinical Trial data for ipilimumab				Pooled chemotherapy-naïve data for ipilimumab			
				DTIC		Vemurafenib		DTIC		Vemurafenib	
				ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*
Varying the approach to modelling utilities											
Source of utility estimates	TTD and Tx effect regression CA184-024	Time to death utilities CA184-024		£31,143	£14,390	Dominant	£17,980	£28,140	£19,828	Dominant	£20,408
		Time to death utilities MDX010-20		£33,946	£11,239	Dominant	£17,573	£30,679	£16,075	Dominant	£19,563
Varying treatment efficacy assumptions											
Overall survival data source	024 trial data [Three part curve fit: Stratified Log Normal]	Five piece exponential fit		£29,120	£16,505	Dominant	£20,715	n/a	n/a	n/a	n/a
		Three part curve fit	Log Normal	£36,047	£9,001	Dominant	£16,735	n/a	n/a	n/a	n/a
			Log-logistic	£34,338	£10,702	Dominant	£16,782	n/a	n/a	n/a	n/a
			Stratified Log Logistic	£31,203	£14,348	Dominant	£17,726	n/a	n/a	n/a	n/a
			Weibull	£32,562	£12,685	Dominant	£17,127	n/a	n/a	n/a	n/a
		Single parametric curve	Stratified Log Normal	£40,923	£4,810	n/a*	n/a*	n/a	n/a	n/a	n/a
			Log Normal	£49,579	£183	n/a*	n/a*	n/a	n/a	n/a	n/a
			Stratified log-logistic	£36,982	£7,775	n/a*	n/a*	n/a	n/a	n/a	n/a
			Weibull	£37,415	£7,377	n/a*	n/a*	n/a	n/a	n/a	n/a
	Pooled chemotherapy-naïve data [Three part curve fit: Log Normal]	Five piece exponential fit		n/a	n/a	n/a	n/a	£28,197	£16,915	Dominant	£21,946
		Three part curve fit	Extreme value	n/a	n/a	n/a	n/a	£28,587	£19,114	Dominant	£19,709
			Weibull	n/a	n/a	n/a	n/a	£28,925	£18,553	Dominant	£19,806
			Log-logistic	n/a	n/a	n/a	n/a	£31,682	£14,637	Dominant	£18,673
		Single	Log Normal	n/a	n/a	n/a	n/a	£34,813	£9,426	n/a+	n/a+

Parameter	Base Case	Sensitivity Analysis		CA184-024 Clinical Trial data for ipilimumab				Pooled chemotherapy-naïve data for ipilimumab			
				DTIC		Vemurafenib		DTIC		Vemurafenib	
				ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*
		parametric curve:	Log-logistic	n/a	n/a	n/a	n/a	£38,872	£6,051	n/a+	n/a+
Progression-free survival data source	024 trial data [Two part curve fit: Weibull]	Two part curve fit	Stratified Weibull	£31,240	£14,182	Dominant	£18,265	n/a	n/a	n/a	n/a
			Extreme value	£34,012	£11,659	Dominant	£16,206	n/a	n/a	n/a	n/a
			Stratified Extreme Value	£34,030	£11,641	Dominant	£16,191	n/a	n/a	n/a	n/a
		Single parametric curve	Stratified Log-logistic	£33,238	£11,474	Dominant	£14,689	n/a	n/a	n/a	n/a
			Log-logistic	£43,074	£4,388	Dominant	£10,001	n/a	n/a	n/a	n/a
			Stratified Log Normal	£36,032	£9,448	Dominant	£14,326	n/a	n/a	n/a	n/a
			Log Normal	£42,813	£4,608	Dominant	£11,253	n/a	n/a	n/a	n/a
	Pooled chemotherapy-naïve data [Three part curve fit: Log Normal]	Two part curve fit	Log-logistic	n/a	n/a	n/a	n/a	£28,566	£19,563	Dominant	£21,532
			Weibull	n/a	n/a	n/a	n/a	£32,921	£14,401	Dominant	£16,498
Vemurafenib overall and time on treatment data source	Vemurafenib NICE submission	ERG increased hazards		£32,326	£12,941	Dominant	£25,731	£28,716	£18,890	Dominant	£28,358
Source of registry data	Balch 2001	Balch 2009		£26,532	£21,683	Dominant	£19,080	£24,160	£28,228	Dominant	£22,316
Curve choice for Balch registry data	Weibull	Log Normal		£31,030	£14,567	Dominant	£18,162	£28,007	£20,092	Dominant	£20,649
		Gompertz		£31,771	£13,622	Dominant	£17,805	£28,655	£18,995	Dominant	£20,185
		Log-logistic		£30,878	£14,768	Dominant	£18,268	£27,874	£20,329	Dominant	£20,777

*willingness to pay threshold £50,000 compared with DTIC and £30,000 compared with vemurafenib, +not provided as no single curve fits are available for vemurafenib.

7.7.10 What were the main findings of each of the sensitivity analyses?

The main finding of the deterministic sensitivity analysis reported in section 7.7.7 is that the model is most sensitive to the curve fit parameters for the overall survival of ipilimumab and DTIC, the time spent on second-line treatment and the time spent on first-line treatment with ipilimumab relative to DTIC. However, for all of the values within the 95% CI of the parameters, ipilimumab remains a cost-effective use of healthcare resources when using analysis based upon the CA184-024 trial, at a threshold of £50,000 per QALY gained vs. DTIC and £30,000 per QALY vs. vemurafenib.

The probabilistic sensitivity analysis indicated that simultaneous variation in the parameter values did not affect the result that ipilimumab was cost-effective. This is illustrated by Figure 54 which shows that the model estimates ipilimumab to have a 96% probability of being the most cost-effective treatment at a willingness-to-pay threshold of £50,000 per QALY, 40% at £30,000 per QALY and 0% at £20,000 per QALY (87%; 49% and 6% when using pooled chemotherapy-naïve data for ipilimumab).

The scenario analyses indicated that the cost-effectiveness of ipilimumab is not sensitive to structural uncertainty. None of the variations made to the base-case specification resulted in an ICER that was no longer cost-effective. The least favourable ICER was £49,579 vs. DTIC, when CA184-024 trial data are used and a single lognormal parametric curve fit is used and proportional hazards are assumed. As the single parametric curve fits are shown earlier to be a poor fit to the data and proportional hazards is not present between ipilimumab and DTIC this does not represent a realistic scenario.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key driver of the cost-effectiveness results is the enhanced efficacy profile of ipilimumab. As the data package presented, consisting of a large number of Phase III and Phase II trials, shows a much larger proportion of patients receiving ipilimumab exhibit long-term survival above what would be expected with current treatments or with treatment with vemurafenib. The trials presented for ipilimumab contain follow-up of up to 10 years, compared with a maximum follow-up of 18 months in the BRIM-3 trial for vemurafenib.

In addition, as ipilimumab is already approved for second-line treatment when patients lose response to vemurafenib and DTIC standard clinical practice would be to treat with ipilimumab if patients are still fit enough (estimated to be 55% of patients following treatment with vemurafenib; 51% following treatment with DTIC). This means that the costs of ipilimumab are then incurred in addition to the costs of the original first-line treatment and additionally a proportion of patients will miss out on treatment with ipilimumab having died before they became eligible for treatment under the existing NICE approval.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Previous appraisal of ipilimumab

The general model structure is consistent with the model used to assess the cost-effectiveness of ipilimumab in previously treated patients, components of which are also included in this model. As outlined in section 7.3.5, these elements were validated by key opinion leaders practising in the UK. The input of these clinicians has been used to inform the methods for survival analyses, dosing and application of adverse events.

Quality of life

The utility values used in the model are similar to those identified in the systematic search presented in section 7.4. This suggests that the approximate values used are consistent with those typically associated with a malignant melanoma population.

The methods used to model quality of life are also consistent with previous estimates. Utility values used in the model are similar to those used in the economic model used previously in the appraisal of second-line ipilimumab. These values were validated by clinicians, as outlined in section 7.4.10. The clinical opinion elicited suggested that there was a preference for direct quality of life measurements collected in clinical trials than alternative sources in published literature, as these were typically based on valuation of vignettes. The clinicians also indicated that progression-based utility estimates might not be sufficient to accurately capture patient quality of life.

Clinical benefit of ipilimumab

Ipilimumab is the only available treatment that is able to provide long-term survival gains for patients. These gains have been demonstrated in a large number of clinical trials, 2 US observational studies and an independent data analysis (Figure 55).[20, 59-61,110]

Figure 55: Long-term survival benefit of treatment with ipilimumab

[redacted]

NCI = National Cancer Institute[110]

Additionally analyses of the 1861 patients included in the ipilimumab Phase II and III trials (MDX010-20, CA184-024, CA184-022, CA184-008, CA184-007, CA184-004, CA184-024) showed similar results. OS showed a plateau around year 3 and extended out to year 10 in some patients, this plateau was similar (slightly lower) for previously treated compared with treatment-naïve patients. Dose or treatment regimen did not appear to impact the plateau. The plateau was also similar when the analysis included expanded access programme data from CA184-045.[38]

Expert validation

The model approach and inputs have been validated by 3 leading external health economists[5] who were approached in order to validate the economic model during a validation meeting and a telephone interview. These experts were selected as key opinion leaders practicing in the UK. The model was presented to the health economists during the interviews including the clinical trial data package, the model structure, the assumptions regarding treatment pathway, the survival analysis undertaken, the quality of life analysis undertaken and the methodology used for costs and resource use.

The opinions provided by these external health economists were used in order to determine the model base case in terms of survival analysis and quality of life. The external health economists did not verify the accuracy of the implementation/ programming of the model, this was conducted via internal quality control processes.

Comparability with UK population

The population included within CA184-024 is generally comparable to the UK population (n=220) receiving 1st line therapy reported in Lorigan et al. The CA184-024 trial population may be slightly more severe, containing more patients with elevated LDH and tumour stage M1c.

Table 80: Comparison of UK population to CA184-024

	CA184-024	Lorigan 2013
Median age	57	59
% male	60	56
Median (mean) time from first diagnosis to diagnosis of advanced melanoma, years	1.7 (3.2)	2.1 (3.7)
Elevated serum LDH level	40%	33%
Tumour stage M0 M1a M1b M1c Unknown	 3% 16% 25% 56% -	 19% 11% 19% 41% 10%

[5] These external health economists included Prof. Andrew Briggs and Prof. Ron Akehurst.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analysis was undertaken.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Within the scope it was stated that if evidence allows, subgroup analyses according to performance status may be considered.

An analysis conducted for the European regulatory body investigated the relationship between discontinuation of treatment and baseline ECOG status for subjects in the DTIC monotherapy and ipilimumab + DTIC groups in CA184-024. In the ipilimumab + DTIC group, the rate of discontinuation due to study drug toxicity was similar for patients with an ECOG performance status of 0 compared with 1 (37% vs. 33%). Furthermore, the rate of discontinuation due to “disease progression” + “clinical deterioration without disease progression” was similar for ECOG performance status of 0 compared with 1 (approximately 50%). Since the analysis concluded that there does not appear to be a clear association in the ipilimumab + DTIC group between ECOG performance status and study drug discontinuation, a subgroup analysis stratified by performance status was not considered.[61]

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No relevant published literature was identified. The results of this submission are, however, consistent with the previous submission for ipilimumab in previously treated patients (see section 7.8). The incremental cost-effectiveness ratio within this analysis when comparing treatment with vemurafenib alone to DTIC alone is higher than in the previous submission for vemurafenib (TA269) £47,687 vs. £44,405 as AJCC registry based mortality rates are used in this analysis (in line with what is assumed for DTIC). These mortality rates are higher than the SEER database which is used in the vemurafenib submission.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the evaluation are that it is based on UK clinical practice and populated by the long-term efficacy data of patients treated with ipilimumab. In

particular, the length of follow-up and amount of follow-up data should be stressed. These include multiple RCTs, including a large number of patients and HRQL data measured through a disease specific metric used to produce trial-based utilities. Extensive sensitivity analyses have been carried out to determine the sensitivity of the model to a variety of structural assumptions surrounding data source, treatment pathway, utilities and modelling of overall survival and time spent on treatments.

The main weaknesses of the model are:

- the trial data available only contain comparative data against DTIC
- the head to head trial data available for ipilimumab compared with DTIC are for a 10mg/kg dose

However, these weaknesses are not critical. As shown in Figure 35 the DTIC arms of the CA184-024 and BRIM-3 are very similar indicating no difference in the prognosis of patients between trials, additionally available evidence shows ipilimumab to be equally effective in BRAF V600 mutation-positive and -negative patients. Available evidence also indicates that there is no difference in efficacy between the 3mg/kg and 10mg/kg dose and this conclusion was accepted by the EMA (see section 6.10 for further information).

It should be noted that the use of registry data after 5 years within the modelling, i.e. assuming that there is no further benefit from ipilimumab beyond the duration of the CA184-024 clinical trial evidence is highly conservative as evidence presented at ESMO indicates continuing benefit above the decline that would be expected using the registry out to 10 years.[85]

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Due to the level of certainty in the results demonstrated both clinically, and in the economic evaluation (96% chance of cost-effectiveness at £50,000 per QALY, only one scenario analysis above £50,000/QALY), it is unlikely that further studies would result in a change in decision. Indeed the only plausible item missing from this submission are directly measured EQ-5D values, with HRQL instead measured by the EORTC QLQ C-30. Long-term registry studies are being undertaken in the US to confirm the efficacy of ipilimumab in a real-world setting. As shown in section 7.8 the initial results from these studies (up to 1.8 years maximum follow-up) confirm the benefits of ipilimumab in terms of overall survival included within this analysis.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The eligible population numbers have been estimated as per the methodologies set out in the NICE costing template,[NICE TA269 Costing] and these are presented in Table 81. The most recently published Incidence rates for malignant melanoma in 2011 in England and Wales were combined to produce estimates for the period 2014-2018.[21]

Table 81: Estimates of incident population

Parameters	Estimate	Source
Total population of England & Wales	56,792,422	NICE costing template[22]
Incidence of advanced melanoma	0.0210%	Average of male and female incidences
	0.0208%	Cancer registrations 2011[21]
	0.0211%	Cancer registrations 2011
Proportion of patient with stage IIIC or IV disease	10.00%	Vemurafenib appraisal ERG report[32]
Estimated incident patients eligible for treatment in England & Wales in 2011	1190	Calculated
% increase in incidence per annum	3.5%	Decision Resources Malignant Melanoma June 2006[22]
Incident patients eligible for treatment in England & Wales in 2014	1319	Calculated
Proportion of patients who are BRAF V600 mutation-positive	48.00%	Long et al. (2011)[111]
BRAF V600 mutation-positive incident patients	633	Calculated
BRAF V600 mutation-negative incident patients	686	Calculated

The number of patients eligible for treatment with ipilimumab was calculated as the proportion of malignant melanoma patients with stage IIIc or IV malignant melanoma from the overall incidence.[32]

The estimated patient numbers for the BRAF V600 mutation-positive and -negative subgroups respectively have been estimated from the expected number of patients eligible for treatment and the proportion that are expected to be BRAF V600 mutation-positive.[111] The increase in incidence per year was assumed to be 3.5%.[22]The total numbers of eligible patients from Year 1 to Year 5 (2014 to 2018) are shown in Table 82.

Table 82: Population eligible for treatment with ipilimumab in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of newly diagnosed malignant melanoma patients	1319	1365	1413	1463	1514
Expected number of BRAF V600 mutation-positive patients	633	655	678	702	727
Expected number of BRAF V600 mutation-negative patients	686	710	735	761	787

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Four main assumptions were made in estimating the number of patients eligible to receive ipilimumab as first-line treatment.

1. It was assumed that all patients are tested for BRAF V600 mutation status.[22]
2. 0% are treated through clinical trials[22]
3. 3.5% incidence change rates per year[22]
4. Only incident patients were considered eligible for treatment, as prevalent patients are assumed to have already received first-line treatment.

8.3 What assumption(s) were made about market share (when relevant)?

The estimated market share of each drug is shown in Table 83. For BRAF V600 mutation-positive patients, the market share of ipilimumab is expected to be 10% in year 1, rising to 23% in year 3 (2016). For BRAF V600 mutation-negative patients, the market share was expected to be 40% in year 1, rising to 63% in year 3. Due to limited forecasts, the market shares projected for years 4 and 5 (2017 and 2018) are assumed to be the same at those for year 3 (2016).

For patients not treated with ipilimumab, the distribution of treatments was expected to be a 75%-share for vemurafenib and a 25%-share for DTIC. This is incorporated into the figures shown below and is assumed to be the distribution of treatments in the absence of ipilimumab. The estimated total number of new patients treated with ipilimumab is 338 in year 1 and 663 in year 5.

Table 83: Eligible population in England and Wales: breakdown by treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
	2014	2015	2016	2017	2018
BRAF V600 mutation-positive patients					
New incident patients per year	633	655	678	702	727
Expected market share of ipilimumab	10%	22%	23%	23%	23%
Expected market share of DTIC	23%	20%	19%	19%	19%
Expected market share of vemurafenib	68%	59%	58%	58%	58%
New patients treated with ipilimumab	63	144	156	161	167
New patients treated with vemurafenib	427	383	392	405	420
New patients treated with DTIC	142	128	131	135	140
BRAF V600 mutation-negative patients					
New incident patients per year	686	710	735	761	787
Expected market share of ipilimumab	40%	60%	63%	63%	63%
Expected market share of DTIC	60%	40%	37%	37%	37%
New patients treated with ipilimumab	274	426	463	479	479
New patients treated with DTIC	412	284	272	281	291

Appendix K shows the movement treatment of patients over time through the budget impact for those patients treated each year.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The costs included in the budget impact estimation are those included in the economic model, as presented in section 7.5.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

All costs considered in the budget impact analysis are those included in the economic model, as reported in section 7.5.

8.6 Were there any estimates of resource savings? If so, what were they?

The differential costs considered, both budget impact and budget savings, are incorporated as the incremental costs as calculated in the economic model.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The incremental budget impact is shown in Table 84, as the difference in costs in the treatment arms over the first five years of the economic model, scaled up to account for the number of patients expected to receive each treatment each year.

Table 84: Estimated budget impact over five years

Using data for ipilimumab from CA184-024

Total Budget Impact over 5 years	Year				
	1	2	3	4	5
First-line drug costs - ipilimumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
First-line drug costs - vemurafenib	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
First-line drug costs - DTIC	-£61,230	-£97,479	-£105,899	-£109,606	-£113,442
First-line administration costs	-£70,609	-£91,594	-£99,806	-£103,299	-£106,915
Second-line drug costs - ipilimumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Second-line drug costs - vemurafenib	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Second-line drug costs - BSC	£10,484	£16,889	£18,905	£19,970	£20,940
Second-line administration costs	-£56,798	-£144,886	-£200,514	-£223,581	-£235,601
Third-line drug costs - BSC	-£666	-£1,220	-£2,192	-£2,637	-£2,811
Third-line administration costs	-£1,166	-£973	-£3,898	-£5,208	-£5,563
Resource use costs	£46,352	£200,390	£399,874	£603,224	£812,333
Palliative care costs	-£262,559	-£446,686	-£511,708	-£537,188	-£561,373
Adverse events costs	£10,056	£17,183	£20,071	£22,813	£25,836
Total costs	**£5,251,133**	**£6,320,854**	**£4,859,371**	**£4,399,302**	**£4,505,867**

Using data for ipilimumab from pooled chemotherapy-naïve data

Total Budget Impact over 5 years	Year				
	1	2	3	4	5
First-line drug costs - ipilimumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
First-line drug costs - vemurafenib	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
First-line drug costs - DTIC	-£61,409	-£97,764	-£106,209	-£109,926	-£113,774
First-line administration costs	-£62,317	-£77,623	-£84,640	-£87,602	-£90,668
Second-line drug costs - ipilimumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Second-line drug costs - vemurafenib	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Second-line drug costs - BSC	£12,224	£19,606	£21,679	£22,614	£23,517
Second-line administration costs	-£46,139	-£120,294	-£167,587	-£187,954	-£199,001
Third-line drug costs - BSC	-£614	-£755	-£1,556	-£1,962	-£2,158
Third-line administration costs	-£412	£2,080	-£139	-£1,360	-£1,833
Resource use costs	£155,327	£418,287	£665,286	£897,050	£1,139,209
Palliative care costs	-£384,515	-£597,020	-£576,565	-£562,246	-£593,755
Adverse events costs	£10,630	£18,280	£21,255	£23,967	£26,960
Total costs	**£5,699,448**	**£7,454,213**	**£6,505,563**	**£6,258,640**	**£6,449,914**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

All costs expected to be relevant to the NHS budget are included.

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10 Appendices

10.1 Appendix 1 Ipilimumab (Yervoy®) SPC

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 5 mg ipilimumab.
One 10 ml vial contains 50 mg of ipilimumab.
One 40 ml vial contains 200 mg of ipilimumab.

Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody (IgG1κ) produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipients with known effect:

Each ml of concentrate contains 0.1 mmol sodium, which is 2.30 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates and has a pH of 7.0 and an osmolarity of 260-300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

4.2 Posology and method of administration

Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Posology

Adults

The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Tables 1A, 1B, and section 4.4).

Permanent discontinuation of treatment or withholding of doses
Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see section 4.4).

Dose reduction is not recommended.
Guidelines for permanent discontinuation or withholding of doses are described in Tables 1A and 1B. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1A When to permanently discontinue YERVOY	
Permanently discontinue YERVOY in patients with the following adverse reactions. Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related (see section 4.4 for detailed management guidelines).	
Severe or life-threatening adverse reactions	**NCI-CTCAE v3 Grade[a]**
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	▪ Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	▪ AST or ALT > 8 x ULN or ▪ Total bilirubin > 5 x ULN
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)	▪ ≥ Grade 3 immune-related reactions[c] ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy

[a] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).

[b] Any other adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to discontinue YERVOY should be based on severity.

[c] Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

ULN = upper limit of normal

Table 1B When to withhold dose of YERVOY	
Withhold YERVOY dose[a] in patients with the following immune-related adverse reactions. See section 4.4 for detailed management guidelines.	
Mild to moderate adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs, resume therapy.[d] 3. If resolution has not occurred, continue to withhold doses until resolution then resume treatment.[d] 4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels	
Skin: Moderate to severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology	
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy	
Neurological: Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse reactions[c]	

[a] No dose reduction of YERVOY is recommended.

[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).

[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. Decision whether to withhold a dose should be based on severity.

[d] Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

ULN = upper limit of normal

Paediatric population

The safety and efficacy of YERVOY in children below 18 years of age have not been established. No data are available. YERVOY should not be used in children below 18 years of age.

Special populations

Older people
No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). No specific dose adjustment is necessary in this population.

Patients with renal impairment
The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see section 5.2).

Patients with hepatic impairment

The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild hepatic impairment (see section 5.2). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see section 5.1).

Method of administration

The recommended infusion period is 90 minutes.

YERVOY can be used for intravenous administration without dilution or may be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection to concentrations between 1 and 4 mg/ml.

YERVOY must not be administered as an intravenous push or bolus injection.

For instructions on the handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ipilimumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions occurred during the induction period, onset months after the last dose of ipilimumab has also been reported. Unless an alternate etiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions. Ipilimumab-specific management guidelines for immune-related adverse reactions are described below.

Immune-related gastrointestinal reactions

Ipilimumab is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in clinical trials (see section 4.8).

In patients who received ipilimumab 3 mg/kg monotherapy in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1), the median time to onset of severe or fatal (Grade 3-5) immune-related gastrointestinal reactions was 8 weeks (range 5 to 13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution (defined as improvement to mild [Grade 1] or less or to the severity at baseline) occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks).
Patients must be monitored for gastrointestinal signs and symptoms that may be indicative of immune-related colitis or gastrointestinal perforation. Clinical presentation may include diarrhoea, increased frequency of bowel movements, abdominal pain, or haematochezia, with or without fever. Diarrhoea or colitis occurring after initiation of ipilimumab must be promptly evaluated to exclude infectious or other alternate etiologies. In clinical trials, immune-related

colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per NCI-CTCAE v3 severity grading classification). Patients with mild to moderate (Grade 1 or 2) diarrhoea (an increase of up to 6 stools per day) or suspected mild to moderate colitis (e.g. abdominal pain or blood in stools) may remain on ipilimumab. Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of ipilimumab should be withheld and corticosteroid therapy (e.g. prednisone 1 mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, ipilimumab may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see section 4.2), and systemic high-dose intravenous corticosteroid therapy should be initiated immediately. (In clinical trials, methylprednisolone 2 mg/kg/day has been used). Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment. In clinical trials, rapid tapering (over periods < 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.
The experience from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis is limited. However, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, a single dose of infliximab 5 mg/kg was added unless contraindicated. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected (see the Summary of Product Characteristics for infliximab).

<u>Immune-related hepatotoxicity</u>

Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials (see section 4.8).

In patients who received ipilimumab 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to severe or fatal (Grade 2-5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. With protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks.

Hepatic transaminase and bilirubin must be evaluated before each dose of ipilimumab, as early laboratory changes may be indicative of emerging immune-related hepatitis (see section 4.2). Elevations in LFTs may develop in the absence of clinical symptoms. Increases in AST and ALT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, tumour progression, or concomitant medication and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

For patients with elevated AST or ALT in the range of > 5-≤ 8 x ULN or total bilirubin in the range of > 3-≤ 5 x ULN that is suspected to be related to ipilimumab, the scheduled dose of ipilimumab should be withheld, and LFTs must be monitored until resolution. After LFT levels improve (AST and ALT ≤ 5 x ULN and total bilirubin ≤ 3 x ULN), ipilimumab may be resumed (see section 4.2).

For patients with AST or ALT elevations > 8 x ULN or bilirubin > 5 x ULN that are suspected to be related to ipilimumab, treatment must be permanently discontinued (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg daily or equivalent) should be initiated immediately. In such patients, LFTs must be monitored until normalization. Once symptoms have resolved and LFTs show sustained improvement or return

to baseline, the initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.

For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, mycophenolate mofetil was used in patients without response to corticosteroid therapy, or who had an LFT elevation during corticosteroid tapering that was not responsive to an increase in the dose of corticosteroids (see the Summary of Product Characteristics for mycophenolate mofetil).

Immune-related skin adverse reactions

Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis has been reported in clinical trials (see section 4.8).

Ipilimumab-induced rash and pruritus were predominantly mild or moderate (Grade 1 or 2) and responsive to symptomatic therapy. In patients who received ipilimumab 3 mg/kg monotherapy in MDX010-20, the median time to onset of moderate to severe or fatal (Grade 2-5) skin adverse reactions was 3 weeks (range 0.9-16 weeks) from start of treatment. With protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

Ipilimumab-induced rash and pruritus should be managed based on severity. Patients with a mild to moderate (Grade 1 or 2) skin adverse reaction may remain on ipilimumab therapy with symptomatic treatment (e.g. antihistamines). For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids, oral corticosteroid therapy should be initiated (e.g. prednisone 1 mg/kg once daily or equivalent).

For patients with a severe (Grade 3) skin adverse reaction, the scheduled dose of ipilimumab should be withheld. If initial symptoms improve to mild (Grade 1) or resolve, ipilimumab therapy may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with a very severe (Grade 4) rash or severe (Grade 3) pruritus (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled, initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

Immune-related neurological reactions

Ipilimumab is associated with serious immune-related neurological adverse reactions. Fatal Guillain-Barré syndrome has been reported in clinical trials. Myasthenia gravis-like symptoms have also been reported (see section 4.8). Patients may present with muscle weakness. Sensory neuropathy may also occur.
Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting > 4 days must be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic syndromes and concomitant medication should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to ipilimumab, the scheduled dose should be withheld. If neurologic symptoms resolve to baseline, the patient may resume ipilimumab (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to ipilimumab (see section 4.2). Patients must be treated

according to institutional guidelines for management of sensory neuropathy, and intravenous corticosteroids (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately.

Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality (see section 4.2).

Immune-related endocrinopathy

Ipilimumab can cause inflammation of the endocrine system organs, manifesting as hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism (see section 4.8), and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioural changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms must be excluded. Clinical experience with ipilimumab-associated endocrinopathy is limited.

For patients who received ipilimumab 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to very severe (Grade 2-4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with immunosuppressive therapy and hormone replacement therapy.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for presence of sepsis or infections. If there are signs of adrenal insufficiency but the patient is not in adrenal crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy (e.g. dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of ipilimumab should be withheld (see section 4.2). It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with ipilimumab may be resumed and initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

Other immune-related adverse reactions

The following additional adverse reactions suspected to be immune-related have been reported in patients treated with ipilimumab 3 mg/kg monotherapy in MDX010-20: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with ipilimumab 3 mg/kg + gp100 peptide vaccine in MDX010-20 (see section 4.8).

If severe (Grade 3 or 4), these reactions may require immediate systemic high-dose corticosteroid therapy and discontinuation of ipilimumab (see section 4.2). For ipilimumab-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

Special populations

Patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the pivotal clinical trial (see section 5.1).

Infusion reaction

There were isolated reports of severe infusion reactions in clinical trials. In case of a severe infusion reaction, ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring. Premedication with antipyretic and antihistamine may be considered.

Patients with autoimmune disease

Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism), including those who require systemic immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance, were not evaluated in clinical trials. Ipilimumab is a T-cell potentiator that enables the immune response (see section 5.1) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In other patients with a history of autoimmune disease, ipilimumab should be used with caution after careful consideration of the potential risk-benefit on an individual basis.

Patients on controlled sodium diet

Each ml of this medicinal product contains 0.1 mmol (or 2.30 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

Concurrent administration with vemurafenib

In a Phase 1 trial, asymptomatic grade 3 increases in transaminases (ALT/AST > 5 × ULN) and bilirubin (total bilirubin > 3 × ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and vemurafenib is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes.
A drug-interaction study of ipilimumab administered alone and in combination with chemotherapy (dacarbazine or paclitaxel/carboplatin) was conducted evaluating interaction with CYP isozymes (particularly CYP1A2, CYP2E1, CYP2C8, and CYP3A4) in patients with treatment-naive advanced melanoma. No clinically relevant pharmacokinetic drug-drug interaction was observed between ipilimumab and paclitaxel/carboplatin, dacarbazine or its metabolite, 5-aminoimidazole-4-carboxamide (AIC).

Other forms of interaction

Corticosteroids
The use of systemic corticosteroids at baseline, before starting ipilimumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after

starting ipilimumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting ipilimumab treatment does not appear to impair the efficacy of ipilimumab.

Anticoagulants
The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab (see section 4.8), patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of ipilimumab in pregnant women. Animal reproduction studies have shown reproductive toxicity (see section 5.3). Human IgG1 crosses the placental barrier. The potential risk of treatment to the developing foetus is unknown. YERVOY is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

Breast-feeding

Ipilimumab has been shown to be present at very low levels in milk from cynomolgus monkeys treated during pregnancy. It is unknown whether ipilimumab is secreted in human milk. Secretion of IgGs in human milk is generally limited and IgGs have a low oral bioavailability. Significant systemic exposure of the infant is not expected and no effects on the breastfed newborn/infant are anticipated. However, because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue from YERVOY therapy taking into account the benefit of breast-feeding for the child and the benefit of YERVOY therapy for the woman.

Fertility

Studies to evaluate the effect of ipilimumab on fertility have not been performed. Thus, the effect of ipilimumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

YERVOY has minor influence on the ability to drive and use machines.

Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that ipilimumab does not adversely affect them.

4.8 Undesirable effects

Summary of safety profile

Ipilimumab has been administered to approximately 10,000 patients in a clinical program evaluating its use with various doses and tumour types. Unless otherwise specified, the data below reflect exposure to ipilimumab at 3 mg/kg in clinical trials of melanoma. In the Phase 3 study MDX010-20, (see section 5.1), patients received a median of 4 doses (range 1-4).

Ipilimumab is most commonly associated with adverse reactions resulting from increased or excessive immune activity. Most of these, including severe reactions, resolved following

initiation of appropriate medical therapy or withdrawal of ipilimumab (see section 4.4 for management of immune-related adverse reactions).

In patients who received 3 mg/kg ipilimumab monotherapy in MDX010-20, the most frequently reported adverse reactions (≥ 10% of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority were mild to moderate (Grade 1 or 2). *Ipilimumab* therapy was discontinued for adverse reactions in 10% of patients.

Tabulated list of adverse reactions

Adverse reactions reported in patients with advanced melanoma who were treated with ipilimumab 3 mg/kg in clinical trials (n= 767) are presented in Table 2.

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Rates of immune-related adverse reactions in HLA-A2*0201 positive patients who received ipilimumab in MDX010-20 were similar to those observed in the overall clinical program.

The safety profile of ipilimumab 3 mg/kg in chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials (N= 75; treated) and in treatment-naive patients in a retrospective observational study (N= 120) was similar to that in previously-treated advanced melanoma.

Table 2: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg (n= 767)[a]	
Infections and infestations	
Uncommon	sepsis[b], septic shock[b], urinary tract infection, respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopenia
Uncommon	haemolytic anaemia[b], thrombocytopenia, eosinophilia, neutropenia
Immune system disorders	
Uncommon	Hypersensitivity
Endocrine disorders	
Common	hypopituitarism (including hypophysitis)[c], hypothyroidism[c]
Uncommon	adrenal insufficiency[c], hyperthyroidism[c], hypogonadism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalemia
Uncommon	hyponatremia, alkalosis, hypophosphatemia, tumour lysis syndrome
Psychiatric disorders	
Common	confusional state
Uncommon	mental status changes, depression, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy
Uncommon	Guillain-Barré syndrome[b,c], meningitis (aseptic), syncope, cranial neuropathy, brain oedema, peripheral neuropathy, ataxia, tremor, myoclonus, dysarthria
Eye disorders	
Common	blurred vision, eye pain
Uncommon	uveitis[c], vitreous haemorrhage, iritis[c], reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Cardiac disorders	
Uncommon	arrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy[b], peripheral ischaemia, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, cough
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis, allergic rhinitis
Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea
Common	gastrointestinal haemorrhage, colitis[b,c], constipation, gastroesophageal reflux disease, abdominal pain
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c], peritonitis[b], gastroenteritis, diverticulitis, pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus[d]
Hepatobiliary disorders	
Common	abnormal hepatic function
Uncommon	hepatic failure[b,c], hepatitis, hepatomegaly, jaundice

Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus[c]
Common	dermatitis, erythema, vitiligo, urticaria, alopecia, night sweats, dry skin
Uncommon	toxic epidermal necrolysis[b,c], leukocytoclastic vasculitis, skin exfoliation
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, musculoskeletal pain, muscle spasms
Uncommon	polymyalgia rheumatica, arthritis
Renal and urinary disorders	
Uncommon	renal failure[b], glomerulonephritis[c], renal tubular acidosis
Reproductive system and breast disorders	
Uncommon	Amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia
Common	chills, asthenia, oedema, pain
Uncommon	multi-organ failure[b,c], infusion related reaction
Investigations	
Common	increased alanine aminotransferase[c], increased aspartate aminotransferase[c], increased blood bilirubin, weight decreased
Uncommon	increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, increased lipase[c], increased blood amylase[c], decreased blood testosterone

a Frequencies are based on pooled data from 9 clinical trials investigating the ipilimumab 3 mg/kg dose in melanoma.
b Including fatal outcome.
c Additional information about these potentially inflammatory adverse reactions is provided in "Description of selected adverse reactions" and section 4.4. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.
d Reported in recent studies outside the completed clinical trials in melanoma.

Additional adverse reactions not listed in Table 2 have been reported in patients who received other doses (either < or > 3 mg/kg) of ipilimumab in clinical trials of melanoma. These additional reactions occurred at a frequency of < 1% unless otherwise noted: meningism, myocarditis, pericardial effusion, cardiomyopathy, autoimmune hepatitis, erythema multiforme, erythema nodosum, hair colour changes, autoimmune nephritis, autoimmune pancreatitis, myasthenia gravis-like symptoms, muscular weakness, autoimmune thyroiditis, hyperpituitarism, secondary adrenocortical insufficiency, hypoparathyroidism, thyroiditis, systemic inflammatory response syndrome, influenza-like illness (4%), mucosal inflammation, infectious peritonitis, episcleritis, blepharitis, eye oedema, scleritis, temporal arteritis, Raynaud's phenomenon, proctitis, palmar-plantar erythrodysaesthesia syndrome, eczema, psoriasis, cytokine release syndrome, sarcoidosis, haematuria, proteinuria, increased blood alkaline phosphatase (4%), increased gamma-glutamyltransferase, decreased blood thyroid stimulating hormone, decreased blood gonadotrophin, decreased thyroxine, positive antinuclear antibody, abnormal blood prolactin, hypocalcaemia, leukopenia, polycythaemia, lymphocytosis, polymyositis, ocular myositis, myositis, neurosensory hypoacusis, and autoimmune central neuropathy (encephalitis).

Description of selected adverse reactions

Except where noted, data for the following selected adverse reactions are based on patients who received either ipilimumab 3 mg/kg monotherapy (n= 131) or ipilimumab 3 mg/kg in combination with gp100 (n= 380) in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related gastrointestinal reactions
Ipilimumab is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100.

In the ipilimumab 3 mg/kg monotherapy group, diarrhoea and colitis of any severity were reported in 27% and 8%, respectively. The frequency of severe (Grade 3 or 4) diarrhoea and severe (Grade 3 or 4) colitis was 5% each. The median time to onset of severe or fatal (Grade 3 to 5) immune-related gastrointestinal reactions was 8 weeks (range 5 to 13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution (defined as improvement to mild [Grade 1] or less or to the severity at baseline) occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks). In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration.

Immune-related hepatotoxicity
Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in < 1% of patients who received ipilimumab 3 mg/kg monotherapy.

Increases in AST and ALT of any severity were reported in 1% and 2% of patients, respectively. There were no reports of severe (Grade 3 or 4) AST or ALT elevation. Time to onset of moderate to severe or fatal (Grade 2 to 5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. With protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks. In clinical trials, liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

In patients receiving ipilimumab at a higher than recommended dose in combination with dacarbazine, immune-related hepatotoxicity occurred more frequently than in patients receiving ipilimumab 3 mg/kg monotherapy.

Immune-related skin adverse reactions
Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis has been reported in < 1% of patients who received ipilimumab in combination with gp100 (see section 5.1).

In the ipilimumab 3 mg/kg monotherapy group, rash and pruritus of any severity were each reported in 26% of patients. Ipilimumab-induced rash and pruritus were predominantly mild (Grade 1) or moderate (Grade 2) and responsive to symptomatic therapy. The median time to onset of moderate to severe or fatal (Grade 2 to 5) skin adverse reactions was 3 weeks from start of treatment (range 0.9 to 16 weeks). With protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

Immune-related neurological reactions
Ipilimumab is associated with serious immune-related neurological reactions. Fatal Guillain-Barré syndrome has been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100. Myasthenia gravis-like symptoms have also been reported in < 1% of patients who received higher doses of ipilimumab in clinical trials.

Immune-related endocrinopathy
In the ipilimumab 3 mg/kg monotherapy group, hypopituitarism of any severity was reported in 4% of patients. Adrenal insufficiency, hyperthyroidism, and hypothyroidism of any severity

were each reported in 2% of patients. The frequency of severe (Grade 3 or 4) hypopituitarism was reported in 3% of patients. There were no reports of severe or very severe (Grade 3 or 4) adrenal insufficiency, hyperthyroidism, or hypothyroidism. Time to onset of moderate to very severe (Grade 2 to 4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with hormone replacement therapy.

Other immune-related adverse reactions
The following additional adverse reactions suspected to be immune-related have been reported in < 2% of patients treated with ipilimumab 3 mg/kg monotherapy: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with ipilimumab 3 mg/kg in combination with gp100 peptide vaccine.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The maximum tolerated dose of ipilimumab has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies
ATC code: L01XC11.

Mechanism of action

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation. Ipilimumab is a T-cell potentiator that specifically blocks the inhibitory signal of CTLA-4, resulting in T-cell activation, proliferation, and lymphocyte infiltration into tumours, leading to tumour cell death. The mechanism of action of ipilimumab is indirect, through enhancing T-cell mediated immune response.

Pharmacodynamic effects

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase was dose-dependent. In MDX010-20 (see section 5.1), ipilimumab at 3 mg/kg with or without gp100 increased ALC throughout the induction dosing period, but no meaningful change in ALC was observed in the control group of patients who received an investigational gp100 peptide vaccine alone.
In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA-DR+ CD4+ and CD8+ T cells was observed after treatment with ipilimumab, consistent

with its mechanism of action. A mean increase in the percent of central memory (CCR7+ CD45RA-) CD4+ and CD8+ T cells and a smaller, but significant, mean increase in the percent of effector memory (CCR7- CD45RA-) CD8+ T cells also was observed after treatment with ipilimumab.

Immunogenicity

Less than 2% of patients with advanced melanoma who received ipilimumab in Phase 2 and 3 clinical trials developed antibodies against ipilimumab. None had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Neutralizing antibodies against ipilimumab were not detected. Overall, no apparent association was observed between antibody development and adverse reactions.

Clinical trials

Overall survival (OS) advantage of ipilimumab at the recommended dose of 3 mg/kg in patients with previously-treated advanced (unresectable or metastatic) melanoma was demonstrated in a Phase 3 study (MDX010-20). Patients with ocular melanoma, primary CNS melanoma, active brain metastases, human immunodeficiency virus (HIV), hepatitis B, and hepatitis C were not included in the pivotal clinical trial. Clinical trials excluded patients with ECOG performance status > 1 and mucosal melanoma. Patients without liver metastasis who had a baseline AST > 2.5 x ULN, patients with liver metastasis who had a baseline AST > 5 x ULN, and patients with a baseline total bilirubin ≥ 3 x ULN were also excluded.

For patients with a history of autoimmune disease, see also section 4.4.

MDX010-20
A Phase 3, double-blind study enrolled patients with advanced (unresectable or metastatic) melanoma who had previously been treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive ipilimumab 3 mg/kg + an investigational gp100 peptide vaccine (gp100), ipilimumab 3 mg/kg monotherapy, or gp100 alone. All patients were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. Patients were enrolled regardless of their baseline BRAF mutation status. Patients received ipilimumab every 3 weeks for 4 doses as tolerated (induction therapy). Patients with apparent tumour burden increase before completion of the induction period were continued on induction therapy as tolerated if they had adequate performance status. Assessment of tumour response to ipilimumab was conducted at approximately Week 12, after completion of induction therapy. Additional treatment with ipilimumab (re-treatment) was offered to those who developed PD after initial clinical response (PR or CR) or after SD (per the modified WHO criteria) > 3 months from the first tumour assessment. The primary endpoint was OS in the ipilimumab+ gp100 group *vs.* the gp100 group. Key secondary endpoints were OS in the ipilimumab+ gp100 group *vs.* the ipilimumab monotherapy group and in the ipilimumab monotherapy group *vs.* the gp100 group.

A total of 676 patients were randomized: 137 to the ipilimumab monotherapy group, 403 to the ipilimumab + gp100 group, and 136 to the gp100 alone group. The majority had received all 4 doses during induction. Thirty-two patients received re-treatment: 8 in the ipilimumab monotherapy group, 23 in the ipilimumab + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across groups. The median age was 57 years. The majority (71-73%) of patients had M1c stage disease and 37-40% of patients had an elevated lactate dehydrogenase (LDH) at baseline. A total of 77 patients had a history of previously treated brain metastases.

The ipilimumab-containing regimens demonstrated a statistically significant advantage over the gp100 control group in OS. The hazard ratio (HR) for comparison of OS between ipilimumab monotherapy and gp100 was 0.66 (95% CI: 0.51, 0.87; p = 0.0026).

By subgroup analysis, the observed OS benefit was consistent within most of the subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline LDH, age, sex, and the type and number of prior therapy). However, for women above 50 years of age, the data supporting an OS benefit of ipilimumab treatment were limited. The efficacy of ipilimumab for women above 50 years of age is therefore uncertain. As the subgroups analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data.

Median and estimated rates of OS at 1 year and 2 years are presented in Table 3.

Table 3: Overall survival in MDX010-20

	Ipilimumab 3 mg/kg n= 137	gp100 [a] n= 136
Median Months (95% CI)	10 months (8.0, 13.8)	6 months (5.5, 8.7)
OS at 1 year % (95% CI)	46% (37.0, 54.1)	25% (18.1, 32.9)
OS at 2 years % (95% CI)	24% (16.0, 31.5)	14% (8.0, 20.0)

[a] gp100 peptide vaccine is an experimental control.

In the ipilimumab 3 mg/kg monotherapy group, median OS was 22 months and 8 months for patients with SD and those with PD, respectively. At the time of this analysis, medians were not reached for patients with CR or PR.

For patients who required re-treatment, the BORR was 38% (3/8 patients) in the ipilimumab monotherapy group, and 0% in the gp100 group. The disease control rate (DCR) (defined as CR+PR+SD) was 75% (6/8 patients) and 0%, respectively. Because of the limited number of patients in these analyses, no definitive conclusion regarding the efficacy of ipilimumab re-treatment can be drawn.

The development or maintenance of clinical activity following ipilimumab treatment was similar with or without the use of systemic corticosteroids.

Other studies
OS of ipilimumab 3 mg/kg monotherapy in chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials (N= 78; randomised) and in treatment-naive patients in two retrospective observational studies (N= 120 and N= 61) were generally consistent. The estimated 1-year survival rates were 59.5% (95% CI: 50.1 - 67.8) and 49.3% (95% CI: 35.6 - 61.6) in the two retrospective observational studies. The estimated 1-year and 2-year survival rates for chemotherapy-naive patients (N= 78) pooled across Phase 2 and 3 clinical trials were 54.1% (95% CI: 42.5 - 65.6) and 32% (95% CI: 20.7 - 42.9), respectively.

The European Medicines Agency has deferred the obligation to submit the results of studies with YERVOY in one or more subsets of the paediatric population in the treatment of melanoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ipilimumab was studied in 785 patients with advanced melanoma who received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. C_{max}, C_{min} and AUC of ipilimumab were found to be dose proportional within the

dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index 1.5 fold or less. Ipilimumab steady-state was reached by the third dose. Based on population pharmacokinetic analysis, the following mean (percent coefficient of variation) parameters of ipilimumab were obtained: terminal half-life of 15.4 days (34.4%); systemic clearance of 16.8 ml/h (38.1%); and volume of distribution at steady-state of 7.47 l (10.1%). The mean (percent coefficient of variation) ipilimumab C_{min} achieved at steady-state with a 3 mg/kg induction regimen was 19.4 µg/ml (74.6%).

Ipilimumab clearance increased with increasing body weight and with increasing LDH at baseline; however, no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis. Clearance was not affected by age (range 23-88 years), gender, concomitant use of budesonide or dacarbazine, performance status, HLA-A2*0201 status, mild hepatic impairment, renal impairment, immunogenicity, and previous anticancer therapy. The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups. No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

Based on an exposure-response analysis in 497 patients with advanced melanoma, OS was independent of prior systemic anti-cancer therapy and increased with higher ipilimumab Cminss plasma concentrations.

Renal impairment
In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild and moderate renal impairment did not influence the clearance of ipilimumab. Clinical and pharmacokinetic data with pre-existing severe renal impairment are limited; the potential need for dose adjustment cannot be determined.

Hepatic impairment
In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild hepatic impairment did not influence the clearance of ipilimumab. Clinical and pharmacokinetic data with pre-existing moderate hepatic impairment are limited; the potential need for dose adjustment cannot be determined. No patients with pre-existing severe hepatic impairment were identified in clinical studies.

5.3 Preclinical safety data

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently (~3%) and included colitis (which resulted in a single fatality), dermatitis, and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate). A decrease in the weight of the thyroid and testes was seen in one study without accompanying histopathologic findings; the clinical relevance of this finding is unknown.

The effects of ipilimumab on prenatal and postnatal development were investigated in a study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through delivery, at exposure (AUC) levels either similar to or higher than those associated with the clinical dose of 3 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, both ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and infant mortality relative to control animals; these findings were dose-dependent. Additionally, developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed *in utero* to ipilimumab. One female infant had unilateral renal agenesis of the left kidney and ureter, and one male infant had an imperforate urethra with

associated urinary obstruction and subcutaneous scrotal edema. The relationship of these malformations to treatment is unclear.

Studies to evaluate the mutagenic and carcinogenic potential of ipilimumab have not been performed. Fertility studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride)
Sodium chloride
Mannitol (E421)
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial: 3 years

After opening:
Solution for infusion: From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 and 4 mg/ml) has been demonstrated for 24 hrs at 25°C and 2 to 8°C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours in a refrigerator (2°C to 8°C) or at room temperature (20°C to 25°C).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml of sterile concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.
40 ml of sterile concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose:
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of YERVOY concentrate may be needed to give the total dose for the patient.

- Each 10 ml vial of YERVOY concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab.
- The total ipilimumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of YERVOY concentrate to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Preparing the infusion:
Take care to ensure aseptic handling when you prepare the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

YERVOY can be used for intravenous administration either:
- without dilution, after transfer to an infusion container using an appropriate sterile syringe;
  or
- after diluting to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the YERVOY concentrate, you can use either:
  - sodium chloride 9 mg/ml (0.9%) solution for injection; or
  - 50 mg/ml (5%) glucose solution for injection

STEP 1
- Allow the appropriate number of vials of YERVOY to stand at room temperature for approximately 5 minutes.
- Inspect the YERVOY concentrate for particulate matter or discoloration. YERVOY concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of YERVOY concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).
- If applicable, dilute with the required volume of sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection. Gently mix the infusion by manual rotation.

Administration:
YERVOY infusion must not be administered as an intravenous push or bolus injection. Administer the YERVOY infusion intravenously over a period of 90 minutes.

YERVOY infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

YERVOY infusion is compatible with:
- PVC infusion sets
- Polyethersulfone (0.2 µm to 1.2 µm) and nylon (0.2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion.

Any unused medicinal product or waste material should be discarded in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/698/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter):

The following databases were searched to identify the clinical evidence base:

- Medline & Medline In-Process & Other Non-Indexed Citations (OVID)
- Embase (OVID)
- Cochrane Library (Wiley Interscience)
    - Cochrane Database of Systematic Reviews: CDSR
    - Cochrane Central Register of Controlled Trials: CCRCT
    - Health Technology Assessment Database: HTA
    - Database of Abstracts of Reviews of Effects: DARE
- Cumulative Index to Nursing and Allied Health: Cinahl (EBSCO)

10.2.2 The date on which the search was conducted.

All databases were searched on 9th May 2013.

10.2.3 The date span of the search.

All databases were searched from 1970 to 9th May 2013.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline In-Process & Other Non-Indexed Citations:

1. ipilimumab.mp.
2. yervoy.mp.
3. MDX-010.mp.
4. MDX-101.mp.
5. or/1-4
6. dacarbazin$.mp.
7. deticene.mp.
8. 4342-03-4.rn.
9. (biocarbazine or dtie or dtic or icdmt or icdt or wr-139007).mp.
10. imidazole carboxamide.mp.
11. or/6-10
12. dabrafenib.mp.
13. 1195765-45-7.rn.
14. vemurafenib.mp.
15. zelboraf.mp.
16. 1029872-54-5.rn.
17. ((braf or b-raf) adj2 inhibitor$).mp.
18. or/12-17

19. exp Melanoma/
20. melanoma$.mp.
21. exp Skin Neoplasms/
22. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
23. or/19-22
24. 11 and 23
25. 5 or 18 or 24
26. Randomized controlled trials as Topic/
27. Randomized controlled trial/
28. Random allocation/
29. randomized controlled trial.pt.
30. Double blind method/
31. Single blind method/
32. Clinical trial/
33. exp Clinical Trials as Topic/
34. controlled clinical trial.pt.
35. or/26-34
36. (clinic$ adj25 trial$).ti,ab.
37. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
38. Placebos/
39. Placebo$.tw.
40. (allocated adj2 random).tw.
41. or/36-40
42. 35 or 41
43. Case report.tw.
44. Letter/
45. Historical article/
46. 43 or 44 or 45
47. exp Animals/
48. Humans/
49. 47 not (47 and 48)
50. 46 or 49
51. 42 not 50
52. 25 and 51
53. limit 52 to yr="1970 -Current"
54. meta-analysis as topic/
55. (meta analy$ or metaanaly$).tw.
56. Meta-Analysis/
57. (systematic adj (review$1 or overview$1)).tw.
58. "Review Literature as Topic"/
59. or/54-58
60. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
61. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
62. ((selection adj criteria) or (data adj extraction)).ab.
63. "review"/
64. 62 and 63
65. comment/ or editorial/ or letter/
66. Animals/
67. Humans/
68. 66 not (66 and 67)
69. 65 or 68
70. 59 or 60 or 61 or 64
71. 70 not 69
72. 25 and 71
73. limit 72 to yr="1970 -Current"

Embase:

1. ipilimumab/
2. ipilimumab.mp.
3. yervoy.mp.
4. MDX-010.mp.
5. MDX-101.mp.
6. or/1-5
7. dacarbazine/
8. dacarbazin$.mp.
9. deticene.mp.
10. 4342-03-4.rn.
11. (biocarbazine or dtie or dtic or icdmt or icdt).mp.
12. imidazole carboxamide.mp.
13. or/7-12
14. dabrafenib/
15. dabrafenib.mp.
16. 1195765-45-7.rn.
17. vemurafenib/
18. vemurafenib.mp.
19. zelboraf.mp.
20. 1029872-54-5.rn.
21. ((braf or b-raf) adj2 inhibitor$).mp.
22. or/14-21
23. exp melanoma/
24. melanoma$.mp.
25. exp skin tumor/
26. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
27. or/23-26
28. 13 and 27
29. 6 or 22 or 28
30. Clinical trial/
31. Randomized controlled trial/
32. Randomization/
33. Single blind procedure/
34. Double blind procedure/
35. Crossover procedure/
36. Placebo/
37. Randomi?ed controlled trial$.tw.
38. Rct.tw.
39. Random allocation.tw.
40. Randomly allocated.tw.
41. Allocated randomly.tw.
42. (allocated adj2 random).tw.
43. Single blind$.tw.
44. Double blind$.tw.
45. ((treble or triple) adj blind$).tw.
46. Placebo$.tw.
47. Prospective study/
48. or/30-47
49. Case study/
50. Case report.tw.
51. Abstract report/ or letter/
52. or/49-51
53. 48 not 52
54. 29 and 53

55. exp Meta Analysis/
56. ((meta adj analy$) or metaanalys$).tw.
57. (systematic adj (review$1 or overview$1)).tw.
58. or/55-57
59. cancerlit.ab.
60. cochrane.ab.
61. embase.ab.
62. (psychlit or psyclit).ab.
63. (psychinfo or psycinfo).ab.
64. (cinahl or cinhal).ab.
65. science citation index.ab.
66. bids.ab.
67. or/59-66
68. reference lists.ab.
69. bibliograph$.ab.
70. hand-search$.ab.
71. manual search$.ab.
72. relevant journals.ab.
73. or/68-72
74. data extraction.ab.
75. selection criteria.ab.
76. 74 or 75
77. review.pt.
78. 76 and 77
79. letter.pt.
80. editorial.pt.
81. animal/
82. human/
83. 81 not (81 and 82)
84. or/79-80,83
85. 58 or 67 or 73 or 78
86. 85 not 84
87. 29 and 86

Cochrane Library:

#1	ipilimumab:ti,ab,kw
#2	yervoy:ti,ab,kw
#3	MDX-010:ti,ab,kw
#4	MDX-101:ti,ab,kw
#5	{or #1-#4}
#6	MeSH descriptor: [Dacarbazine] this term only
#7	dacarbazin*:ti,ab,kw
#8	deticene:ti,ab,kw
#9	(biocarbazine or dtie or dtic or icdmt or icdt or wr-139007):ti,ab,kw
#10	imidazole carboxamide:ti,ab,kw
#11	{or #6-#10}
#12	dabrafenib:ti,ab,kw
#13	vemurafenib:ti,ab,kw
#14	zelboraf:ti,ab,kw
#15	((braf or b-raf) next/2 inhibitor*):ti,ab,kw
#16	{or #12-#15}
#17	MeSH descriptor: [Melanoma] explode all trees
#18	melanoma*:ti,ab,kw
#19	MeSH descriptor: [Skin Neoplasms] explode all trees
#20	(skin next/3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)):ti,ab
#21	{or #17-#20}
#22	#11 and #21
#23	#5 or #16 or #22
#24	#23 from 1970 to 2013

Cinahl:

S45	S22 AND S44
S44	S40 not S43
S43	S41 or S42
S42	(MH "Animals")
S41	PT Commentary or PT Letter or PT Editorial
S40	S36 or S37 or S38 or S39
S39	systematic N2 review or systematic N2 overview
S38	(MH "Literature Review+")
S37	TI ((Meta analys* or Metaanaly*)) or AB ((Meta analys* or Metaanaly*))
S36	(MH "Meta Analysis")
S35	S22 AND S34
S34	S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33
S33	TI clinic* N1 trial* or AB clinic* N1 trial*
S32	TI ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) or AB ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*))
S31	TI Placebos or AB Placebos
S30	TI Placebo* or AB Placebo*
S29	TI Random* allocat* or AB Random* allocat*
S28	TI Allocat* random* or AB Allocat* random*
S27	(MH "Quantitative Studies")
S26	(MH "Random Assignment")
S25	TI Randomi?ed control* trial* or AB Randomi?ed control* trial*
S24	PT Clinical trial
S23	(MH "Clinical Trials+")
S22	S5 or S15 or S21
S21	S10 AND S20
S20	S16 or S17 or S18 or S19
S19	(skin N3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*))
S18	(MH "Skin Neoplasms+")
S17	melanoma*
S16	(MH "Melanoma+")

S15	S11 or S12 or S13 or S14
S14	((braf or b-raf) N2 inhibitor*)
S13	zelboraf
S12	vemurafenib
S11	dabrafenib
S10	S6 or S7 or S8 or S9
S9	imidazole carboxamide
S8	(biocarbazine or dtie or dtic or icdmt or icdt or wr-139007)
S7	deticene
S6	dacarbazin*
S5	S1 or S2 or S3 or S4
S4	MDX-101
S3	MDX-010
S2	yervoy
S1	ipilimumab

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional searches were conducted in clinicaltrials.gov along with the following conference proceedings of 2009-2013:

- Conference proceedings of the American Society of Clinical Oncology (Web of Science)
- Conference proceedings of the European Society for Medical Oncology: (Web of Science)
- Conference proceedings of the Society for Melanoma Research (Wiley Online Library)

10.2.6 The inclusion and exclusion criteria.

Details of inclusion and exclusion criteria applied to the combined results of electronic database searches and additional searches are presented in Table 85.

Table 85: Inclusion and exclusion criteria applied to systematic search results

	Description	Justification
Inclusion Criteria		
Population	Adult patients with previously untreated advanced (unresectable or metastatic) malignant melanoma	According to final scope
Interventions	Ipilimumab DTIC Vemurafenib Dabrafenib	According to final scope
Outcomes	Survival (overall survival (OS) or progression-free survival (PFS)) Response (overall response rate, time to response, duration of response, disease control) Safety (adverse effects of treatment) Health-related quality of life (HRQL)	Clinically relevant endpoints
Study design	Randomised controlled trials (RCTs) of any design; phase II & III	Highest level of evidence available
Language restrictions	English abstract	
Exclusion Criteria		
Population	Paediatric patients; pre-treated patients; stage 0 - II melanoma patients	According to final scope; in line with licence terms
Interventions	Treatments used off-licence	According to final scope
Outcomes	Non-clinical outcomes	Not of relevance to benefit assessment
Study design	Prospective non-RCTs; observational studies	Higher level of evidence available
Language restrictions	Non-English abstracts	

10.2.7 The data abstraction strategy.

Two reviewers independently extracted pre-defined data items from included trials. In case of disagreement between the two reviewers, a third would have extracted data and final results attained by consensus but this was not necessary.

The pre-defined data extraction table, designed in access®, comprised data items related to the basic characteristics of each selected study and study results and was developed based on conventions in to systematic reviews; taking into account information of relevance to the treatment of advanced melanoma, pre-defined outcomes of interest and specific requirements for subsequent quantitative synthesis.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

CA184-024		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate: centralised randomisation scheme utilised with stratification according to baseline M stage; ECOG; study site	Yes
Was the concealment of treatment allocation adequate?	Adequate: placebo used in place of ipilimumab as applicable.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: patient characteristics between treatment arms well balanced; prognostic factors: M stage, ECOG, baseline LDH similarly distributed.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: patients, care providers and on site outcome assessors blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: overall discontinuations comparable; as expected a priori more patients randomised to DTIC discontinued due to disease progression and more patients randomised to ipi discontinued due to adverse events.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes presented in primary publication.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: except for safety analysis, all efficacy outcomes analysed using randomised (ITT) population.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

MDX010-08		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate: centralised randomisation scheme utilised with stratification by random block size.	Yes
Was the concealment of treatment allocation adequate?	Open-label study	n/a
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: patient characteristics between treatment arms well balanced; prognostic factors: M stage, ECOG, baseline LDH similarly distributed	Yes

MDX010-08		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open-label study. Adequate: no likely impact on the risk of bias for each outcome as they are not patient reported outcomes.	n/a
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: overall discontinuations comparable; in accordance with the pre-defined study protocol, cross-over to ipi + DTIC was reported for 13 patients.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes presented in primary publication.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: except for safety analysis, all efficacy outcomes analysed using randomised (ITT) population though the per protocol (PP) population reported as primary analysis: included all randomised patients who had received at least a partial dose of study treatment.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

BREAK-3		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate: centralised, computerised, interactive voice activated randomisation scheme utilised with stratification according to baseline M stage.	Yes
Was the concealment of treatment allocation adequate?	Open-label study	n/a
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: patient characteristics between treatment arms well balanced; prognostic factors: M stage, ECOG, baseline LDH similarly distributed	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open-label study. Adequate: no likely impact on the risk of bias for each outcome as they are not patient reported outcomes.	n/a
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: overall discontinuations comparable; in accordance with the pre-defined study protocol, cross-over to dabrafenib was reported for 28 patients.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes presented in primary publication or planned in secondary publication (HRQL).	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: except for safety analysis, all efficacy outcomes analysed using randomised (ITT) population.	Yes

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

BRIM-3		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate: randomisation scheme utilised with stratification according to baseline M stage; ECOG; location; serum LDH.	Yes
Was the concealment of treatment allocation adequate?	Open-label study	n/a
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: patient characteristics between treatment arms well balanced; prognostic factors: M stage, ECOG, baseline LDH similarly distributed	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open-label study. Adequate: no likely impact on the risk of bias for each outcome as they are not patient reported outcomes.	n/a
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: overall discontinuations comparable; in accordance with the pre-defined study protocol, cross-over to vemurafenib was reported for 81 patients.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for primary outcomes and secondary response outcomes presented in primary publication (duration of response not reported).	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: except for safety analysis, all efficacy outcomes analysed using randomised (ITT) population.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

As per section 10.2.1

10.4.2 The date on which the search was conducted.

As per section 10.2.2

10.4.3 The date span of the search.

As per section 10.2.3

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

As per section 10.2.4

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

As per section 10.2.5

10.4.6 The inclusion and exclusion criteria.

As per section 10.2.6

10.4.7 The data abstraction strategy.

As per section 10.2.7

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

As per section 10.3.1

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable

10.6.2 The date on which the search was conducted.

Not applicable

10.6.3 The date span of the search.

Not applicable

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

10.6.6 The inclusion and exclusion criteria.

Not applicable

10.6.7 The data abstraction strategy.

Not applicable

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Pooled chemotherapy-naïve dataset		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with advanced malignant melanoma who had not previously received UK approved first-line therapy and thus represent the indication of relevance to this submission.	Yes
How was selection bias minimised?	Adequate: all chemotherapy-naïve patients previously randomised to receive ipilimumab 3mg/kg monotherapy in phase II or III RCTs included.	Yes
Were all participants accounted for at study conclusion?	Adequate: survival analysed using randomised (ITT) population.	Yes
Did the setting reflect UK practice?	Adequate: eligible for 1st line therapy in the UK as not previously received chemotherapy or BRAF inhibitor therapy; baseline characteristics and demographics reflect typical advanced, malignant melanoma patients who present in UK clinical practice. Of note, both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients were enrolled.	Yes
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Adequate: overall survival – clinically relevant endpoint; directly referenced in the decision problem.	Yes
Did the analysis include an intention-to-treat analysis?	Adequate: survival analysed using randomised (ITT) population.	Yes
Are the study results internally valid?	Adequate: analyses conducted in accordance with approved statistical methods; outcomes directly comparable with alternative ipilimumab trials; application of korn model shows survival improvement over BSC.	Yes
Are the findings externally valid?	Adequate: of direct relevance to the decision problem, presenting survival data for the UK licensed use of ipilimumab 3mg/kg monotherapy as first-line therapy for advanced malignant melanoma.	Yes

CA184-332		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Do the selected patients represent the eligible population for the intervention?	Adequate: previously untreated patients with advanced malignant melanoma; of direct relevance to the submission.	Yes
How was selection bias minimised?	Adequate: patients were identified programmatically via a database, without input from site or sponsor, based solely on eligibility criteria and time period of treatment.	Yes
Were all participants accounted for at study conclusion?	Study ongoing	n/a
Did the setting reflect UK practice?	Adequate: baseline characteristics and demographics reflect typical advanced, malignant melanoma patients who present in UK clinical practice for first-line therapy. Of note, both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients were enrolled. Patients not excluded on the basis of laboratory abnormalities, performance status (PS), non-cutaneous primaries, life expectancy < 4 months, underlying co-morbid diseases, or presence of brain metastasis (all of which are associated with worse outcome).	Yes
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Adequate: overall survival – clinically relevant endpoint; directly referenced in the decision problem. Safety – clinically relevant endpoint; directly referenced in the decision problem. Demographic & clinical characteristics; patterns of care; healthcare resource use – clinically relevant endpoints.	Yes
Did the analysis include an intention-to-treat analysis?	Adequate: survival analysed using randomised (ITT) population.	Yes
Are the study results internally valid?	Adequate: analyses conducted in accordance with approved statistical methods; outcomes directly comparable with alternative ipilimumab trials; application of korn model shows survival improvement over BSC.	Yes
Are the findings externally valid?	Adequate: of direct relevance to the decision problem, presenting survival data for the UK licensed use of ipilimumab 3mg/kg monotherapy as first-line therapy for advanced malignant melanoma.	Yes

CA184-338		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Do the selected patients represent the eligible population for the intervention?	Adequate: previously untreated patients with advanced malignant melanoma; of direct relevance to the submission.	Yes
How was selection bias minimised?	Adequate: sites were instructed to enrol all sequentially treated patients during the indicated time period and who met eligiblity, regardless of outcome.	Yes
Were all participants accounted for at study conclusion?	Study ongoing	n/a
Did the setting reflect UK practice?	Adequate: baseline characteristics and demographics reflect typical advanced, malignant melanoma patients who present in UK clinical practice for first-line therapy. Of note, both BRAF V600 mutation-positive and BRAF V600 mutation-negative patients were enrolled. Patients not excluded on the basis of laboratory abnormalities, performance status (PS), non-cutaneous primaries, life expectancy < 4 months, underlying co-morbid diseases, or presence of brain metastasis (all of which are associated with worse outcome).	Yes
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Adequate: overall survival – clinically relevant endpoint; directly referenced in the decision problem. Safety – clinically relevant endpoint; directly referenced in the decision problem. Demographic & clinical characteristics; patterns of care; healthcare resource use – clinically relevant endpoints.	Yes
Did the analysis include an intention-to-treat analysis?	Adequate: survival analysed using randomised (ITT) population.	Yes
Are the study results internally valid?	Adequate: analyses conducted in accordance with approved statistical methods; outcomes directly comparable with alternative ipilimumab trials; application of korn model shows survival improvement over BSC.	Yes
Are the findings externally valid?	Adequate: of direct relevance to the decision problem, presenting survival data for the UK licensed use of ipilimumab 3mg/kg monotherapy as first-line therapy for advanced malignant melanoma.	Yes

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- The Cochrane Library.

As per section 10.2.1

10.8.2 The date on which the search was conducted.

As per section 10.2.2

10.8.3 The date span of the search.

As per section 10.2.3

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

As per section 10.2.4

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

As per section 10.2.5

10.8.6 The inclusion and exclusion criteria.

As per section 10.2.6

10.8.7 The data abstraction strategy.

As per section 10.2.7

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified

As per section 10.3.1

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Databases Searched:

- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- Cochrane Library
- Cochrane database of systematic reviews
- NHS EED
- HTA database
- Dare
- CINAHL
- Econlit

10.10.2 The date on which the search was conducted.

Database	**Date searched**
Medline	09/05/13
Embase	09/05/13
HTA	09/05/13
DARE	09/05/13
CDSR	09/05/13
NHS EED	09/05/13
Cinahl	09/05/13
EconLit	09/05/13

10.10.3 The date span of the search.

Date limits can be found within the search strategies presented below.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A precise search strategy was utilised, incorporating terms for Ipilimumab and its comparators (1-18), together with terms for melanoma (19-25) and an economics filter (26-47), as reported on the Centre for Reviews and Dissemination (CRD) [CRD website]

Medline and Medline In-Process & Other Non-Indexed Citations: Ovid. 1946 to Present

1. ipilimumab.mp.
2. yervoy.mp.
3. MDX-010.mp.
4. MDX-101.mp.
5. or/1-4
6. dacarbazin$.mp.
7. deticene.mp.
8. 4342-03-4.rn.
9. (biocarbazine or dtie or dtic or icdmt or icdt or wr-139007).mp.
10. imidazole carboxamide.mp.
11. or/6-10
12. dabrafenib.mp.
13. 1195765-45-7.rn.
14. vemurafenib.mp.
15. zelboraf.mp.
16. 1029872-54-5.rn.
17. ((braf or b-raf) adj2 inhibitor$).mp.
18. or/12-17
19. exp Melanoma/
20. melanoma$.mp.
21. exp Skin Neoplasms/
22. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
23. or/19-22
24. 11 and 23
25. 5 or 18 or 24
26. exp "Costs and Cost Analysis"/
27. Economics/
28. exp Economics, Hospital/
29. exp Economics, Medical/
30. Economics, Nursing/
31. exp models, economic/
32. Economics, Pharmaceutical/
33. exp "Fees and Charges"/
34. exp Budgets/
35. budget$.tw.
36. ec.fs.
37. cost$.ti.
38. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
39. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
40. (price$ or pricing$).tw.
41. (financial or finance or finances or financed).tw.
42. (fee or fees).tw.
43. (value adj2 (money or monetary)).tw.
44. quality-adjusted life years/
45. (qaly or qalys).af.
46. (quality adjusted life year or quality adjusted life years).af.
47. or/26-46
48. 25 and 47
49. limit 48 to yr="1970 -Current"

Embase: Ovid. 1974 to 2013 May 08

1. ipilimumab/
2. ipilimumab.mp.
3. yervoy.mp.
4. MDX-010.mp.
5. MDX-101.mp.
6. or/1-5
7. dacarbazine/
8. dacarbazin$.mp.
9. deticene.mp.
10. 4342-03-4.rn.
11. (biocarbazine or dtie or dtic or icdmt or icdt).mp.
12. imidazole carboxamide.mp.
13. or/7-12
14. dabrafenib/

15. dabrafenib.mp.
16. 1195765-45-7.rn.
17. vemurafenib/
18. vemurafenib.mp.
19. zelboraf.mp.
20. 1029872-54-5.rn.
21. ((braf or b-raf) adj2 inhibitor$).mp.
22. or/14-21
23. exp melanoma/
24. melanoma$.mp.
25. exp skin tumor/
26. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
27. or/23-26
28. 13 and 27
29. 6 or 22 or 28
30. Socioeconomics/
31. Cost benefit analysis/
32. Cost effectiveness analysis/
33. Cost of illness/
34. Cost control/
35. Economic aspect/
36. Financial management/
37. Health care cost/
38. Health care financing/
39. Health economics/
40. Hospital cost/
41. (fiscal or financial or finance or funding).tw.
42. Cost minimization analysis/
43. (cost adj estimate$).mp.
44. (cost adj variable$).mp.
45. (unit adj cost$).mp.
46. or/30-45
47. 29 and 47

Cochrane Library
Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	ipilimumab:ti,ab,kw
#2	yervoy:ti,ab,kw
#3	MDX-010:ti,ab,kw
#4	MDX-101:ti,ab,kw
#5	{or #1-#4}
#6	MeSH descriptor: [Dacarbazine] this term only
#7	dacarbazin*:ti,ab,kw
#8	deticene:ti,ab,kw
#9	(biocarbazine or dtie or dtic or icdmt or icdt or wr-139007):ti,ab,kw
#10	imidazole carboxamide:ti,ab,kw
#11	{or #6-#10}
#12	dabrafenib:ti,ab,kw
#13	vemurafenib:ti,ab,kw
#14	zelboraf:ti,ab,kw
#15	((braf or b-raf) next/2 inhibitor*):ti,ab,kw
#16	{or #12-#15}
#17	MeSH descriptor: [Melanoma] explode all trees
#18	melanoma*:ti,ab,kw
#19	MeSH descriptor: [Skin Neoplasms] explode all trees
#20	(skin next/3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)):ti,ab
#21	{or #17-#20}
#22	#11 and #21
#23	#5 or #16 or #22
#24	#23 from 1970 to 2013

Cinahl: EBSCO. 1981 to present

S39	S22 AND S38
S38	S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37
S37	quality adjusted life year or quality adjusted life years
S36	qaly or qalys
S35	value and (money or monetary)
S34	fee or fees
S33	financial or finance or finances or financed
S32	price* or pricing*
S31	TI economic* or pharmacoeconomic* or pharmaco-economic*
S30	AB cost* and (effective* or utilit* or benefit* or minimi*)
S29	cost*
S28	budget*
S27	(MH "Budgets")
S26	(MH "Fees and Charges+")
S25	(MH "Economics, Pharmaceutical")
S24	(MH "Economics")
S23	(MH "Costs and Cost Analysis+")
S22	S5 or S15 or S21 Limiters - Published Date from: 19700101-20130631
S21	S10 AND S20
S20	S16 or S17 or S18 or S19
S19	(skin N3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)) (MH "Skin Neoplasms+")
S18	melanoma*
S17	(MH "Melanoma+")
S16	
S15	S11 or S12 or S13 or S14
S14	((braf or b-raf) N2 inhibitor*)
S13	zelboraf
S12	vemurafenib
S11	dabrafenib
S10	S6 or S7 or S8 or S9
S9	imidazole carboxamide
S8	(biocarbazine or dtie or dtic or icdmt or icdt or wr-139007)
S7	deticene
S6	dacarbazin*
S5	S1 or S2 or S3 or S4
S4	MDX-101
S3	MDX-010
S2	yervoy
S1	ipilimumab

EconLit: Ovid. 1961 to April 2013

1. ipilimumab.tw.
2. yervoy.tw.
3. MDX-010.tw.
4. MDX-101.tw.
5. or/1-4
6. dacarbazin$.tw.
7. deticene.tw.
8. (biocarbazine or dtie or dtic or icdmt or icdt or wr-139007).tw.
9. imidazole carboxamide.tw.
10. or/6-9
11. dabrafenib.tw.
12. vemurafenib.tw.
13. zelboraf.tw.
14. ((braf or b-raf) adj2 inhibitor$).tw.
15. or/11-14
16. melanoma$.tw.
17. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
18. 16 or 17
19. 10 and 18
20. 5 or 15 or 19

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Not applicable.

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.
- Databases searched:
- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- HTA database
- DARE
- NHS EED
- CINAHL
- EconLit

10.12.2 The date on which the search was conducted.

Database	Date searched
Medline	24/05/13
Embase	24/05/13
HTA	24/05/13
DARE	24/05/13
NHS EED	22/05/13
Cinahl	24/05/13
EconLit	22/05/13

10.12.3 The date span of the search.

Date spans are provided within the search strategies below.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline In-Process & Other Non-Indexed Citations: Ovid. 1946 to Present

1. Melanoma/
2. melanoma$.tw.
3. Skin Neoplasms/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4
6. "Quality of Life"/
7. (qol or (quality adj2 life)).ab,ti.
8. (value adj2 (money or monetary)).tw.
9. value of life/
10. quality adjusted life year/
11. quality adjusted life.tw.
12. (qaly$ or qald$ or qale$ or qtime$).tw.
13. disability adjusted life.tw.
14. daly$.tw.
15. health status indicators/
16. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
17. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
18. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
19. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
20. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
21. (euroqol or euro qol or eq5d or eq 5d).tw.
22. (hql or hqol or h qol or hrqol or hr qol).tw.
23. (hye or hyes).tw.
24. health$ year$ equivalent$.tw.
25. health utilit$.tw.
26. (hui or hui1 or hui2 or hui3).tw.
27. disutilit$.tw.
28. rosser.tw.
29. (quality adj2 wellbeing).tw.
30. qwb.tw.
31. (willingness adj2 pay).tw.
32. standard gamble$.tw.
33. time trade off.tw.
34. time tradeoff.tw.
35. tto.tw.
36. letter.pt.
37. editorial.pt.
38. comment.pt.
39. 36 or 37 or 38
40. or/6-35
41. 40 not 39
42. 5 and 41
43. limit 42 to yr="1970 -Current"

Embase: Ovid. 1974 to 2013 May 08

1. melanoma/
2. melanoma$.tw.
3. skin tumor/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4

6. "Quality of Life"/
7. (qol or (quality adj2 life)).ti,ab.
8. (value adj2 (money or monetary)).tw.
9. socioeconomics/
10. quality adjusted life year/
11. (qaly$ or qald$ or qale$ or qtime$).tw.
12. disability adjusted life.tw.
13. daly$.tw.
14. health survey/
15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
16. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
20. (euroqol or euro qol or eq5d or eq 5d).tw.
21. (hql or hqol or h qol or hrqol or hr qol).tw.
22. (hye or hyes).tw.
23. health$ year$ equivalent$.tw.
24. health utilit$.tw.
25. (hui or hui1 or hui2 or hui3).tw.
26. disutilit$.tw.
27. rosser.tw.
28. (quality adj2 wellbeing).tw.
29. qwb.tw.
30. (willingness adj2 pay).tw.
31. standard gamble$.tw.
32. time trade off.tw.
33. time tradeoff.tw.
34. tto.tw.
35. letter.pt.
36. editorial.pt.
37. comment.pt.
38. 35 or 36 or 37
39. or/6-34
40. 39 not 38
41. 5 and 40

Cochrane Library
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Quality of Life] this term only
#2	(qol or (quality next/2 life)):ti,ab,kw
#3	MeSH descriptor: [Value of Life] this term only
#4	value and (money or monetary):ti,ab,kw
#5	MeSH descriptor: [Quality-Adjusted Life Years] this term only
#6	(quality adjusted life):ti,ab,kw
#7	(qaly* or qald* or qale* or qtime*):ti,ab,kw
#8	disability adjusted life:ti,ab,kw
#9	daly*:ti,ab,kw
#10	MeSH descriptor: [Health Status Indicators] explode all trees
#11	sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six:ti,ab,kw
#12	sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw
#13	sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve:ti,ab,kw
#14	sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen:ti,ab,kw
#15	sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty:ti,ab,kw
#16	euroqol or euro qol or eq5d or eq 5deuroqol or euro qol or eq5d or eq 5d:ti,ab,kw
#17	hql or hqol or h qol or hrqol or hr qol:ti,ab,kw
#18	hye or hyes:ti,ab,kw
#19	health* year* equivalent*:ti,ab,kw
#20	health utilit*:ti,ab,kw
#21	hui or hui1 or hui2 or hui3:ti,ab,kw
#22	disutilit*:ti,ab,kw
#23	rosser:ti,ab,kw
#24	qwb:ti,ab,kw
#25	standard gamble*:ti,ab,kw
#26	willingness to pay:ti,ab,kw
#27	quality of wellbeing:ti,ab,kw
#28	time trade off:ti,ab,kw
#29	time tradeoff:ti,ab,kw
#30	tto:ti,ab,kw
#31	letter:pt
#32	editorial:pt
#33	comment:pt
#34	#31 or #32 or #33
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#36	#35 not #34
#37	MeSH descriptor: [Melanoma] explode all trees
#38	melanoma*:ti,ab,kw
#39	MeSH descriptor: [Skin Neoplasms] explode all trees
#40	(skin next/3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)):ti,ab
#41	#37 or #38 or #39 or #40
#42	#36 and #41 from 1970 to 2013

Cinahl: EBSCO. 1981 to present

S42	S5 AND S41 Limiters - Published Date from: 19700101-20130631
S41	S40 NOT S39
S40	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S39	S36 or S37 or S38
S38	PT comment
S37	PT editorial
S36	PT letter
S35	TI tto or AB tto
S34	TI time tradeoff or AB time tradeoff
S33	TI time trade off or AB time trade off

S32	TI standard gamble* or AB standard gamble*
S31	TI willingness N2 pay or AB willingness N2 pay
S30	TI qwb or AB qwb
S29	TI quality N2 wellbeing or AB quality N2 wellbeing
S28	TI rosser or AB rosser
S27	TI disutilit* or AB disutilit*
S26	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S25	TI health utilit* or AB health utilit*
S24	TI health* year* equivalent* or AB health* year* equivalent*
S23	TI (hye or hyes) or AB (hye or hyes)
S22	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S21	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S20	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S19	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S18	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S17	TI quality adjusted life or AB quality adjusted life
S16	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S15	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
	(MH "Health Status Indicators")
S14	TI daly* or AB daly*
S13	TI disability adjusted life or AB disability adjusted life
S12	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S11	(MH "Quality-Adjusted Life Years")
S10	(MH "Economic Value of Life")
S9	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S8	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S7	(MH "Quality of Life")
S6	S1 or S2 or S3 or S4
	(skin N3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*))
	(MH "Skin Neoplasms")
	melanoma*
S5	(MH "Melanoma")
S4	
S3	
S2	
S1	

EconLit: Ovid. 1961 to April 2013

1. melanoma$.tw.
2. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
3. 1 or 2

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.12.6 The inclusion and exclusion criteria.

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Studies reporting utilities or HRQL data	The aim of the review was to identify relevant utility data
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To identify all relevant papers
Outcomes	Any reported measurement in the form of utilities was included. Also utility values mapped from a measure of HRQL or a measure of HRQL that can be mapped using only published information	The aim of the review was to identify relevant utility studies
Exclusion Criteria		
Category	**Exclusion criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were being hand-searched)	Primary study articles were required

10.12.7 The data abstraction strategy.

Explained previously as part of the full submission.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.
- Databases searched:
- Medline and Medline in Process & Other Non-Indexed citations
- EMBASE
- HTA database
- DARE
- NHS EED
- CINAHL
- EconLit

10.13.2 The date on which the search was conducted.

Database	**Date searched**
Medline	24/05/13
Embase	24/05/13
HTA	24/05/13
DARE	24/05/13
NHS EED	24/05/13
Cinahl	24/05/13
EconLit	22/05/13

10.13.3 The date span of the search.

Provided with the searches below.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline In-Process & Other Non-Indexed Citations: Ovid. 1946 to Present

1. Melanoma/
2. melanoma$.tw.
3. Skin Neoplasms/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4
6. "Quality of Life"/
7. (qol or (quality adj2 life)).ab,ti.
8. (value adj2 (money or monetary)).tw.
9. value of life/
10. quality adjusted life year/
11. quality adjusted life.tw.
12. (qaly$ or qald$ or qale$ or qtime$).tw.
13. disability adjusted life.tw.
14. daly$.tw.
15. health status indicators/
16. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
17. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
18. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
19. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
20. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
21. (euroqol or euro qol or eq5d or eq 5d).tw.
22. (hql or hqol or h qol or hrqol or hr qol).tw.
23. (hye or hyes).tw.
24. health$ year$ equivalent$.tw.
25. health utilit$.tw.
26. (hui or hui1 or hui2 or hui3).tw.
27. disutilit$.tw.
28. rosser.tw.
29. (quality adj2 wellbeing).tw.
30. qwb.tw.
31. (willingness adj2 pay).tw.
32. standard gamble$.tw.
33. time trade off.tw.
34. time tradeoff.tw.
35. tto.tw.
36. letter.pt.
37. editorial.pt.
38. comment.pt.
39. 36 or 37 or 38
40. or/6-35
41. 40 not 39
42. 5 and 41
43. limit 42 to yr="1970 -Current"

Embase: Ovid. 1974 to 2013 May 08

1. melanoma/
2. melanoma$.tw.
3. skin tumor/
4. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
5. or/1-4

6. "Quality of Life"/ 7. (qol or (quality adj2 life)).ti,ab. 8. (value adj2 (money or monetary)).tw. 9. socioeconomics/ 10. quality adjusted life year/ 11. (qaly$ or qald$ or qale$ or qtime$).tw. 12. disability adjusted life.tw. 13. daly$.tw. 14. health survey/ 15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 16. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw. 19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 20. (euroqol or euro qol or eq5d or eq 5d).tw. 21. (hql or hqol or h qol or hrqol or hr qol).tw. 22. (hye or hyes).tw. 23. health$ year$ equivalent$.tw. 24. health utilit$.tw. 25. (hui or hui1 or hui2 or hui3).tw. 26. disutilit$.tw. 27. rosser.tw. 28. (quality adj2 wellbeing).tw. 29. qwb.tw. 30. (willingness adj2 pay).tw. 31. standard gamble$.tw. 32. time trade off.tw. 33. time tradeoff.tw. 34. tto.tw. 35. letter.pt. 36. editorial.pt. 37. comment.pt. 38. 35 or 36 or 37 39. or/6-34 40. 39 not 38
41. 5 and 40

Cochrane Library
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Quality of Life] this term only
#2	(qol or (quality next/2 life)):ti,ab,kw
#3	MeSH descriptor: [Value of Life] this term only
#4	value and (money or monetary):ti,ab,kw
#5	MeSH descriptor: [Quality-Adjusted Life Years] this term only
#6	(quality adjusted life):ti,ab,kw
#7	(qaly* or qald* or qale* or qtime*):ti,ab,kw
#8	disability adjusted life:ti,ab,kw
#9	daly*:ti,ab,kw
#10	MeSH descriptor: [Health Status Indicators] explode all trees
#11	sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six:ti,ab,kw
#12	sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw
#13	sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve:ti,ab,kw
#14	sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen:ti,ab,kw
#15	sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty:ti,ab,kw
#16	euroqol or euro qol or eq5d or eq 5deuroqol or euro qol or eq5d or eq 5d:ti,ab,kw
#17	hql or hqol or h qol or hrqol or hr qol:ti,ab,kw
#18	hye or hyes:ti,ab,kw
#19	health* year* equivalent*:ti,ab,kw
#20	health utilit*:ti,ab,kw
#21	hui or hui1 or hui2 or hui3:ti,ab,kw
#22	disutilit*:ti,ab,kw
#23	rosser:ti,ab,kw
#24	qwb:ti,ab,kw
#25	standard gamble*:ti,ab,kw
#26	willingness to pay:ti,ab,kw
#27	quality of wellbeing:ti,ab,kw
#28	time trade off:ti,ab,kw
#29	time tradeoff:ti,ab,kw
#30	tto:ti,ab,kw
#31	letter:pt
#32	editorial:pt
#33	comment:pt
#34	#31 or #32 or #33
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#36	#35 not #34
#37	MeSH descriptor: [Melanoma] explode all trees
#38	melanoma*:ti,ab,kw
#39	MeSH descriptor: [Skin Neoplasms] explode all trees
#40	(skin next/3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*)):ti,ab
#41	#37 or #38 or #39 or #40
#42	#36 and #41 from 1970 to 2013

Cinahl: EBSCO. 1981 to present

S42	S5 AND S41 Limiters - Published Date from: 19700101-20130631
S41	S40 NOT S39
S40	S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S39	S36 or S37 or S38
S38	PT comment
S37	PT editorial
S36	PT letter
S35	TI tto or AB tto
S34	TI time tradeoff or AB time tradeoff
S33	TI time trade off or AB time trade off

S32	TI standard gamble* or AB standard gamble*
S31	TI willingness N2 pay or AB willingness N2 pay
S30	TI qwb or AB qwb
S29	TI quality N2 wellbeing or AB quality N2 wellbeing
S28	TI rosser or AB rosser
S27	TI disutilit* or AB disutilit*
S26	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S25	TI health utilit* or AB health utilit*
S24	TI health* year* equivalent* or AB health* year* equivalent*
S23	TI (hye or hyes) or AB (hye or hyes)
S22	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S21	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S20	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S19	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S18	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S17	TI quality adjusted life or AB quality adjusted life
S16	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S15	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
	(MH "Health Status Indicators")
S14	TI daly* or AB daly*
S13	TI disability adjusted life or AB disability adjusted life
S12	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S11	(MH "Quality-Adjusted Life Years")
S10	(MH "Economic Value of Life")
S9	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S8	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S7	(MH "Quality of Life")
S6	S1 or S2 or S3 or S4
	(skin N3 (cancer* or oncolog* or malignan* or carcinoma* or adenocarcinoma* or tumour*))
	(MH "Skin Neoplasms")
	melanoma*
S5	(MH "Melanoma")
S4	
S3	
S2	
S1	

EconLit: Ovid. 1961 to April 2013

1. melanoma$.tw.
2. (skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumour$)).ti,ab.
3. 1 or 2

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.13.6 The inclusion and exclusion criteria.

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Study Type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with advanced (unresectable or metastatic) melanoma	This is the relevant patient population
Interventions	There was no restriction to intervention	To ensure all relevant studies were included
Outcomes	Studies reporting the resource use and costs associated with the treatment and ongoing management of advanced melanoma	The aim of the review was to identify relevant costs and data about resource use
Country of Study	UK	Costs and use of resources from a K perspective were required
Exclusion Criteria		
Category	**Exclusion criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were being hand-searched)	Primary study articles were required

10.13.7 The data abstraction strategy.

Provided within the full submission above.

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted

- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data

have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.