NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Ipilimumab for previously treated unresectable malignant melanoma

Submitted by Bristol-Myers Squibb Pharmaceuticals Ltd

Single technology appraisal (STA)

17 June 2011

Contents

List of Tables 5
List of Figures 8
Abbreviations 10
Executive summary 12
Section A – Decision problem 16
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. 16
1.2 What is the principal mechanism of action of the technology? 16
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). 18
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 licence). 19
1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use. 19
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. 19
1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK. 19
1.8 Does the technology have regulatory approval outside the UK? If so, please provide details. 19
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? 19
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. 20
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. 20
1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology? 20
1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology? 21
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? 21

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 ... 22
2.2 How many patients are assumed to be eligible? How is this figure derived? ... 24
2.3 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 ... 24
2.4 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. ... 25
2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice. ... 27
2.6 Please identify the main comparator(s) and justify their selection. ... 27
2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised. ... 27
2.8 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. ... 28
2.9 Does the technology require additional infrastructure to be put in place? ... 28
3.1 Identification of equity and equalities issues ... 29
Section B – Clinical and cost effectiveness ... 32
5.1 Identification of studies ... 34
5.2 Study selection ... 34
5.3 Summary of methodology of relevant RCTs ... 41
5.4 Critical appraisal of relevant RCTs ... 62
5.5 Results of the relevant RCTs ... 63
5.6 Meta-analysis ... 71
5.7 Indirect and mixed treatment comparisons ... 71
5.8 Non-RCT evidence ... 72
5.9 Adverse events ... 73
5.10 Interpretation of clinical evidence ... 81
6.1 Published cost-effectiveness evaluations ... 88
6.2 De novo analysis ... 92
6.3 Clinical parameters and variables ... 101
6.4 Measurement and valuation of health effects ... 126
6.5 Resource identification, measurement and valuation ... 132
6.6 Sensitivity analysis ... 141
6.7 Results ... 143

6.8 Validation 155
6.9 Subgroup analysis 156
6.10 Interpretation of economic evidence 157
Section C – Implementation 159
7.1 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. 159
7.2 What assumption(s) were made about current treatment options and uptake of technologies? 159
7.3 What assumption(s) were made about market share (when relevant)? 160
7.4 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). 160
7.5 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? 160
7.6 Were there any estimates of resource savings? If so, what were they? 161
7.7 What is the estimated annual budget impact for the NHS in England and Wales? 161
7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify? 161
9.1 Appendix 1 168
9.2 Appendix 2: Search strategy for Section 5.1 (Identification of studies) 169
9.3 Appendix 3: Quality assessment of RCT(s) 185
9.4 Appendix 4: Search strategy for Section 5.7 (Indirect and mixed treatment comparisons) 188
9.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 5.7 189
9.6 Appendix 6: Search strategy for Section 5.8 (Non-RCT evidence) 190
9.7 Appendix 7: Quality assessment of non-RCT(s) in Section 5.8 194
9.8 Appendix 8: Search strategy for Section 5.9 (Adverse events) 195
9.9 Appendix 9: Quality assessment of adverse event data in Section 5.9 196
9.10 Appendix 10: Search strategy for Section 6.1 (Cost-effectiveness studies) ... 197
9.11 Appendix 11: Quality assessment of cost-effectiveness studies 203
9.12 Appendix 12: Search strategy for Section 6.4 (Measurement and valuation of health effects) 206
9.13 Appendix 13: Search strategy for Section 6.5 (Resource identification, measurement and valuation) 209
9.14 Appendix 14: Kaplan-Meier curve fits 209
9.15 Appendix 15: Model assumptions relating to comparator data 219
9.16 Appendix 16: [redacted] 226

List of Tables

Table 1: Base-case cost-effectiveness results 14
Table 2: Unit costs of technology being appraised 20
Table 3: Eligibility criteria used in search strategy 36
Table 4: List of relevant RCTs 40
Table 5: Comparative summary of methodology of the RCTs 42
Table 6: Eligibility criteria of the RCTs 45
Table 7: Characteristics of participants in the RCTs across randomised groups 48
Table 8: Primary and secondary outcomes of the RCTs 54
Table 9: Summary of statistical analyses in RCTs 57
Table 10: Quality assessment results for RCTs 62
Table 11: Overall survival in Study MDX010-20 (Hodi2010) 64
Table 12: Summary of key efficacy results in study MDX010-20 (Hodi 2010) 66
Table 13: Summary of key efficacy results in study CA184-022 (Wolchok2010) 68
Table 14: Overall tolerability of ipilimumab with or without prophylactic budesonide (Weber 2009) 74
Table 15: Rate of grade ≥2 diarrhoea in patients receiving ipilimumab with or without prophylactic budesonide (Weber 2009) 75
Table 16: Summary of safety in MDX010-20 (Hodi 2010) 77
Table 17: Summary of safety in CA184-022 (Wolchok 2010) 79
Table 18: Summary list of other cost-effectiveness evaluations 91
Table 19: Current Practice in Second Line Treatment of Stage III or Stage IV Melanoma 96
Table 20: Key features of analysis 99
Table 21: Clinical trial dosing for all treatments in trial MDX010-20 (Hodi 2010) 100
Table 22: AIC for One Curve Parametric Fits 102
Table 23: AIC for 18-months onwards curve 105
Table 24: Parameters used to estimate PFS and OS for Ipilimumab and gp100 from 548 days onwards 108
Table 25: Comparison of Kaplan Meier and estimated median PFS and OS for Ipilimumab and gp100 108
Table 26: Comparison of Kaplan Meier and estimated mean PFS and OS for Ipilimumab and GP100 – trial period data (1565-day horizon) 109
Table 27: Comparison of Kaplan Meier and estimated mean PFS and OS for Ipilimumab and GP100 (over 30-year time horizon) 110
Table 28: Estimated incidence of AEs among ipilimumab patients and gp100 patients 113
Table 29: HRQL results, Beusterien et al 113
Table 30: Utility Values Mapped from EORTC QLQ-C30 Trial Data 114
Table 31: Utility Values Mapped from SF-36 Trial Data 117

Table 32: Summary of variables applied in the economic model 119
Table 33: HRQL Results, Beusterien et al 129
Table 34: Summary of quality of life values for cost-effectiveness analysis 131
Table 35: Kind et al Utilities by Age Band 131
Table 36: Unit costs associated with the technology in the economic model – vials of ipilimumab required (assuming dose of 3 mg/kg) 134
Table 37: Disease management microcosting information 136
Table 38: Unit costs associated with the technology in the economic model 139
Table 39: List of health states and associated costs in the economic model 139
Table 40: List of adverse events and summary of costs included in the economic model 140
Table 41: Comprehensive list of analyses presented 141
Table 42: Summary of model results compared with clinical data - days 143
Table 43: Model outputs by clinical outcomes and treatment arm - discounted 144
Table 44: Summary of QALY gain by health state - discounted 144
Table 45: Summary of costs by health state - discounted 144
Table 46: Summary of predicted resource use by category of cost - discounted 145
Table 47: Base-case results 145
Table 48: Impact of Vial Sharing Assumptions 148
Table 49: Impact of Dose Required 148
Table 50: Impact of the Utility of Progressive Disease 148
Table 51: No discounting, results of structural sensitivity analysis and scenario analysis 150
Table 52: Scenario 2: Alternative comparators, results of structural sensitivity analysis and scenario analysis 150
Table 53: Alternative utility estimates, results of structural sensitivity analysis and scenario analysis 151
Table 54: Scenario 4: Maximum dosing assumption, results of structural sensitivity analysis and scenario analysis 151
Table 55: Scenario 5: Alternative curve fits, results of structural sensitivity analysis and scenario analysis 152
Table 56: Scenario 6: Use of alternative data for ipilimumab 153
Table 57: Scenario 7: Use of alternative time horizons 154
Table 58: Scenario 8: Use of alternative weight data 154
Table 59: Estimated patient numbers, 2011 - 2015 159
Table 60: Estimated treated patients, 2011 - 2015 160
Table 61: Estimated budget impact in England & Wales, 2011 - 2015 162
Table 62 Search strategy/history in Datastar - performed on 8th April, 2010 170
Table 63 Search strategy/history in the Cochrane Library - performed on 26th March, 2010 172

Table 64 Search strategy/history in EMBASE 1980 to 2011 Week 17 - performed on 6th May 2011 173

Table 65: Search strategy/history in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present - performed on 6th May 2011 174

Table 66: Search strategy/history in Cochrane Wiley – performed on 6th May 2011 176

Table 67: Studies identified through hand searching – reasons for exclusion 178

Table 68: Ongoing trials identified 181

Table 69: EMBASE 1980 to 2011 Week 17 - performed on 4th May 2011 190

Table 70: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present - performed on 4th May 2011 191

Table 71: Embase: accessed 9th December 2010 197

Table 72: Medline and Medline In Process: accessed 9th December 2009 198

Table 73: Econlit: Accessed 9th December 2010 199

Table 74: NHS EED: Accessed 9th December 2010 199

Table 75: Embase: accessed 14th August 2009 206

Table 76: Medline: accessed 19th November 2010 206

Table 77: Econlit 207

Table 78: NHS EED 207

List of Figures

Figure 1 Mode of action of ipilimumab 17

Figure 2 General recommendations for the management of ipilimumab immune-related adverse events 21

Figure 3 Schematic for the first systematic review of RCT evidence (to April 2010) .. 38

Figure 4 Schematic for the second systematic review of RCT evidence (2010-2011) 39

Figure 5 Participant flow in MDX010-20 (Hodi 2010) 59

Figure 6 Participant flow in CA184-022 (Wolchok 2010) 60

Figure 7 Participant flow in CA184-007 (Weber 2009) 61

Figure 8 Overall survival by treatment (ITT population) in MDX010-20 (Hodi 2010) .. 65

Figure 9 Overall survival by treatment (randomised population) in CA184-022 (Wolchok 2010) 69

Figure 10 Schematic for the review of non-RCT evidence 72

Figure 11 Flowchart of economic study inclusions/exclusions..... 90

Figure 12 Model Health States 94

Figure 13 Standard Pathway of Care for Metastatic Melanoma Grade III and IV 96

Figure 14 Overall survival – modelled data vs Kaplan Meier data, single curve fit 103

Figure 15 Progression free survival – modelled data vs Kaplan Meier data, single curve fit 103

Figure 16 Nelson-Aalen cumulative hazard estimates for overall survival 104

Figure 17 Progression Free Survival – Modelled Data vs Kaplan Meier Data, two-part curve fit 105

Figure 18 Overall Survival – Modelled Data vs Kaplan Meier Data, two-part curve fit 106

Figure 19 Progression Free Survival – Modelled Data vs Kaplan Meier Data, Adjusted for Background Mortality 107

Figure 20 Overall Survival – Modelled Data vs Kaplan Meier Data, Adjusted for Background Mortality..... 107

Figure 21 Long Term Survival in Metastatic Melanoma, IL-2 111

Figure 22 Validation of survival curve approach in melanoma applied to Atkins (1999) 112

Figure 23 EORTC Utilities For Patients Who Have Not Progressed..... 114

Figure 24 EORTC Utilities For Patients Who Have Progressed 115

Figure 25 EORTC Utilities For Patients Who Have Not Progressed..... 117

Figure 26 EORTC Utilities For Patients Who Have Progressed 118

Figure 27 Tornado diagram presenting results of sensitivity analysis for all variables that cause a change of ≥ ± £200 147

Figure 28 Scatterplot of PSA results (1,000 simulations) 149

Figure 29 Schematic for hand-searching conference proceedings (2008-2010) 177

Figure 30 Schematic for updated conference proceeding and specific journal searches 180

Figure 31 Schematic for ongoing research identification..... 181

Abbreviations

AE	adverse event
AES	adverse events
AIC	Akaike information criterion
ANA	antinuclear antibody
BOR	best overall response
BORR	best overall response rate
BSC	best supportive care
BUD	budesonide
CCRT	Central Register of Controlled Trials
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for adverse events
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T lymphocyte antigen 4
DARE	Database of Abstracts of Reviews of Effects
DCR	disease control rate
DTIC	dacarbazine
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol five dimension instrument
GI	gastrointestinal
HR	hazard ratio
HRG	Healthcare Resource Group
HRQL	health-related quality of life
HLA	human leukocyte antigen
ICER	incremental cost-effectiveness ratio
IFN-a	interferon alfa
IgG	immunoglobulin g
IL-2	interleukin-2
IPI	ipilimumab
irAE	immune-related adverse event
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
ITT	intention to treat
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mWHO	Modified World Health Organisation criteria
NCI	National Cancer Institute
NHS	National Health Service
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY(s)	quality-adjusted life year(s)
RCT	randomised controlled trial
RF	rheumatoid factor
SAE	serious adverse event
SD	stable disease
SF36	Short-form 36 questionnaire

SPC	Summary of Product Characteristics
TCR	T-cell receptor
TEN	toxic epidermal necrolysis
TNM	Classification of malignant tumours
TTP	time to tumour progression
ULN	upper limit of normal
WHO	World Health Organisation

Executive summary

The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.

Brand name: Yervoy; Approved name: ipilimumab;

Therapeutic class: Antineoplastic agents, monoclonal antibodies

The Committee for Medicinal Products for Human Use (CHMP) issued a positive approval opinion for ipilimumab on 19th May 2011. The European Commission (EC) issued a Marketing Authorisation for YERVOY™ (ipilimumab) for the treatment of adult patients with previously-treated advanced melanoma on 13th July 2011 (European Commission 2011).

Ipilimumab is a fully human monoclonal immunoglobulin antibody (IgG1κ) which works in a novel way to stimulate the body's own immune system to fight cancer. This mechanism of action, which we believe to be highly innovative, is 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.

This is a completely novel mode of action and so ipilimumab should be viewed as a new treatment paradigm for malignant melanoma. We hope that the Appraisal Committee will keep this, together with the high unmet need in what is a severe and ultimately terminal disease area, in mind when considering the product.

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.

Ipilimumab is available as a concentrate for solution for infusion in 50mg/10ml and 200mg/40ml (5mg/ml) vials. Administration is by intravenous infusion. The pack sizes are to be confirmed.

The indication(s) and any restriction(s).

Ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

The recommended course of treatment.

Induction dose: 3mg/kg every 3 weeks for a total of 4 doses. Clinicians may consider re-induction treatment if necessary. The average length of treatment is anticipated to be 3 months. In the pivotal clinical trial, 6% of patients received re-induction, 1% had a second re-induction and 0.1% had a third re-induction course of treatment. The median time from 1st treatment to re-induction was 1 year in the pivotal clinical trial.

No dose adjustments are required; for adverse event handling doses are either omitted or discontinued.

The main comparator(s).

For the purposes of this submission as defined by the NICE scope, the base-case comparator is Best Supportive Care (BSC); other comparators such as carboplatin-based chemotherapy and dacarbazine are included in the sensitivity analysis.

Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.

The key clinical evidence comes from 3 RCTs. As there were such a small number of RCTs an indirect or mixed treatment comparison was considered inappropriate.

The main results of the RCTs and any relevant non-RCT evidence.

The survival data shown in the ipilimumab studies are very promising and highly remarkable in view of the usual poor prognosis of patients with malignant melanoma.

- Based on meta-analysis data on a variety of agents, patients with advanced melanoma have a median overall survival of 6.2 months and a 1 year survival rate of 25.5%.
- In contrast, the main RCT of this submission, MDX010-20 (Hodi 2010), showed a 10-10.1 months' median overall survival in the ipilimumab arms and a 43.6-45.6% 1 year survival rate.
- This is equivalent to a 60% improvement in median overall survival, and an 80% improvement in 1 year survival. This is a hugely significant outcome, given that such patients are normally expected to only live for 6-9 months.
- Importantly, the patients recruited into the ipilimumab clinical trials were very representative of the UK advanced malignant melanoma population.

Economic evaluation

Section B details the creation of a *de novo* economic model for ipilimumab, with Table 1 providing the results. Ipilimumab shows an increase of 1.86 Life Years compared to BSC, with a corresponding gain in QALYs of 1.37.

The ICER is £60,737 in the base case, with the model being most sensitive to choice of curve used to extrapolate ipilimumab overall survival, utility in progressive disease, and acquisition cost of ipilimumab. This should however be considered in the context of NICE 'End of Life' criteria, as well as the innovative nature of the technology.

Table 1: Base-case cost-effectiveness results

Technology	Total			Incremental			ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£12,837	1.33	1.01				
Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737

When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance.

This is not required as there is only one base case comparator. Other comparators are considered in sensitivity analysis.

Subgroup analyses, considered and clinical- and cost-effectiveness results.

No subgroup analyses have been considered as there are no relevant subgroups.

In Summary

Clinical setting

Melanoma is the most aggressive form of skin cancer; it can be fatal if undetected and untreated, and its incidence is increasing.

The mean age of diagnosis is 50 years, with approximately 20% of cases occurring in young adults aged between 15 and 39 years old. In its early stages, melanoma is normally asymptomatic and, if detected before it has spread, it can be cured. However, 10% of cutaneous melanomas will have already metastasised by the time they are diagnosed. For stage III disease (i.e. regional lymph nodes involved), 5-year survival rates range from 40% to 50%, while stage IV disease (i.e. the melanoma has spread to distant sites) has an extremely poor prognosis (5-year survival rate is approximately 5-15%; median survival is 6-9 months).

Unresectable (i.e. complete removal of the tumour is not possible by surgery) stage III or IV (metastatic) disease is usually managed by a specialist oncologist. The first line standard of care is usually dacarbazine, although radiotherapy, immunotherapy and combination chemotherapy have been studied in randomised clinical trials. However, up to now, there have been no approved agents for previously treated malignant melanoma, with the result that there are only limited treatment options available for second or subsequent line therapy.

To exacerbate the problem, there is currently no agreed-upon standard of care in previously treated advanced malignant melanoma. Dacarbazine, vindesine, interferon and carboplatin are amongst the treatments used, but these are of limited benefit. As a consequence, participation in clinical trials is the main treatment option for these patients.

Thus, there is a high unmet medical need for effective treatment for previously treated, unresectable malignant melanoma.

Ipilimumab

It is important to recognise that the survival data shown in the ipilimumab studies are very promising and highly remarkable in view of the usual poor prognosis of patients with malignant melanoma. A meta-analysis of phase II trials with a variety of agents in stage IV melanoma showed a median overall survival of 6.2 months and a 1 year survival rate of 25.5%. In contrast, the main RCT of this submission MDX010-20 (Hodi 2010), which had gp100 vaccine as the comparator, showed a 10-10.1 months' median overall survival in the ipilimumab arms and a 43.6-45.6% 1 year survival rate – in essence a 60% improvement in median overall survival, and an 80% improvement in 1 year survival. Importantly, the patients recruited into the ipilimumab clinical trials were very representative of the UK advanced malignant melanoma population, and these data can be considered highly applicable to the UK situation.

Ipilimumab has a well-characterised safety profile and is mostly defined by mechanism of action-driven immune-related adverse events (irAEs). These side effects are generally manageable using standard side effect management algorithms, which sometimes require omission or discontinuation of dosing. Resolution of irAEs usually occurs within 2-14 weeks from first occurrence. Severe irAEs occurred in 10-15% of patients treated with ipilimumab and overall there were 14 (2.2%) treatment-related deaths in the pivotal trial, 7 of which were due to irAEs. Thus, ipilimumab offers an exciting and very promising effective treatment for advanced malignant melanoma where currently very limited treatment options exist.

In summary, ipilimumab has a new, innovative mode-of-action and should be viewed as a new treatment paradigm in terms of health outcomes, providing a step change in the health benefits it offers advanced malignant melanoma patients, and representing a novel shift from "no effective treatment" to "effective treatment" for previously treated, unresectable malignant melanoma.

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 (poisonous) 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 which 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.

Principal approaches in tumour immunotherapy

The rationale behind the commonly used patient specific immunotherapies, and tumour specific immunotherapies, is to attack specific processes within the tumour. Examples are:

- Augmenting the patient's immune response by introducing vaccines. Triggering an immune response within tumour cells that affects cell survival or proliferation (Armstrong et al 2001, Maloney et al 1997)
- Infusing tumour associated antigen (TAA)-specific autologous CTLs that can directly attack tumour cells (Finn et al 2008)
- Modulating the immune response with monoclonal-antibodies specific for particular T-cell receptors (TCRs) (Finn et al 2008)
- Augmenting the patient's immune response using cytokines (Kim-Schulze et al 2007)

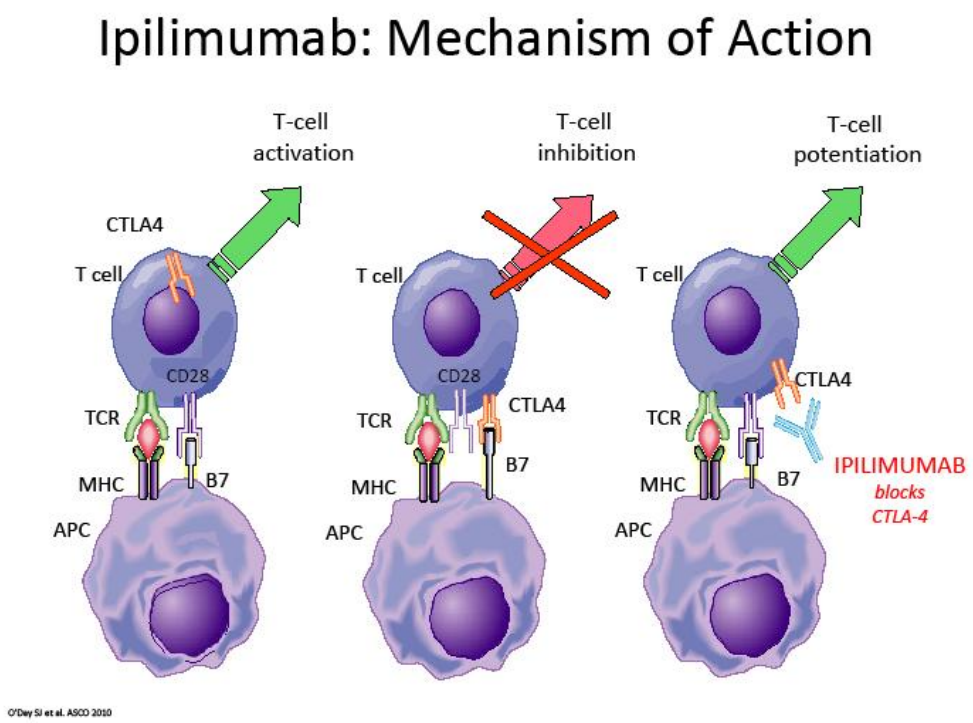
Ipilimumab is a fully human monoclonal immunoglobulin antibody (IgG1κ) which works in a novel way to stimulate the body's own immune system to fight cancer. It has an

innovative mode of action compared with other cytotoxic agents, and also compared with other immunotherapeutic agents.

This mechanism of action is 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.

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

Figure 1 Mode of action of ipilimumab



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 the patient continues 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.

It is important to recognise that patients who receive ipilimumab, as a consequence of its novel mode-of action, do not follow the conventional response pattern. Typically, chemotherapeutic agents will “shrink” a tumour, meaning that the overall tumour burden decreases within a few weeks (after a couple of cycles of initiating cytotoxic therapy) and if this shrinkage is large enough, it would be classified as a response.

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.

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

Although the tumour burden seems to increase in the short term (before it decreases), current data suggest this has minimal negative impact on patient’s health-related quality-of-life (Revicki et al 2010).

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).

The Committee for Medicinal Products for Human Use (CHMP) issued a positive approval opinion on 19th May 2011. A Marketing Authorisation was issued 13th July 2011 (European Commission 2011).

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 licence).

Upon EC approval on 13th July 2011, the EPAR has been

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

Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

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.

Data from a study (CA184-025) for patients previously enrolled in ipilimumab studies may become available within the next 12 months when the final analysis is complete. The purpose of this study is to evaluate the continued use of ipilimumab in patients who obtained clinical benefit in a prior study. Further information on this can be found at http://www.clinicaltrials.gov under the identifier: NCT00162123. However, the database does not contain any EU patients.

Other studies are ongoing for which data may become available in the next 12 months; however, these use different ipilimumab dose and drug combinations to this submission and are therefore not highlighted here.

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

A Marketing Authorisation was issued on 13th July 2011 (European Commission 2011)

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

Yes, the US Food and Drug Administration (FDA) approved the use of ipilimumab for the treatment of patients with late-stage (metastatic) melanoma on 25th March 2011.

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?

The Scottish Medicines Consortium (SMC) will conduct a health technology of 'ipilimumab for previously treated unresectable advanced melanoma' on 7th November 2011. The date of completion of this assessment is to be confirmed.

A NICE Technology Appraisal of 'Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma' is anticipated. The deadline for the submission is expected to be late July 2012.The date of completion is to be confirmed.

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.

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	Concentrate for solution for infusion
Acquisition cost (excluding VAT)	A UK price has not been decided yet
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	A UK price has not been decided yet
Anticipated average interval between courses of treatments	Clinicians may consider re-induction treatment. In the pivotal clinical trial only a small percentage of patients (40/676 [6%]) received re-induction treatment. The median time of re-induction from 1st treatment was 1 year (range 6 months to 4.2 years) (Hodi ASCO 2010) (Hodi 2010).
Anticipated number of repeat courses of treatments	Clinicians may consider re-induction treatment. In the pivotal clinical trial, 6% (40/676) had 1 re-induction, 1% (7/676) had a 2nd re-induction and 0.1% (1/676) had a 3rd re-induction course of treatment (Hodi ASCO 2010) (Hodi 2010).
Dose adjustments	No dose adjustments are used. For adverse event handling, doses are either omitted or treatment is discontinued.

SPC=Summary of Product Characteristics

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.

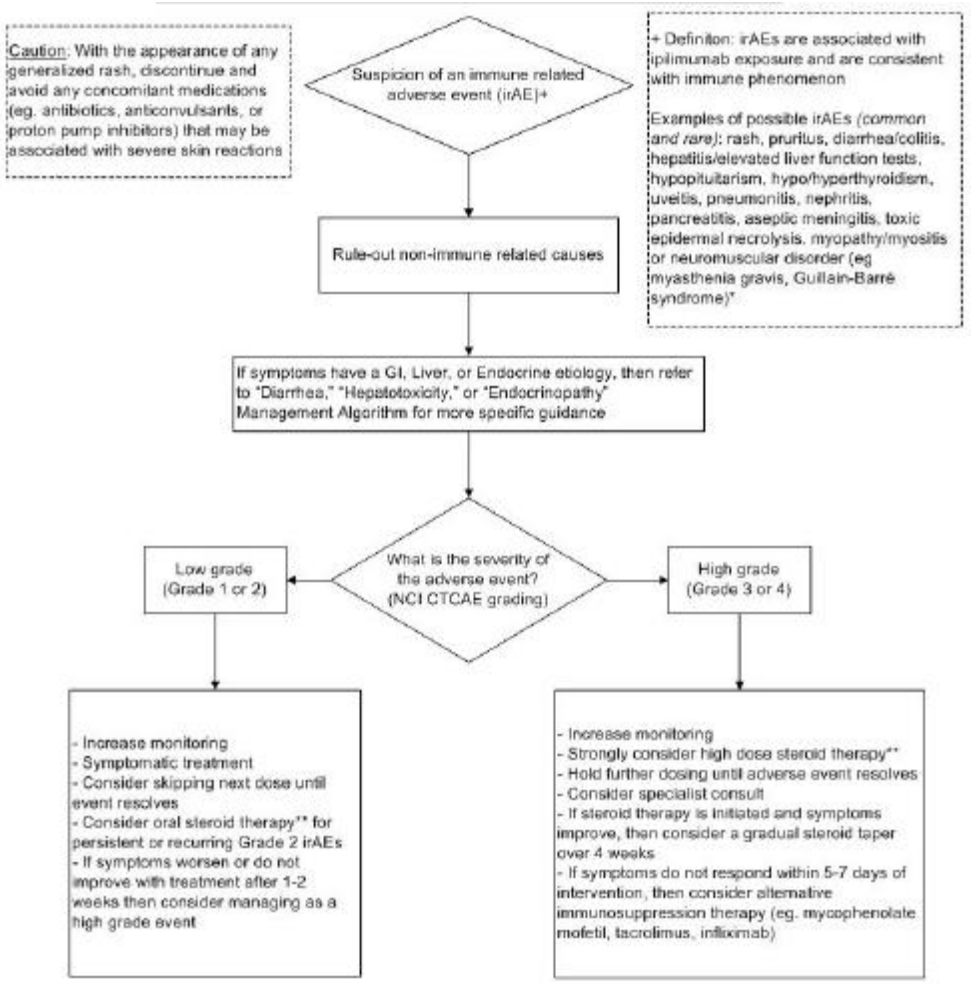
1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Ipilimumab 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?

Liver function tests and thyroid function tests should be evaluated at baseline, which is normal clinical practice, and additionally before each dose of ipilimumab. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with ipilimumab. An algorithm for the management of irAEs is shown in Figure 2.

Figure 2 General recommendations for the management of ipilimumab immune-related adverse events



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?

Not applicable.

2 Context

Melanoma is the most aggressive form of skin cancer and is generally fatal if undetected and untreated. The mean age of diagnosis is 50 years, with approximately 20% of cases occurring in young adults aged between 15 and 39 years old. In its early stages, melanoma is normally asymptomatic and, if detected before it has spread, it can be cured. However, 10% of cutaneous melanomas will have already metastasised by the time they are diagnosed. For stage III disease (i.e. regional lymph nodes involved) 5-year survival rates range from 40% to 50%, while stage IV disease (i.e. the melanoma has spread to distant sites) has an extremely poor prognosis (5-year survival rate is approximately 5-15%; median survival is 6-9 months).

If complete removal of the tumour is not possible by surgery, then it is termed unresectable. Unresectable stage III or IV (metastatic) disease is usually managed by a specialist oncologist, and the first line standard of care is usually dacarbazine, although radiotherapy, immunotherapy and combination chemotherapy have been studied in randomised clinical trials. Only limited treatment options are available for second or subsequent line therapy, and there is currently no standard of care in this setting. Also, up to now there have been no approved therapies for previously treated, advanced disease. Dacarbazine, vindesine, interferon and carboplatin are amongst the treatments used, but these are of limited benefit. Participation in clinical trials is the main treatment option for these patients.

Thus, there is a high unmet medical need for effective treatment of previously treated, unresectable malignant melanoma.

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.

Melanoma is the most aggressive form of skin cancer and is fatal if undetected and untreated. Its global incidence is increasing faster than all other types of cancer (Lens 2004). Some estimates suggest that the incidence of melanoma is doubling every 10-20 years (Garbe 2000), and the mortality rate continues to increase faster than that of most other cancers (Lens 2004).

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 approximately 20% of cases occur in young adults aged between 15 and 39 years. Its incidence is slightly higher in males than in females (IARC 2010).

The disease

The cells that become cancerous in malignant 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 malignant 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) (Balch 2009).

Survival

Prognostic factors in patients with advanced melanoma include, age, gender, primary tumour characteristics, tumour burden and LDH level (Balch 2009, Korn 2008). When diagnosed early, the chance of survival is considered relatively high. Early recognition of malignant 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 40% to 50% (NICE scope, ipilimumab 2011), 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 rate is approximately 5-15% (NICE scope, ipilimumab 2011), and the median survival is 6-9 months (Agarwala 2009).

Treatment of advanced melanoma

A small minority of people with advanced disease can still have their entire tumour removed. People with unresectable stage III or IV (metastatic) disease are usually managed by a specialist oncologist and first line standard of care normally involves the administration of dacarbazine. Radiotherapy, immunotherapy and combination chemotherapy have been studied in randomised clinical trials. Limited treatment options are currently available for second or subsequent line therapy (NICE scope, ipilimumab 2011) and there is no standard of care in this setting. Up to now, there have been no approved therapies for previously treated advanced disease. Dacarbazine, vindesine, interferon and carboplatin are amongst the treatments used but these offer limited benefit. None of these agents have demonstrated a significant survival benefit in randomised phase III clinical studies (Agarwala 2009). Participation in clinical trials is the main treatment option for these patients.

High unmet medical need

Given the absence of approved, effective and life-prolonging therapies, there is a high unmet medical need for effective treatment for previously treated malignant melanoma.

2.2 How many patients are assumed to be eligible? How is this figure derived?

It is difficult to quantify the likely number of patients. [redacted]

2.3 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.

NICE Clinical Guideline No. 27, June 2005, 'Referral guidelines for suspected cancer'.

NICE Clinical Guideline (in preparation), 'Diagnosis and management of metastatic malignant disease of unknown primary origin', anticipated date of publication July 2011.

Revised UK Guidelines for the management of cutaneous melanoma 2010 (British Association of Dermatologists 2010).

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.

Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline (Garbe 2010).

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ Melanoma 2010. National Comprehensive Cancer Network, Inc. (NCCN 2010).

Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow up (Dummer 2010).

Cutaneous Melanoma. A national clinical guideline- No.72. Scottish Intercollegiate Guidelines Network (SIGN 2003).

Related Public Health Guidance:

NICE Public Health Guidance No.32, 2011, 'Skin cancer: prevention using public information, sun protection resources and changes to the environment'.

Other 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).

NICE Guidance on Cancer Services, February 2006, 'Improving outcomes for people with skin tumours including melanoma: the manual (2006 guidance).

NICE Guidance on Cancer Services, March 2004, 'Improving supportive and palliative care for adults with cancer': the manual.

2.4 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.

There is no standard treatment for malignant melanoma. The definitive treatment of primary cutaneous melanoma is a wide local excision of the tumour. If complete removal of the tumour is not possible by surgical excision, then it is termed unresectable. The treatment options (NICE Guidance on Cancer Services 2006) for an unresectable melanoma include:

Radiotherapy - this has a very limited role in the management of patients with malignant melanoma, as it is generally regarded as a radioresistant tumour. It is occasionally used for localised metastases and in the palliative setting.

Chemotherapy - is often used for patients with malignant melanoma. There is no evidence to support the use of adjuvant chemotherapy following surgery.

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. Systemic therapies include immunotherapy (e.g. interferon alfa), chemotherapy (e.g. dacarbazine, carboplatin, paclitaxel), immuno/biochemotherapy, and experimental vaccine immunotherapy (Dummer 2010, Lui 2007).

In aggressive metastatic disease multi-agent chemotherapy containing paclitaxel and carboplatin or cisplatin, vindesine and dacarbazine produce partial responses and stabilisations in a meaningful number of patients (Dummer 2010). Patients are often referred to clinical trials, due to questionable survival rates with the current treatment

options. 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).

In the absence of a validated standard of care, the melanoma treatment guidelines of the British Association of Dermatologists (2010), the Royal College of Physicians (2007), the European Dermatology Forum (2009), the European Association of Dermato-Oncology and the European Organisation of Research and Treatment of Cancer (Garbe 2010), the European Society for Medical Oncology (Dummer 2010) and the National Comprehensive Cancer Network in the US (American Cancer Society 2008) all recommend that healthcare providers utilise clinical trials to manage advanced melanoma. However, as mentioned above, it is important to realise that not all patients are eligible for such clinical trials, and so have limited further treatment options.

When a treatment of an unresectable malignant melanoma has not been successful, there are no approved therapies or agreed standards of care for 'previously treated' advanced melanoma (i.e. no standard second-line therapy).

Several studies have reported that 60% or more patients receive BSC as second line therapy (Middleton et al 2010; Oxford Outcomes 2011; IMS 2011). According to Collinson and Marples (2010) the main active therapies after dacarbazine are carboplatin with or without paclitaxel (see Section 6.2.3).

In summary, there is a clear unmet need for effective treatment options for advanced metastatic melanoma.

How does ipilimumab change the existing treatment pathway?

Ipilimumab is an intravenous human monoclonal antibody which inhibits CTLA-4 and is a potential treatment for unresectable stage III and IV melanoma. Melanoma is considered an "immunogenic" cancer because of its ability to undergo spontaneous regression (Sznol 2009, Komenaka 2004, Gogas 2006). CTLA-4, a member of the immunoglobulin super-family, is a negative regulator of the immune system and plays a key role in induced antitumour immunity (Hodi 2008, Read 2006, Korman 2006).

Results of previous clinical research, and in particular results from the BMS pivotal trial (MDX010-20) comparing ipilimumab versus gp100 vaccine, show promising long-term survival benefits with ipilimumab in second-line treatment for patients with advanced melanoma (Hodi 2010). A small proportion of patients received re-induction treatment on disease progression.

These data (Hodi 2010) showed that there was a significant improvement in overall survival among patients with malignant melanoma (see Section 5). In ipilimumab studies some melanoma patients have survived up to 4 years and longer (Hodi 2010). This is a highly significant outcome, given that such patients normally are expected to only live for less than 12 months.

This means that the availability of ipilimumab now offers advanced melanoma patients, and their clinicians, a legitimate treatment option where previously none existed.

Summary

Ipilimumab, as an anti-CTLA-4 antibody, is a novel ground breaking immunotherapy treatment with a valid place in the pathway of care for treating patients with advanced melanoma, whose disease has progressed despite receiving previous therapy. Through its new mode of action ipilimumab offers a paradigm shift in the effective treatment of advanced melanoma.

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

The main issue is that there is currently no agreed standard of care for previously treated advanced melanoma patients.

Treatment options include:

- Clinical trials
- Available systemic treatments (dacarbazine, carboplatin, paclitaxel, etc)

Current treatment guidelines recommend enrolment in clinical trials (Dummer 2010, British Association of Dermatologists 2010). The choice of treatment is influenced by (a) the availability of clinical trials and (b) the patient's eligibility for inclusion in them. A patient's fitness to receive a drug and their personal preference regarding treatment is also a deciding factor. Therefore there is a wide variation in clinical practice.

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

The standard comparators for this appraisal are those identified by the NICE scope:

- Best supportive care, carboplatin-based chemotherapy and dacarbazine.

2.7 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 adverse events are immune-related in nature. 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 (ipilimumab Draft SPC June 2011). If an endocrinopathy occurs it may require ongoing hormone replacement therapy, which may be life-long. Management of irAEs is usually paired with omission of dosing for mild or moderate events and permanent discontinuation for severe irAEs.

The time to onset for most irAEs is generally between 3-10 weeks from first dose. Most irAEs usually resolve within 2-14 weeks from first occurrence, depending on the grade of event (see Section 5.9).

2.8 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. Most hospitals have established oncology units which 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, which should be normal clinical practice, and additionally before each dose of ipilimumab. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with ipilimumab.

[redacted]

2.9 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 Equity and equality

3.1 Identification of equity and equalities issues

Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

None expected.

Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None expected.

How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

4 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with previously treated unresectable stage III or IV malignant melanoma.	People with previously treated unresectable stage III or IV malignant melanoma.	No difference.
Intervention	Ipilimumab	Ipilimumab	No difference.
Comparator(s)	Best supportive care: carboplatin-based chemotherapy dacarbazine.	Best supportive care: carboplatin-based chemotherapy dacarbazine.	No difference.
Outcomes	Overall survival progression free survival, response rate, adverse effects of treatment, health-related quality of life.	Overall survival, progression free survival, response rate, adverse effects of treatment, health-related quality of life.	No difference.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost effectiveness of treatments will be expressed in terms of cost per quality-adjusted life year. The time horizon will be 30 years. Costs will be considered from an NHS and Personal Social Services perspective.	30 years is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Subgroups to be considered	None.	None.	No difference.

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Special considerations, including issues related to equity or equality	None.	None.	No difference.

Section B – Clinical and cost effectiveness

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
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 in 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

5 Clinical evidence

Summary

3 randomised controlled trials (RCTs) are included in this submission:

MDX010-20 (Hodi 2010), a large phase III study, is the main RCT of this submission as it was the pivotal licensing trial and used the UK licensed dose of ipilimumab (3mg/kg).

CA184-022 (Wolchok 2010) is a randomised, double-blind phase II dose-ranging study comparing 0.3 mg/kg, 3 mg/kg and 10 mg/kg ipilimumab.

CA184-007 (Weber 2009) is a randomised, double-blind, phase II study comparing the tolerability of ipilimumab when administered with or without budesonide. As the dose of ipilimumab used, 10mg/kg, is not licensed in UK, this study has been included for safety and tolerability data only.

- The survival data shown in the ipilimumab studies are very promising and highly remarkable in view of the usual poor prognosis of patients with malignant melanoma.
  - Based on meta-analysis data from a variety of agents, patients with advanced melanoma have a median overall survival of 6.2 months and a 1 year survival rate of 25.5%, results similar to that obtained with gp100 in the main RCT.
  - In contrast, the main RCT of this submission MDX010-20 (Hodi 2010) showed a 10-10.1 months' median overall survival in the ipilimumab arms and a 43.6-45.6% 1 year survival rate.
  - This is equivalent to a 60% improvement in median overall survival, and an 80% improvement in 1 year survival. This is a hugely significant outcome, given that such patients are normally expected to only live for 6-9 months.
  - Importantly, the patients recruited into the ipilimumab clinical trials were very representative of the UK advanced malignant melanoma population.

Ipilimumab has an established, well-characterised and generally manageable safety profile mostly defined by mechanism of action-driven immune-related adverse events (irAEs). Resolution of irAEs usually occurs within 2-14 weeks from first occurrence with established medical management.

Through its new, innovative mode-of-action, ipilimumab should be viewed as a new treatment paradigm in terms of health outcomes, providing a step change in the health benefits it offers patients, and representing a novel shift from "no effective treatment" to "effective treatment" for previously treated, unresectable malignant melanoma.

5.1 Identification of studies

Database searches for randomised controlled trials (RCTs)

Two systematic literature searches were performed to identify randomised controlled trials (RCTs): the first covering the period 1970 to April 8, 2010; the second the period Jan 1 2010 to May 6 2011.

The first search identified RCTs investigating the efficacy and safety of ipilimumab and relevant alternative systemic therapies in the treatment of unresectable stage III and stage IV malignant melanoma. The search was performed in Medline, Medline In-Process® and Embase using Datastar and in the Cochrane Library, combining 'disease terms' with 'drug names' and with 'RCT terms'. The search was limited to human and English language publications and excluded case reports, review articles, editorials, letters and practice guidelines.

The second search, conducted following publication of the final scope, identified RCTs of the efficacy and safety of ipilimumab or of best supportive care comparators in the treatment of unresectable stage III and stage IV malignant melanoma. Best supportive care was taken to include dacarbazine, temozolomide, aldesleukin, carboplatin-based therapies or palliative care/radiation. The search was performed in Medline, Medline In-Process® and Embase using OVID and in the Cochrane Library, again combining 'disease terms' with 'drug names or best supportive care options' and with 'RCT terms'. The search was limited to human publications and excluded case reports, review articles, historical articles and letters. Only studies published in English were considered.

Additional searches were also performed in order to identify relevant studies from conference proceedings, specific journals not fully indexed on standard search databases and on-going clinical trials.

Details of the search strategies are provided in Appendix 2.

5.2 Study selection

Eligibility criteria

Selection of randomised controlled trials (RCTs) from searches

For the first systematic literature search for RCTs, studies were selected initially on the following basis;

- Population – adults diagnosed with unresectable (stage III or IV) melanoma, with or without brain metastases, for 1st or 2nd line therapy (treatment naive, or pre-treated, patients who had progressed/relapsed after 1st line therapy, respectively),

- Interventions - ipilimumab, bevacizumab, DTIC, other chemotherapy agents (temozolomide, cisplatin, vinblastine, carmustine, lomustine, docetaxel or paclitaxel), interleukin-2 (IL-2), interferon alfa (IFN-a/IFN-a2b), oblimersen, fotemustine (nitrosourea alkylating agent), DTIC or temozolomide-based combination therapies (biochemotherapy/immunochemotherapy), melanoma

vaccines, plexxikon (PLX4032), and experimental therapies (monoclonal antibodies, gene therapies, cellular therapies (adoptive immunotherapy), targeted and anti-angiogenic agents),

- Comparators - agents listed under 'interventions', as monotherapies or in combination, placebo, or best supportive care,
- Outcomes – Overall Survival (OS), Progression Free Survival (PFS), time to tumour progression (TTP), complete/partial/objective response rate(s), discontinuations or withdrawals,
- Study designs – blinded or open-label RCTs, of parallel or crossover design,
- Language – full reports in English only were included.

Following publication of the final scope, the studies selected by the first search were reviewed, applying the below selection criteria. These were also used for the second systematic literature search (2010-2011) and for searching conference abstracts;

- Population – adults diagnosed with unresectable (stage III or IV) malignant melanoma, with or without brain metastases, undergoing 2nd line therapy, having been pretreated with chemo- and/or immuno-therapy and having progressed/relapsed after 1st line systemic therapy. Studies with mixed 1st and 2nd line patients were excluded,
- Interventions – restricted to second line systemic treatments – ipilimumab, dacarbazine, temozolomide with or without aldesleukin, carboplatin-based chemotherapy (carboplatin chemotherapy, Paraplatin, Paraplatin-AQ, platinum therapy or platinum chemotherapy), palliative radiation,
- Comparators - agents listed under 'interventions', as monotherapies or in combination, placebo, or best supportive care,
- Outcomes – Overall Survival (OS), Progression Free Survival (PFS), time to tumour progression (TTP), response rates, adverse effects of treatment,
- Study designs – blinded or open-label RCTs, of parallel or crossover design, phases II-IV,
- Language – English only.

Secondary publications or subgroup analyses were excluded where the principal publication for the trial was already included, unless they provided additional data on any outcomes of interest.

Study selection process

Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded. Papers included after this stage were then assessed based on the full text; further papers were excluded and (for the second search)

allocated an "exclusion code" to document the rationale for exclusion, yielding the final data set for inclusion.

Inclusion and exclusion selection criteria are shown in Table 3.

Table 3: Eligibility criteria used in search strategy

	Description	Justification
Inclusion criteria		
Population	Adults, unresectable (stage III or IV) malignant melanoma with or without brain metastases, undergoing 2nd line therapy, having been pretreated with chemo- and/or immunotherapy	According to final scope
Interventions	Ipilimumab, Dacarbazine or temozolomide (oral dacarbazine analogue) with or without aldesleukin, Carboplatin-based chemotherapy (carboplatin chemotherapy, Paraplatin, Paraplatin-AQ, platinum therapy or platinum chemotherapy), Palliative radiation	According to final scope
Outcomes	Overall Survival (OS), Progression Free Survival (PFS), response rates, adverse effects of treatment, health related quality-of-life	According to final scope
Study design	Blinded or open-label RCTs, of parallel or crossover design, phases II-IV	To assess studies that meet the highest level in the hierarchy of evidence
Language restrictions	English only	
Exclusion criteria		
Population	Studies with mixed 1st and 2nd line patients, studies with any number of treatment-naive patients. Stage I or stage II (localised primary) melanoma. Basal cell carcinoma. Squamous cell carcinoma. Bowen's disease (intraepidermal squamous cell carcinoma).	According to final scope
Interventions	Dicarbosil®, procarbazine. Cisplatin. Oxaliplatin.	According to final scope
Outcomes	No outcomes were excluded	All outcomes were deemed important to include
Study design	Phase I, pre-clinical	To assess studies that meet the highest level in the hierarchy of evidence

	Description	Justification
Language restrictions	Non-English studies excluded on final pass	

Flow diagram of included and excluded studies

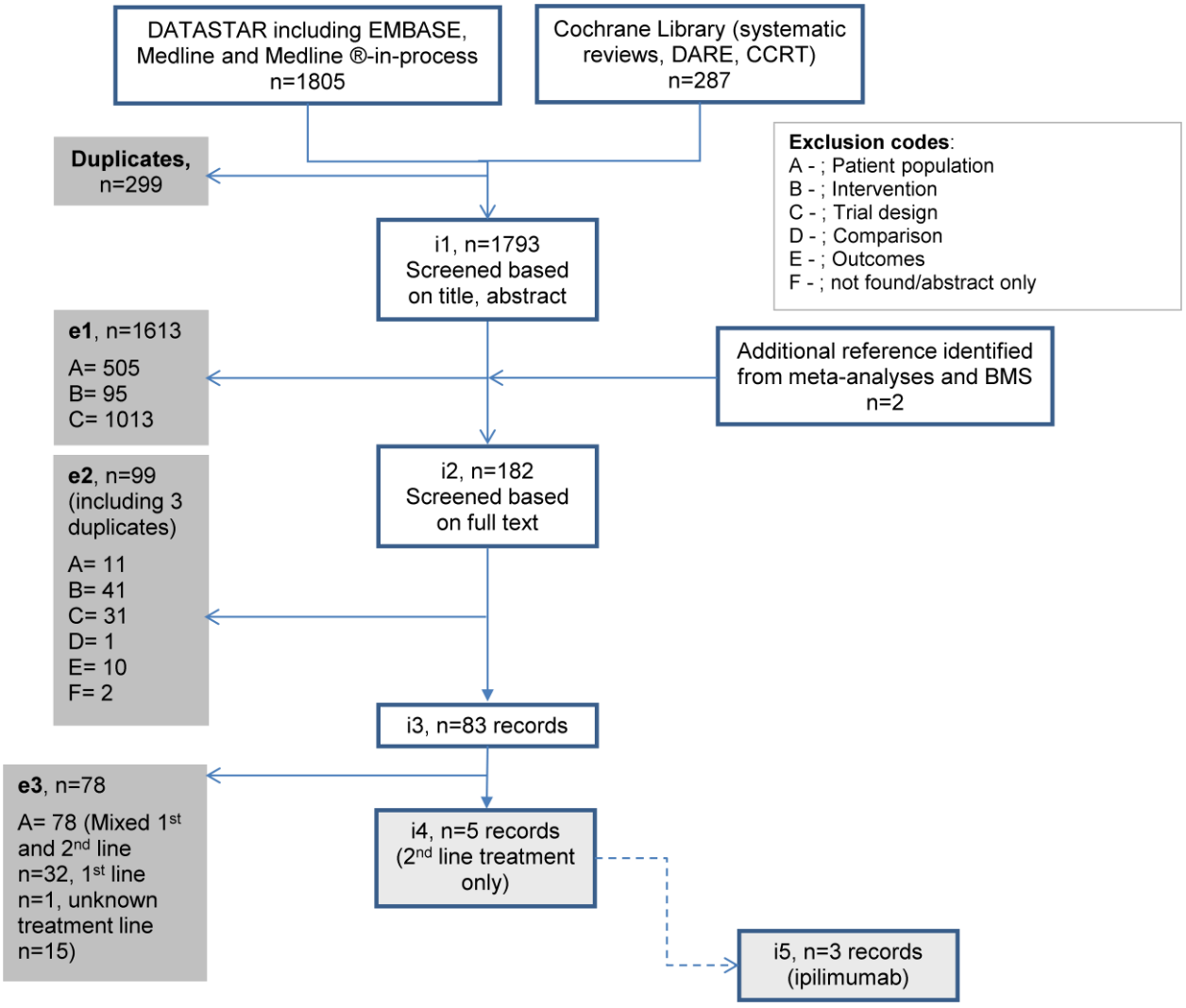
In the first systematic review, following assessment and exclusion of studies based on title, abstract and full text, 5 studies were included in the final data set (Eisen 2010, Hauschild 2009, Hodi 2010, Wolchok 2010, Zimpfer 2003). Hodi 2010 was included after being provided by BMS in this initial search (as shown in the flow diagram below). Of the 5 included studies, 2 trials examined the intervention of interest (Hodi 2010, Wolchok 2010). The remaining 3 studies reported on comparator interventions. One additional randomised, double-blind, phase 2 study comparing the tolerability of ipilimumab when administered with or without budesonide was identified (Weber 2009). As a 10mg/kg dose (unlicensed in UK) of ipilimumab was used, this study has been included for safety and tolerability data only and is reported in further detail in Section 5.9.

In the second systematic review, 43 studies were identified for full text screening. Of these, 3 studies (Hodi 2010, Maio 2010, Wolchok 2010) had already been identified by the first systematic review. Hodi 2010 and Wolchok 2010 were included in the review and Maio 2010 was excluded as the study was not specific to second line therapy. The remaining studies identified by this search were excluded according to the eligibility criteria outlined in Section 5.2.1. Therefore, no additional RCTs or safety studies were identified during this second search.

No additional RCTs were identified through hand searching of conference proceedings or specific journals (see Appendix 2 for further details of the hand searches conducted).

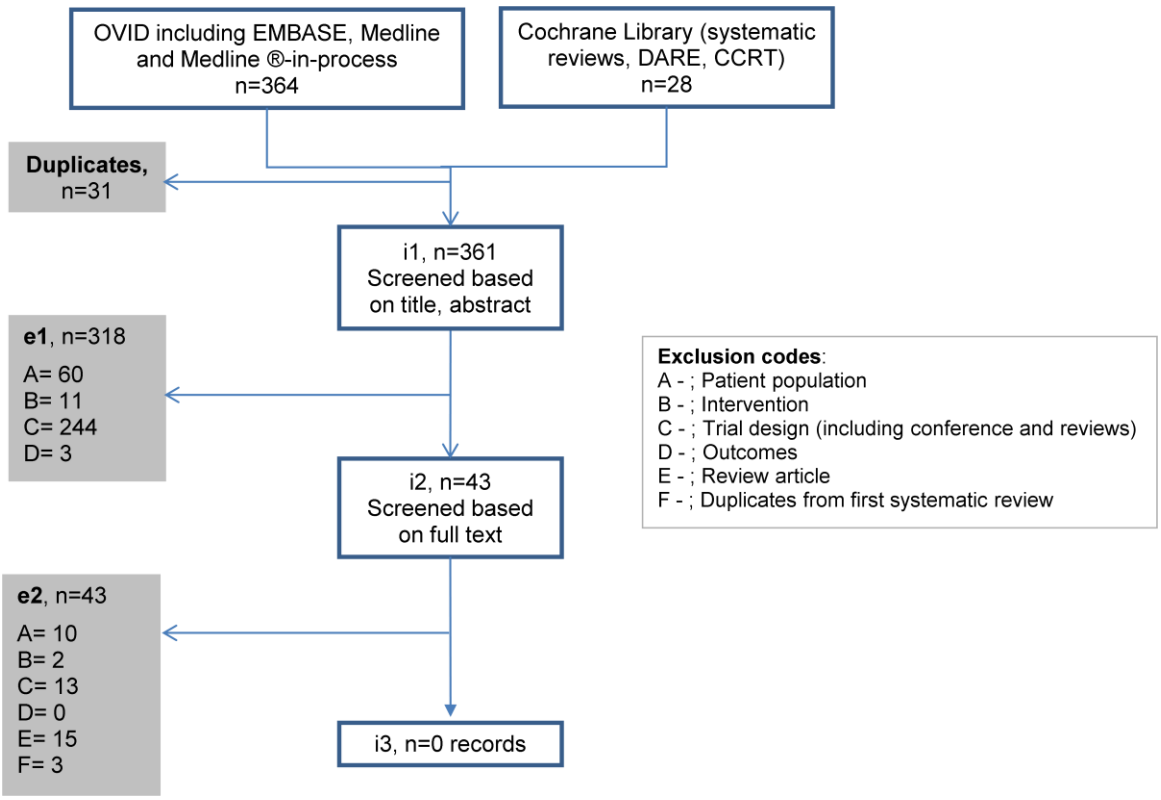
The systematic review schematics are shown in Figure 3.

Figure 3 Schematic for the first systematic review of RCT evidence (to April 2010)



i1, studies included at first pass; i2, studies included at second pass; i3, studies included at third pass; i4, studies included at forth pass; i5, studies included at fifth and final pass; e1 studies excluded from i1; e2, studies excluded from i2; e3, studies excluded from i3.

Figure 4 Schematic for the second systematic review of RCT evidence (2010-2011)



Abbreviations: DARE, Database of Abstracts of Reviews of Effects; CCRT, Central Register of Controlled Trials; i1, studies included at first pass; i2, studies included at second pass; i3, studies included at third and final pass; e1 studies excluded from i1; e2, studies excluded from i2; e3.

Data sources of identified studies

The pivotal clinical trial (Hodi et al 2010) and the trial of Wolchok (2010) are reported using the publication alongside extracts from the clinical study report and the registration dossier. The trial of Weber (2009) is reported using the publication.

Complete list of relevant RCTs

The systematic review of clinical evidence identified 3 RCTs of ipilimumab in the population of interest to this submission (Table 4). Hodi et al 2010 examined the effect of ipilimumab or ipilimumab plus the gp100 vaccine versus the gp100 vaccine alone. Wolchok et al 2010 was a dose ranging study for ipilimumab and Weber et al 2009 was a study to examine the effect of adding prophylactic budesonide to ipilimumab therapy in a mixed population of previously treated and treatment naïve patients (described in full in Section 5.9).

Table 4: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
NCT00094653 (MDX010-20)	Ipilimumab or Ipilimumab + gp100 vaccine	gp100 vaccine alone	HLA-A2*0201-positive patients with unresectable stage III or IV metastatic melanoma	Hodi 2010
NCT00289640 (CA184-022)	Ipilimumab monotherapy 10mg/kg	Ipilimumab monotherapy 3mg/kg and ipilimumab 0.3mg/kg	Stage III (unresectable) or stage IV melanoma, from 12 countries, at least 16 yrs old, previously treated (failed or progressed)	Wolchok 2010
NCT00135408 (CA184-007)	Prophylactic budesonide 9 mg + ipilimumab 10 mg/kg	Prophylactic placebo + ipilimumab 10 mg/kg	Unresectable Stage III or IV melanoma Mix of previously treated and treatment naïve	Weber 2009

Studies comparing the intervention directly with the appropriate comparator(s) stated in the decision problem

None of the trials identified represent a head-to-head comparison of the intervention with any of the comparators listed in the scope.

Studies excluded from further discussion

No identified studies were excluded from further discussion.

List of relevant non-RCTs

No non-RCTs relevant to this submission were identified.

5.3 Summary of methodology of relevant RCTs

Methods

The methodology of the relevant RCTs is summarised in Table 5.

Table 5: Comparative summary of methodology of the RCTs

Trial no. (acronym)	Hodi (2010) (MDX010-20)	Wolchok (2010) (CA184-022)	Weber (2009) (CA184-007)
Location	125 centres in 13 countries	66 centres in 12 countries	Canada, Israel, Italy, UK, USA
Design	Randomised, double-blind, multicentre, Phase III	Randomised, double-blind, multicentre, dose-ranging, Phase II	Randomised, double-blind, multicentre, Phase II
Method of randomisation	Centralised randomisation scheme 3:1:1 ratio Stratification according to baseline TNM status, and previous IL-2 therapy	Permuted block procedure, 1:1:1 ratio Stratification according to previous treatment received	1:1 ratio Stratification according to previous treatment received
Method of blinding (care provider, patient and outcome assessor)	Not reported	Not reported	Not reported
Intervention(s) (n =) and comparator(s) (n =)	1) IPI 3 mg/kg + gp100 peptide vaccine (n=403) 2) IPI 3 mg/kg + gp100 placebo (n=137) 3) IPI placebo + gp100 peptide vaccine (n=136)	1) IPI 10 mg/kg (n=72) 2) IPI 3 mg/kg (n=72) 3) IPI 0.3 mg/kg (n=73)	1) Prophylactic budesonide 9 mg + IPI 10 mg/kg (n=58) 2) Prophylactic placebo + IPI 10 mg/kg (n=57)

Trial no. (acronym)	Hodi (2010) (MDX010-20)	Wolchok (2010) (CA184-022)	Weber (2009) (CA184-007)
Primary outcomes (including scoring methods and timings of assessments)	Best overall response rate, later amended to overall survival (group 1 vs group 3) Tumour assessments: Weeks 12, 16, 24, thereafter q 3 months, according to modified WHO criteria	Best overall response rate (proportion of patients with complete or partial responses confirmed at least 4 weeks after first response) Tumour assessments: Weeks 12, 16, 24, thereafter q 3 months, according to modified WHO criteria Measurable disease: lesions ≥20 mm diam and ≥10 mm perpendicular CR = full disappearance of all designated tumours PR = at least 50% decrease from baseline in sum of the products of 2 largest perpendicular diameters of index lesions Stable disease = not meeting criteria for CR or PR in absence of progressive disease PD = ≥25% increase in sum of the products of all lesions relative to nadir, appearance of new tumours, or both.	AEs evaluated by NCI CTCAE v 3.0 Rate of grade ≥2 diarrhoea during first 24 weeks Tumour assessments: Weeks 12, 16, 20 and 24. Patients on maintenance IPI: Weeks 30, 36, 42 and 48 and q 3 months Modified WHO criteria for tumour assessment

Trial no. (acronym)	Hodi (2010) (MDX010-20)	Wolchok (2010) (CA184-022)	Weber (2009) (CA184-007)
Secondary outcomes (including scoring methods and timings of assessments)	Overall survival group 2 vs group 3 Overall survival group 1 vs group 3 Best overall response rate Duration of response Progression free survival at week 24	Disease control rate (proportion of patients with complete or partial responses plus stable disease), median overall survival and survival at 1 year. Progression-free survival at week 24.	Best overall response rate (proportion of patients with complete or partial responses) Disease control rate (proportion of patients with complete or partial responses plus stable disease), Overall survival Survival at 1 year Duration of response Proportion of patients with duration of response ≥24 weeks Time to response
Duration of follow-up	55 months (median f/u times for survival 17.2-27.8 months)	Median f/u times for survival 8.3-10.7 months	38 months

Participants

The inclusion and exclusion criteria for the relevant RCTs are summarised in Table 6.

Table 6: Eligibility criteria of the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Hodi (2010) (MDX010-20)	Unresectable Stage III or IV melanoma and previous therapy with dacarbazine, temozolomide, fotemustine, carboplatin or IL-2. Age ≥18 years Life expectancy ≥4 months ECOG performance status 0 or 1 HLA-A2*0201 positive Normal haematological, hepatic and renal function. No systemic treatment in previous 28 days	Any other cancer from which disease free for <5 years (except treated /cured basal cell or squamous cell skin cancer, superficial bladder cancer or treated carcinoma in situ of cervix, breast or bladder) Primary ocular melanoma Previous anti-CTLA-4 antibody or cancer vaccine Autoimmune disease Active untreated metastases in CNS Pregnancy or lactation Concomitant non-study anticancer therapy or immunosuppressant Long-term use of corticosteroids
Wolchok (2010) (CA184-022)	Unresectable Stage III or IV melanoma and measurable disease (by modified WHO criteria) Received previous therapy with dacarbazine, temozolomide, fotemustine, carboplatin or IL-2, or other, and progressed after CR or PR, or failed to show CR or PR within 12 weeks, or unable to tolerate treatment regimen Age ≥16 years	Concomitant therapy with any anti-cancer agent; immunosuppressive agents; any non-oncology vaccine therapy; surgery or radiotherapy, other investigational anti-cancer therapies; or chronic use of systemic corticosteroids Previous treatment with other investigational products, including cancer immunotherapy, within 30 days Previous treatment in another ipilimumab clinical trial or prior treatment with a CD137 agonist, CTLA-4 inhibitor or agonist Autoimmune disease: a documented history of inflammatory bowel disease, including ulcerative colitis and Crohn's disease, symptomatic autoimmune disease (e.g. rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, autoimmune vasculitis Evidence of brain metastases Any other malignancy from which disease-free for < 5 years, (except adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma *in situ* of the cervix) Primary ocular or mucosal melanoma Pregnancy

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Weber (2009) (CA184-007)	Unresectable Stage III or IV melanoma Previous therapy or none Age ≥18 years Life expectancy ≥4 months ECOG performance status 0 or 1	Any other cancer from which disease free for <5 years (except treated /cured basal cell or squamous cell skin cancer, superficial bladder cancer or treated carcinoma in situ of cervix, breast or bladder) Primary ocular melanoma Previous anti-CTLA-4 antibody Autoimmune disease Active untreated metastases in CNS Long-term use of corticosteroids Received investigational drugs within 4 weeks of starting protocol therapy

Baseline characteristics

Patient characteristics at baseline are summarised in Table 7.

In the MDX010-20 (Hodi 2010) trial, the demographic and other baseline characteristics of randomised subjects were comparable and the distributions were balanced across the three groups. The overall median age was 56.2 years. Most subjects were male (59.3%), with age <65 years (71.0%) and of White race (94.4%). At study entry, nearly all subjects (98.2%) had unresectable Stage IV metastatic melanoma and the majority of subjects were M1c stage (71.4%). Approximately one-third of subjects (37.6%) had an elevated lactate dehydrogenase (LDH) at baseline. Only a minority of subjects had previous exposure to IL-2 (22.8%). Eastern Cooperative oncology Group (ECOG) performance status was mainly (98.3%) 0 or 1.

The median duration of time since first diagnosis was 3.11 years (range 0-38.9 years). The disease stage and histopathology type at initial diagnosis were consistent across the 3 treatment groups.

The types and extent of prior therapies were consistent across the 3 treatment groups.

In the CA184-022 (Wolchok 2010) study, more men than women (66.4% vs 33.6%) were randomised; the majority were white (98.7%) and their median age was 58.0 years. All but 1 of the subjects had an ECOG performance status of 0 or 1 and 118 (54.4%) subjects were staged as M1c at study entry. The demography and subject characteristics were similar across all three treatment groups except for the M-stage and gender at study entry. The number of subjects at study entry with M1c-stage disease was similar between the 3 mg/kg and the 10 mg/kg groups (50%, and 51%, respectively) but was higher in the 0.3 mg/kg group (62%). Seventy-one percent of subjects were males in the 0.3 mg/kg group compared to 67% and 61% in the 3 mg/kg and 10 mg/kg groups, respectively.

All 217 randomised subjects had unresectable stage III or IV malignant melanoma at study entry; 95% had Stage IV disease. The number of subjects with Stage IV disease was evenly distributed across the 3 treatment groups. The median time from initial diagnosis to the first dose of study therapy was consistent across the 3 treatment groups (range of 43 to 47 months). The primary tumour sites at the time of initial diagnosis were consistent across the treatment groups, with the most common primary tumour sites reported as trunk, leg or other.

The types and extent of prior therapies were again consistent across the 3 treatment groups.

In the CA184-007 (Weber 2009) study, baseline demographics and characteristics were generally similar between the two arms; however, in the ipilimumab + budesonide arm, more patients had received prior systemic therapy. All patients had unresectable stage III or IV metastatic melanoma; 97% had stage IV disease.

Table 7: Characteristics of participants in the RCTs across randomised groups

Trial no. MDX010-20 (Hodi 2010) (n = 676) Baseline characteristics	**IPI + gp100 (n = 403)**	**IPI alone (n = 137)**	**gp 100 alone (n = 136)**
Age (mean, years)	55.6	56.8	57.4
Gender (M/F) n (%)	247 (61.3) / 156 (38.7)	81 (59.1) / 56 (40.9)	73 (53.7) / 63 (46.3)
ECOG performance status, n (%)			
0	232 (57.6)	72 (52.6)	70 (51.5)
1	166 (41.2)	64 (46.7)	61 (44.9)
2	4 (1.0)	1 (0.7)	4 (2.9)
3	1 (0.2)	0	0
M stage, n (%)			
M0	5 (1.2)	1 (0.7)	4 (2.9)
M1a	37 (9.2)	14 (10.2)	11 (8.1)
M1b	76 (18.9)	22 (16.1)	23 (16.9)
M1c	285 (70.7)	100 (73.0)	98 (72.1)
LDH level, n (%)			
≤ ULN	252 (62.5)	84 (61.3)	81 (59.6)
> ULN	149 (37.0)	53 (38.7)	52 (38.2)
Unknown	2 (0.5)	0	3 (2.2)
CNS metastases at baseline, n (%)	46 (11.4)	15 (10.9)	21 (15.4)
Received study drug	42 (10.4)	15 (10.9)	20 (14.7)
Had had previous treatment for CNS metastases	39 (9.7)	15 (10.9)	19 (14.0)
Previous systemic therapy for metastatic disease, n (%)	403 (100.0)	137 (100.0)	136 (100.0)
Previous IL-2 therapy, n (%)	89 (22.1)	32 (23.4)	33 (24.3)

CA184-022 (Wolchok 2010) (n = 217)	IPI 0.3 mg/kg (n = 73)	IPI 3 mg/kg (n = 72)	IPI 10 mg/kg (n = 72)
Age (years, mean and range,)	59 (25-85)	59 (29-78)	56 (19-83)
Gender (M), n (%)	52 (71)	48 (67)	44 (61)
Ethnic origin (white), n (%)	72 (99)	72 (100)	70 (97)
LDH			
Within ULN	38 (52)	40 (56)	33 (46)
> ULN	35 (48)	32 (44)	39 (54)
M stage at entry, n (%)			
M0	5 (7)	4 (6)	3 (4)
M1a	10 (14)	11 (15)	17 (24)
M1b	13 (18)	21 (29)	15 (21)
M1c	45 (62)	36 (50)	37 (51)
ECOG performance status, n (%)			
0	46 (63)	44 (61)	41 (57)
1	26 (36)	28 (39)	31 (43)
2	1 (1)*	0	0
Sites of commonest index lesions, n (%)**			
Lymph nodes	41 (56)	42 (58)	41 (57)
Liver	27 (37)	25 (35)	30 (42)
Lung	26 (36)	24 (33)	24 (33)
Skin	11 (15)	6 (8)	12 (17)
Chest wall	11 (15)	2 (3)	5 (7)
Adrenal gland	9 (12)	4 (6)	2 (3)
Spleen	8 (11)	1 (1)	4 (6)
Previous systemic treatment regimens, n (%)			
1	23 (32)	22 (31)	27 (38)
2	21 (29)	32 (44)	19 (26)

CA184-022 (Wolchok 2010) (n = 217)	IPI 0.3 mg/kg (n = 73)	IPI 3 mg/kg (n = 72)	IPI 10 mg/kg (n = 72)
3	16 (22)	16 (22)	19 (26)
4	8 (11)	2 (3)	5 (7)
≥ 5	5 (7)	0	2 (3)
Previous systemic treatment, n (%)			
Dacarbazine	47 (64)	38 (53)	45 (63)
Temozolomide	23 (32)	26 (36)	29 (40)
Fotemustine	12 (16)	6 (8)	9 (13)
Other chemotherapeutic agent	38 (51)	35 (49)	36 (50)
IL-2	16 (22)	17 (24)	7 (10)
Best response to previous therapy, n (%)***			
Complete response	4 (5)	2 (3)	3 (4)
Partial response	6 (8)	10 (14)	8 (11)
Stable disease	31 (42)	31 (43)	26 (36)
Progressive disease	30 (41)	29 (40)	33 (46)
Unable to ascertain	2 (3)	0	2 (3)

CA184-007 (Weber 2009) (n = 115)		IPI + BUD (n = 58)	IPI + placebo (n = 57)
Gender (M/F) n (%)		43 (74) / 15 (26)	38 (67) / 19 (33)
Race, n (%)			
	Caucasian	56 (97)	54 (95)
	Asian	0	2 (4)
	Black/African American	0	1 (1.8)
	Other/unknown	2 (3)	0
Age (years, median and range)		58 (30-82)	61 (26-86)
M stage at entry, n (%)			
	M0	1 (2)	1 (2)
	M1a	11 (19)	9 (16)
	M1b	18 (31)	18 (31)
	M1c	28 (48)	29 (51)
ECOG performance status, n (%)			
	0	40 (69)	42 (74)
	1	17 (29)	15 (26)
	2	1 (2)	0
Disease stage at study entry, n (%)			
	III	1 (2)	3 (5)
	IV	57 (98)	54 (95)
Baseline LDH, n (%)			
	Within ULN	33 (57)	38 (67)
	>ULN	25 (43)	19 (33)
Previous systemic regimens, n (%)		50 (86)	41 (72)
	1	22 (38)	18 (32)
	2	13 (22)	14 (25)
	3	12 (21)	7 (12)

CA184-007 (Weber 2009) (n = 115)		IPI + BUD (n = 58)	IPI + placebo (n = 57)
	4	2 (3)	0
	≥5	1 (2)	2 (3)
Systemic therapy settings, n (%)			
	Adjuvant therapy	20 (34)	26 (46)
	Metastatic disease	38 (66)	25 (44)
	Neoadjuvant therapy	1 (2)	0

Outcomes

The outcomes investigated in the identified RCTs and their relevance to the decision problem are presented in Table 8.

In the MDX010-20 (Hodi 2010) study, the parameters used to assess efficacy of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population. With regard to safety assessments, attention was paid to the identification and assessment of AEs that could represent the biological consequences of CTLA-4 inhibition, i.e., irAEs considered characteristic of ipilimumab. This included monitoring for signs of autoimmunity, including serological assessments for antinuclear antibody (ANA) and rheumatoid factor (RF). Since ipilimumab is a fully human anti-CTLA-4 monoclonal antibody (mAb), immunogenicity was assessed by titration of reactivity of blood by enzyme-linked immunosorbent assay (ELISA). Disease status was monitored at all study visits by physical examination and diagnostic imaging was performed at frequent intervals throughout all phases of the study.

Ipilimumab acts indirectly by inducing T-cell immunity, which leads to clinical effects that can take time to develop. In addition to early signs of anticancer activity, and consistent with the known late onset of ipilimumab activity in some subjects, clinical observations of the reduction in tumour burden in ipilimumab studies show heterogeneous patterns of measurable reduction in tumour burden from baseline. These patterns of response are observed in the absence of any intervening new therapy.

To obtain a better understanding of these heterogeneous effects, a systematic categorisation of the kinetics of ipilimumab activity was undertaken in the CA184-022 (Wolchok 2010) study, and exploratory immune-related response (irResponse) criteria were developed, using modified WHO criteria (mWHO) as a basis on which to characterise the tumour burden over time, both before and after progression by mWHO. Determination of the irResponse was based solely on objective measurements of index and new lesions. Non-index lesions, (i.e. non-measurable lesions), were not considered in the irResponse assessment, but were included in mWHO assessments. A comparison of mWHO and irResponse criteria for overall response is provided in the clinical study report.

Table 8: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
MDX010-20 (Hodi 2010)	BORR, later amended to OS (IPI 3 mg/kg + gp100 peptide vaccine versus gp100 peptide vaccine).	Parameters used to assess efficacy of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population.	OS IPI 3 mg/kg versus gp100 peptide vaccine OS IPI 3 mg/kg + gp100 peptide vaccine versus gp100 peptide vaccine BORR Duration of response PFS	Parameters used to assess efficacy of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population.
CA184-022 (Wolchok2010)	BORR (proportion of patients with CR or PR confirmed at least 4 weeks after first response). BORR measured at end of primary observation period (week 24).	Parameters used to assess efficacy of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population.	Disease control rate (proportion of patients with CR or PR plus stable disease), median OS and survival at 1 year. PFS at week 24.	Parameters used to assess efficacy of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
CA184-007 (Weber 2009)	Rate of grade ≥2 diarrhoea during first 24 weeks	Parameters used to assess safety of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population.	BORR (proportion of patients with CR or PR) Disease control rate (proportion of patients with CR or PR plus stable disease), OS Survival at 1 year Duration of response Proportion of patients with duration of response ≥24 weeks Time to response	Parameters used to assess efficacy of ipilimumab are consistent with other studies of immunotherapy and chemotherapy agents in this subject population.

Statistical analysis and definition of study groups

The statistical analyses in the identified RCTs are presented in Table 9.

Table 9: Summary of statistical analyses in RCTs

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation
MDX010-20 Hodi (2010)	To determine whether IPI, with or without gp100, improves OS compared with gp100 alone.	Event-time distributions estimated by Kaplan-Meier method. Cox proportional hazard models, stratified according to metastasis status and previous IL-2 therapy (or not) used to estimate hazard ratios. All reported p values 2-sided with 95% CI. Survival rates based on Kaplan-Meier estimation and CI calculated by bootstrap method.	385 events (deaths) among 500 pts randomly assigned to IPI + gp100 and gp100 alone, would give at least 90% power to detect a difference on OS, at a 2-sided α of 0.05, with log-rank test. A total of 481 events required in all 3 groups (3:1:1 distribution). Therefore all patients to be followed until at least 481 events occurred in study. *Post hoc* power analysis showed 219 events in 273 pts in IPI alone and gp100 alone provided at least 80% power to detect a difference in OS between the 2 groups, at a 2-sided α of 0.05, assuming IPI alone had same effect as IPI + gp100.
CA184-022 Wolchok (2010)	To assess the efficacy, Pharmacokinetics/Pharmacodynamics and safety of IPI at 0.3, 3 and 10 mg/kg, choosing 0.3 mg/kg to characterise the low range of the therapeutic window.	BORR with exact 2-sided 95% CI (Clopper & Pearson 1934). Dose-response for BORR assessed using 1-sided exact Cochran-Armitage trend test with 0.05 significance level. OS and PFS calculated using Kaplan-Meier product-limit method to provide median with 2-sided 95% CI calculated (Brookmeyer & Crowley 1982). 2-sided 95% CI for survival calculated using bootstrap method	70 pts in each group, whereby max width of exact 95% CI for BORR at 10, 3 and 0.3 mg/kg would be ~18%, 15% and 12% if the true BORR lay in the anticipated 10-15%, 6-9% and 2-5% ranges, respectively.
CA184-007 Weber (2009)	Prophylactic BUD could ameliorate the GI side effects of IPI without impairing its antitumour activity	Rate of grade ≥2 diarrhoea with exact 2-sided 95% CI (Clopper & Pearson 1934) and a 2-sided 95% CI for the difference was computed using Mantel-Haenszel (1959) weighting method. BORR and DCR calculated with 2-sided	Determined by estimated rate of grade 2/3 diarrhoea of 28%. With 50 pts on IPI alone, anticipated grade 2-4 diarrhoea rate of 30-40% would give max width of 95% CI of 28% With 50 pts on IPI + BUD, anticipated grade

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation
		95% CI. OS calculated using Kaplan-Meier product-limit method to provide median with 2-sided 95% CI (Brookmeyer & Crowley 1982). 2-sided 95% CI for survival: bootstrap method	2-4 diarrhoea rate of 15-25% would give max width of 95% CI of 26%

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

Not applicable.

Participant flow

CONSORT flow charts showing the numbers of patients who were eligible to enter the relevant RCTs, and who were randomised and allocated to each treatment are presented in Figure 5, Figure 6 and Figure 7.

Figure 5 Participant flow in MDX010-20 (Hodi 2010)

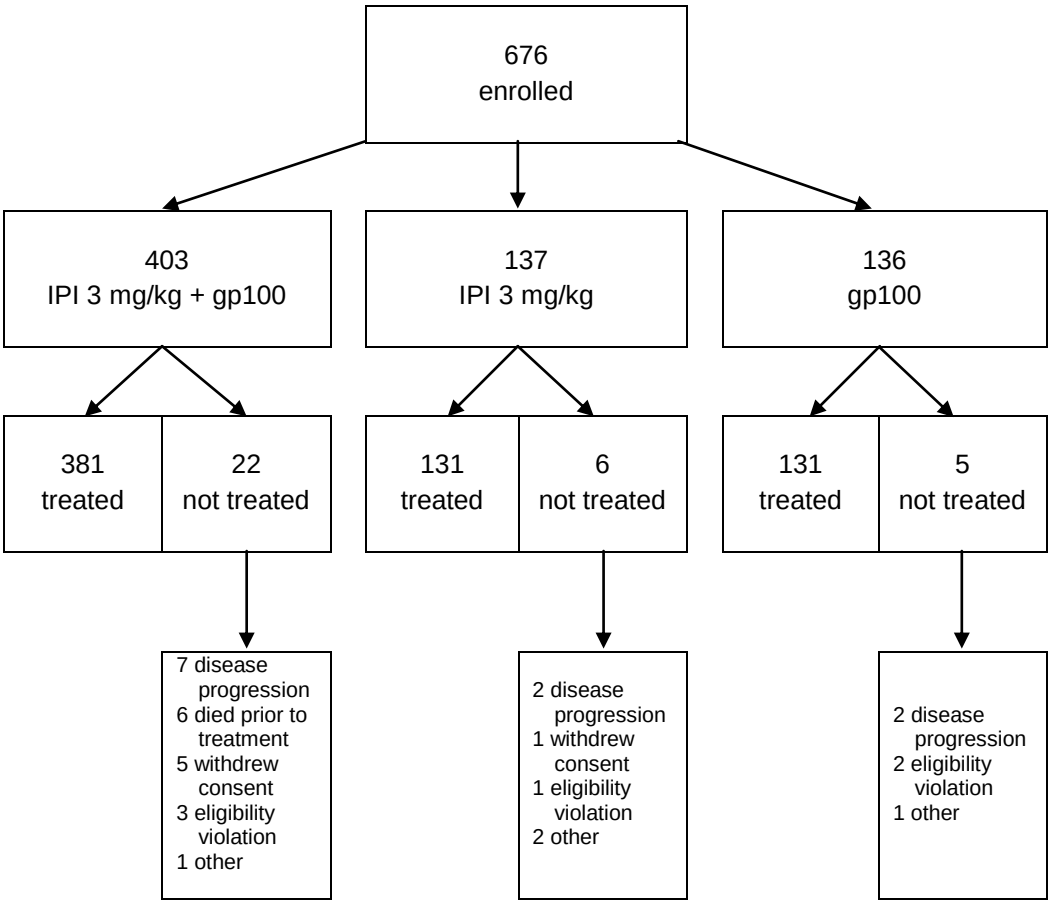


Figure 6 Participant flow in CA184-022 (Wolchok 2010)

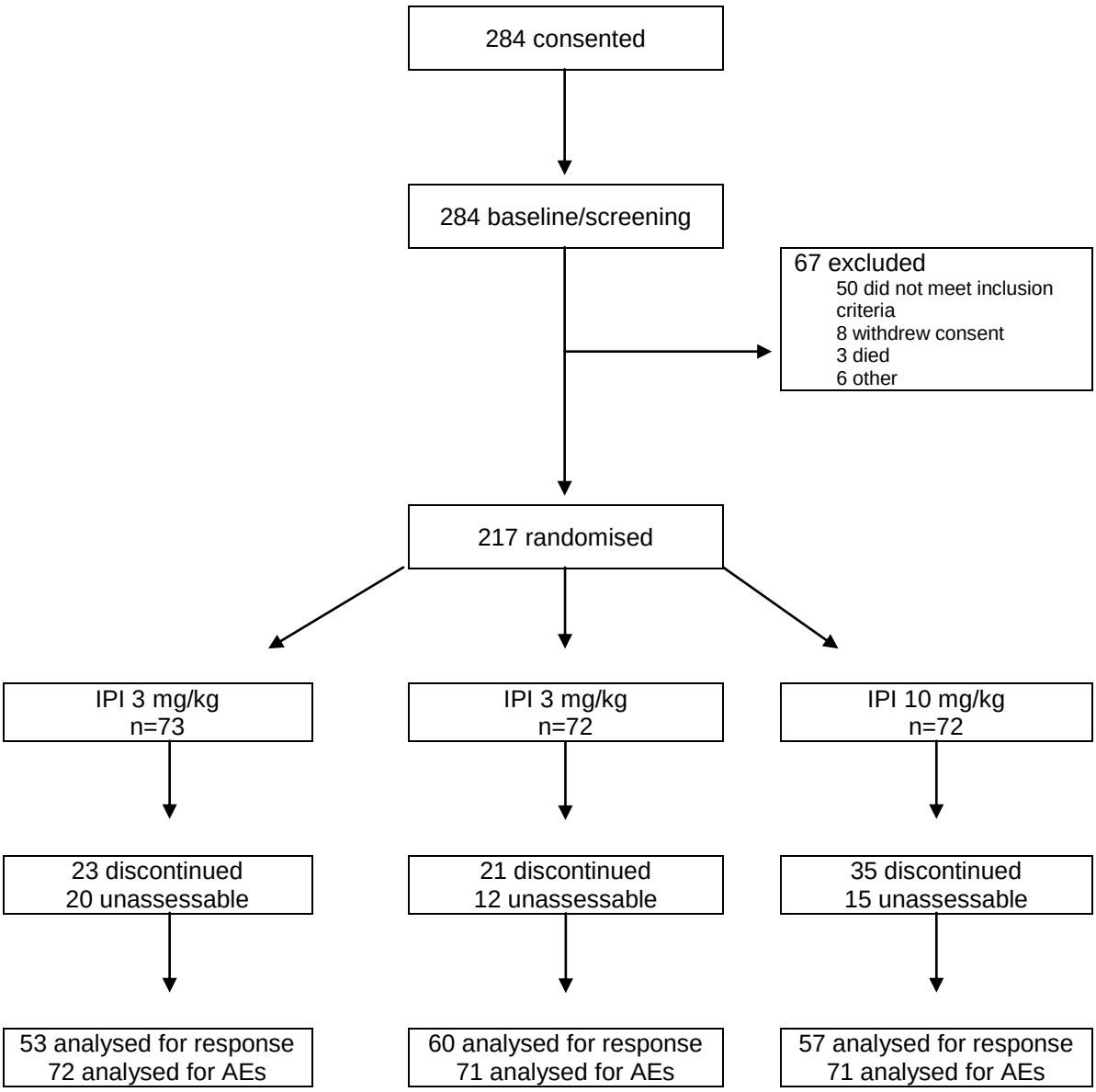
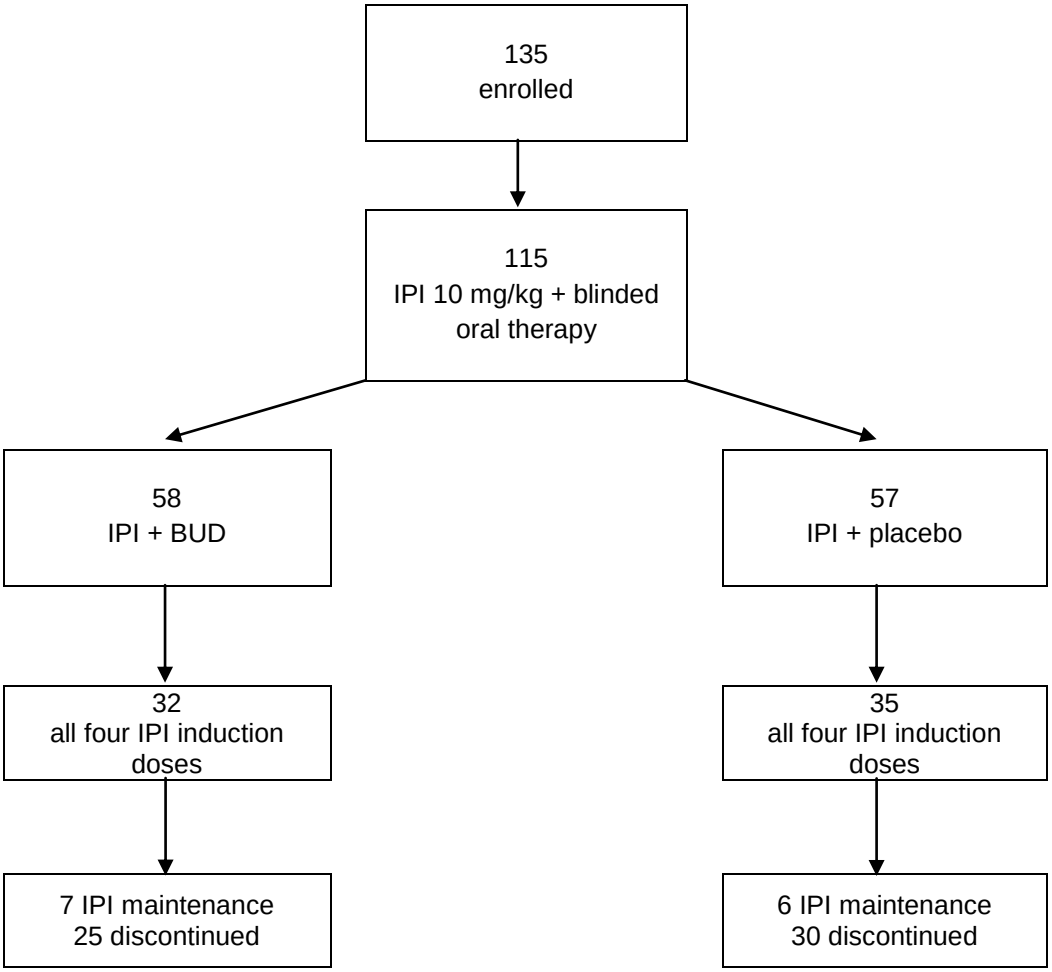


Figure 7 Participant flow in CA184-007 (Weber 2009)



5.4 Critical appraisal of relevant RCTs

Critical appraisals of the relevant RCTs are summarised in Table 10. A complete quality assessment for each RCT is provided in Appendix 3.

Table 10: Quality assessment results for RCTs

Trial no. (acronym)	MDX010-20 (Hodi 2010)	CA184-022 (Wolchok 2010)	CA184-007 (Weber 2009)
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	No
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	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?	Yes	Yes, for efficacy analyses; No, for safety analyses	Yes

5.5 Results of the relevant RCTs

This section discusses the efficacy data from the MDX010-20 (Hodi 2010) and CA184-022 (Wolchok 2010) RCTs. The RCT of CA184-007 (Weber 2009), described in Section 0, is primarily a safety study and the efficacy results are not included here. Safety data are discussed in Section 5.9.

Study MDX010-20 (Hodi 2010)

Summary

- This is the pivotal RCT concerning the subject of this submission, a large phase III RCT, involving 676 patients, using the dose of ipilimumab licensed in the UK (3 mg/kg).
- The study demonstrated clinically meaningful and statistically significantly prolonged survival for the 2 ipilimumab-containing groups relative to the gp100 monotherapy group.
- Ipilimumab (3mg/kg) alone showed an improvement in OS of a further 3.7 months, over and above that seen with gp100 vaccine alone (6.4 months), an increase of approximately 50%.
- Whilst the median overall survival (OS) observed in the ipilimumab-containing groups differs by 3.6-3.7 months from that observed in the gp100 alone group, this may not fully characterise the survival benefit with ipilimumab. This may be better reflected in the long-term survival effect estimated by 1-year and 2-year survival rates.
- The study demonstrated long-term benefit with the 2-year survival rate of 23.5% for the ipilimumab monotherapy group and 21.6% for the ipilimumab + gp100 group compared to 13.7% for the gp100 monotherapy group.
- Two ipilimumab patients maintained their response for >36 months. None of the subjects treated with gp100 alone remained in response at the 2-year time point. This suggests a durable biologic effect with ipilimumab.
- All response-related endpoints [best overall response rate (BORR), disease control rate (DCR), progression-free survival (PFS)] showed consistent, positive results for the ipilimumab-containing groups relative to the gp100 group.

The primary objective of study MDX010-20 was to compare overall survival (OS) in subjects who received ipilimumab + gp100 vs gp100. A key secondary objective compared the OS of ipilimumab monotherapy vs. gp100. The results of these 2 comparisons are presented in Table 11.

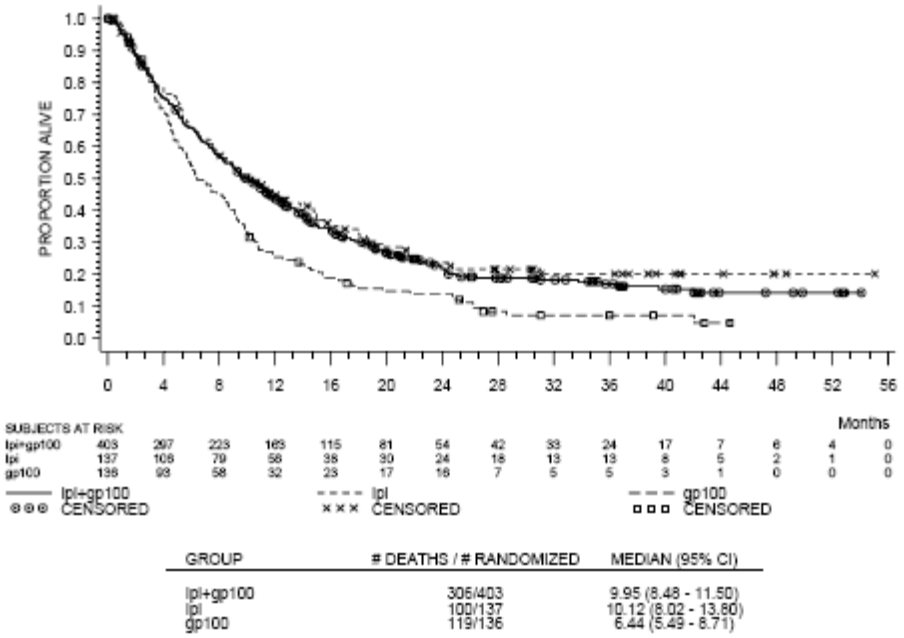
Table 11: Overall survival in Study MDX010-20 (Hodi2010)

	Primary Comparison	**Ipilimumab + gp100**	**gp100**
Overall Survival	N	403	136
p-value = 0.0004	Number of deaths	306	119
	Number censored	97	17
	Hazard ratio (95% CI)	0.68 (0.55, 0.85)	
	Median OS, months (95% CI)	9.95 (8.48, 11.50)	6.44 (5.49, 8.71)
	Secondary Comparisons	**Ipilimumab**	**gp100**
Overall Survival	N	137	136
p-value = 0.0026	Number of deaths	100	119
	Number censored	37	17
	Hazard ratio (95% CI)	0.66 (0.51, 0.87)	
	Median OS, months (95% CI)	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)
		Ipilimumab + gp100	**Ipilimumab**
Overall Survival	N	403	137
p-value = 0.7575	Number of deaths	306	100
	Number censored	97	37
	Hazard ratio (95% CI)	1.04 (0.83, 1.30)	
	Median OS, months (95% CI)	9.95 (8.48, 11.50)	10.12 (8.02, 13.80)

Source: [redacted]
CI = confidence interval; OS = overall survival

Ipilimumab improved survival by 32 - 34% as indicated by the 0.68 and 0.66 hazard ratios (HRs) and increased median survival by approximately 4 months for the 2 ipilimumab-containing groups compared with gp100 (Figure 8). There was no survival difference between the ipilimumab + gp100 vs. ipilimumab monotherapy groups, supporting the conclusion that gp100 did not influence the OS outcome with ipilimumab treatment.

Figure 8 Overall survival by treatment (ITT population) in MDX010-20 (Hodi 2010)



GROUP	# DEATHS / # RANDOMIZED	MEDIAN (95% CI)
Ipi+gp100	306/403	9.95 (8.48 - 11.50)
Ipi	100/137	10.12 (8.02 - 13.80)
gp100	119/136	6.44 (5.49 - 8.71)

The Kaplan-Meier survival curves were similar for the 3 treatment groups through approximately the first 4 months of treatment, after which a separation occurred, demonstrating an OS advantage for ipilimumab. Subsequently, the separation of the curves increased and was sustained over time, with up to 55 months follow-up, this was consistent with a durable biologic effect. The median OS observed in the ipilimumab-containing groups differs by 4 months from that observed in the gp100 alone group, but may not optimally characterise the survival effect, which may be better reflected as a long-term survival effect estimated by 1-year and 2-year survival rates. The 1- and 2-year survival rates for the ipilimumab-containing groups, together with the other key study endpoints, are presented in Table 12.

All response-related endpoints [best overall response rate (BORR), disease control rate (DCR), progression-free survival (PFS)] showed consistent, positive results for the ipilimumab-containing groups relative to the gp100 alone group.

The survival benefit in MDX010-20 was observed across all relevant subgroups for advanced melanoma, including age, gender, race, HLA-A2*0201 subtype, M-stage (M0, M1a, M1b, M1c), Eastern Cooperative Oncology Group (ECOG) performance status, LDH level, prior use of immunotherapy, prior use of interleukin-2 (IL-2), response to prior systemic therapy, and region (Europe, North America, and South America). The results of these sub-population analyses suggest a consistent survival effect with HRs favouring either of the ipilimumab-containing groups relative to the gp100 group.

Table 12: Summary of key efficacy results in study MDX010-20 (Hodi 2010)

	Ipilimumab 3 mg/kg + gp100 N=403	**Ipilimumab 3 mg/kg** N=137	**gp100** N=136
Overall Survival	**9.95**	**10.12**	**6.44**
median (95% CI) (months)	**(8.48, 11.50)**	**(8.02, 13.80)**	**(5.49, 8.71)**
Treatment comparison for Overall Survival	**Hazard Ratio (95% CI)[a]**		**p-value[b]**
Ipilimumab + gp100 vs gp100	0.68 (0.55, 0.85)		0.0004
Ipilimumab vs gp100	0.66 (0.51, 0.87)		0.0026
Ipilimumab + gp100 vs Ipilimumab	1.04 (0.83, 1.30)		0.7575
Survival Rate at 1 Year	43.6	45.6	25.3
% (95% CI)	(38.6, 48.5)	(37.0, 54.1)	(18.1, 32.9)
Survival Rate at 2 Years	21.6	23.5	13.7
% (95% CI)	(17.2, 26.1)	(16.0, 31.5)	(8.0, 20.0)
Extent of follow-up	0.03 – 54.08	0.36 – 55.06	0.03 – 44.65
Range, months (Median)	(9.43)	(9.46)	(6.16)
BORR (CR/PR), n (%) (95% CI)	**23 (5.7)**	**15 (10.9)**	**2 (1.5)**
	(3.7, 8.4)	**(6.3, 17.4)**	**(0.2, 5.2)**
CR	1 (0.2)	2 (1.5)	0
PR	22 (5.5)	13 (9.5)	2 (1.5)
SD	58 (14.4)	24 (17.5)	13 (9.6)
PD	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated, missing or unknown	83 (20.6)	28 (20.4)	32 (23.5)

Durability of Response: In study MDX010-20, response duration was longer than 2 years in 60.0% (9/15) of responders in the ipilimumab monotherapy group (range: 26.5+ to 44.2+ months) and 17.4% (4/23) of responders in the ipilimumab + gp100 group (range: 27.9+ to 44.4+ months).None of the subjects treated with gp100 remained in response at the 2-year time point.

Response Beyond Week 24: Response to ipilimumab continued to improve after the first tumour assessment. Progression improved to stabilisation (stable disease, SD) in some subjects, SD to partial response (PR) and PR to complete response (CR) months after the last dose of ipilimumab was administered – indicating a durable biologic effect. In MDX010-20, 12 subjects in the ipilimumab-containing groups with a Week 24 best overall response (BOR) of progressive disease (PD), SD or PR had a confirmed response that was improved by at least 1 category (PD to SD [3 subjects], SD to PR [5 subjects], and PR to CR [4 subjects]).

Response Following Re-induction: Re-induction was included in this study to allow subjects who had a measurable benefit from study therapy (CR, PR, or SD ≥ 3 months) and subsequently progressed to receive additional therapy for potential additional benefit. Given the immunological mechanism of action, subjects were not expected to be refractory to ipilimumab after progression. Of the 40 subjects who received re-induction therapy in MDX010-20, 32 were included in the efficacy analysis (8 in the ipilimumab monotherapy group, 23 in the ipilimumab+gp100 group, and 1 in the gp100 group). Eight treated subjects were excluded from the efficacy analysis because they were considered

ineligible: 3 were identified as having eligibility violations on their original enrolment into the study and therefore did not meet the per-protocol population definition required for the re-induction analyses. Another 5 subjects had a Week 24 BOR of PD and were therefore excluded from the analyses of efficacy endpoints for the re-induction subjects (all 5 were in the ipilimumab+gp100 group). Following re-induction, 65% (15/23) subjects in the ipilimumab + gp100 group and 75% (6/8) of subjects in the ipilimumab monotherapy groups achieved objective response or disease stabilisation.

Study CA184-022 (Wolchok 2010)

Summary

This is a randomised, double-blind phase II dose-ranging study comparing 0.3 mg/kg, 3 mg/kg and 10 mg/kg ipilimumab.

- The primary endpoint, the best overall response rate, was 4.2% of patients showing a complete or partial response to the ipilimumab 3mg/kg dose.
- The secondary endpoints of overall survival were 8.7 months for ipilimumab 3mg/kg patients and a 39.3% survival at 1 year.
- There was a statistically significant trend (p = 0.0015) of increased best overall response rate (BORR) with increased dose, suggesting a dose effect.

The results of overall survival (OS) and survival rates from CA184-022 are consistent with the outcomes from MDX010-20 and suggest a consistent long-term survival effect.

The primary objective of study CA184-022 was to estimate BORR (as per modified WHO (mWHO) criteria) in subjects receiving ipilimumab doses of 0.3, 3, and 10 mg/kg. Secondary objectives included the dose-response relationship based on BORR, progression-free survival (PFS), disease control rate (proportion of subjects with best response of CR + PR + SD), OS, survival rate at 1 year, duration of response, and time to best overall response (BOR).

The results for these endpoints are presented in Table 13.

Table 13: Summary of key efficacy results in study CA184-022 (Wolchok2010)

	Ipilimumab 0.3 mg/kg (N=73)	Ipilimumab 3 mg/kg (N=72)	Ipilimumab 10 mg/kg (N=72)
Overall Survival, months	**8.6**	**8.7**	**11.4**
median (95% CI)	**(7.7, 12.7)**	**(6.9, 12.1)**	**(6.9, 16.1)**
Survival Rate at 1 Year, %	39.6	39.3	48.6
(95% CI)	(28.2, 51.2)	(28.0, 50.9)	(36.9, 60.4)
Survival Rate at 2 Years, %	18.4	24.2	29.8
(95% CI)	(9.6, 28.2)	(14.4, 34.8)	(19.1, 41.1)
Extent of follow-up, months	0.5 – 35.5	0.4 – 32.1	0.4 – 31.2
range, (median)	(8.3)	(8.7)	(10.7)
BORR (CR/PR), n (%) (95% CI)	**0**	**3 (4.2)**	**8 (11.1)**
	(0.0, 4.9)	**(0.9, 11.7)**	**(4.9, 20.7)**
CR	0	0	2 (2.8)
PR	0	3 (4.2)	6 (8.3)[a]
SD	10 (13.7)	16 (22.2)	13 (18.1)
PD	43 (58.9)	41 (56.9)	36 (50.0)
Unknown	20 (27.4)[b]	12 (16.7)[c]	15 (20.8)[d]
Disease Control Rate, %	**13.7**	**26.4**	**29.2**
(95% CI)	**(6.8, 23.8)**	**(16.7, 38.1)**	**(19.0, 41.1)**
PFS at 24 weeks, %	**2.7**	**12.9**	**18.9**
(95% CI)	**(0, 7.3)**	**(0, 25.9)**	**(7.9, 28.9)**

[a] 2 additional subjects had an overall response of PR after a BOR of PD; 1 of these responses was confirmed

[b] Unknown=early censoring therapy (n=1), no post-baseline assessments (n=17), no Week 12 assessment (n=2)

[c] Unknown=no post-baseline assessments (n=11), no Week 12 assessment (n=1)

[d] Unknown=early censoring therapy (n=4), no post baseline assessments (n=10), no Week 12 assessment (n=1)

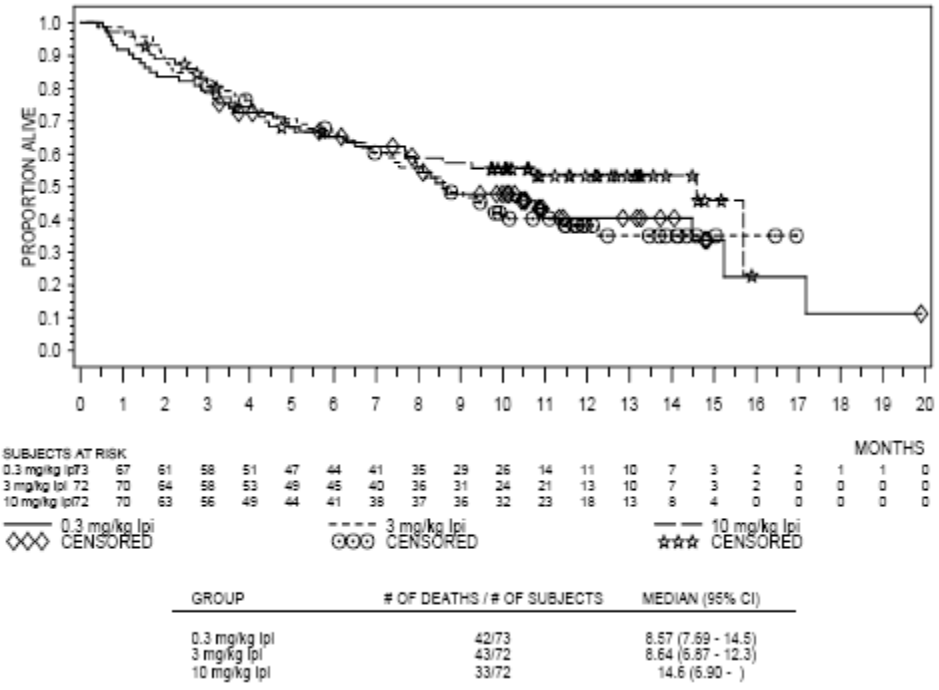
Numbers in the table above have been taken from the publication (Wolchok 2010).

The BORR was 11.1% (95% CI 4.9-20.7) for 10 mg/kg, 4.2% (0.9-11.7) for 3 mg/kg and 0% (0-4.9) for 0.3 mg/kg (p= 0.0015, trend test).

In the 3 mg/kg and 10 mg/kg groups, BORR was similar by age (< 65 and ≥ 65 years). At 3 mg/kg, BORR was numerically higher for males compared to females while the converse was true at 10 mg/kg. At 3 mg/kg there was 1 responder each in the M1a, M1b and M1c subgroups. None of the responders had received prior immunotherapy or had response to systemic therapy. At 10 mg/kg, there were 4 responders each in the M1a and M1b subgroups. None of these responders had received prior chemotherapy, 2/8 had prior immunotherapy and 2/8 had response to prior systemic therapy.

Kaplan-Meier plots for OS are shown in Figure 9.

Figure 9 Overall survival by treatment (randomised population) in CA184-022 (Wolchok 2010)



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
0.3 mg/kg Ipi	42/73	8.57 (7.69 - 14.5)
3 mg/kg Ipi	43/72	8.64 (6.87 - 12.3)
10 mg/kg Ipi	33/72	14.6 (6.90 -)

The results of OS and survival rates from CA184-022 are consistent with outcomes from MDX010-20 and suggest a consistent long-term survival effect.

Disease control rate: The disease control rate in the 10 mg/kg group was 29.2% (21/72, 95% CI: 19.0, 41.1) and 26.4% (19/72, 95%CI: 16.7, 38.1) in the 3 mg/kg group.

Progression-free survival: 66 (90.4%) subjects in the 0.3 mg/kg group, and 57 (79.2%) subjects each in the 3 and 10 mg/kg groups had progressed or died at the time of database lock (19 months from start of study). The median progression-free survival (PFS) for each treatment group was approximately 2.6 months (~ 10 weeks), the first scheduled tumour assessment being at Week 12. The hazard ratio for comparison of PFS between 10 mg/kg and 0.3 mg/kg was 0.709 (95% CI: 0.494, 1.019), 10 mg/kg and 3 mg/kg groups was 1.032 (95% CI: 0.714, 1.492), and between 3 mg/kg and 0.3 mg/kg was 0.695 (95% CI: 0.485, 0.995).

Time to response and duration of response: The short follow-up in this study due to database lock for BORR reporting limited the assessment of time to response, duration of response, major durable response rate, duration of stable disease and disease control, and major durable disease control rate. At the time of database lock, 6 of the 8 responders in the 10 mg/kg treatment group and 2 of the 3 responders in the 3 mg/kg treatment group reported an ongoing response, with response durations ranging from 0.95+ to 5.5+ months. In the 0.3, 3 and 10 mg/kg groups, ongoing stable disease (SD) were observed in 5, 9, and 8subjects, respectively, at the last evaluable tumour assessment.

Immune related response: Three (4.2%) subjects in the 3 mg/kg and 7 (9.7%) subjects in the 10 mg/kg group had immune-related partial response (irPR) (≥ 50% reduction in tumour burden) prior to appearance of new lesions. Of these, 2 subjects in the 3 mg/kg group and 5 subjects in the 10 mg/kg group had ongoing responses at the time of database lock. In addition, late irPR (irPR post immune-related progressive disease (irPD)) was reported in 1 subject in the 3 mg/kg group.

The number of subjects with immune-related stable disease (irSD) was 15 (20.5%), 14 (19.4%), and 17 (23.6%) in the 0.3, 3 and 10 mg/kg groups, respectively. Of these, 2 subjects in the 0.3 mg/kg (1 with a new lesion and 1 without a new lesion), 2 subjects in 3 mg/kg (both without new lesions), and 3 subjects in the 10 mg/kg group (all 3 without new lesions) demonstrated a slow steady decline in tumour burden (≥ 25% decline in total tumour burden). The percentage tumour reduction from baseline in these 7 subjects with slow steady decline ranged from 27% to 54%.

5.6 Meta-analysis

As the results of the systematic review identified just 3 clinical studies, one of which was a tolerability study of 10 mg/kg ipilimumab (rather than the UK licensed dose of 3 mg/kg), it was considered that a meta-analysis was not appropriate.

5.7 Indirect and mixed treatment comparisons

Not applicable.

5.8 Non-RCT evidence

Database search for evidence from other types of study (non-RCTs)

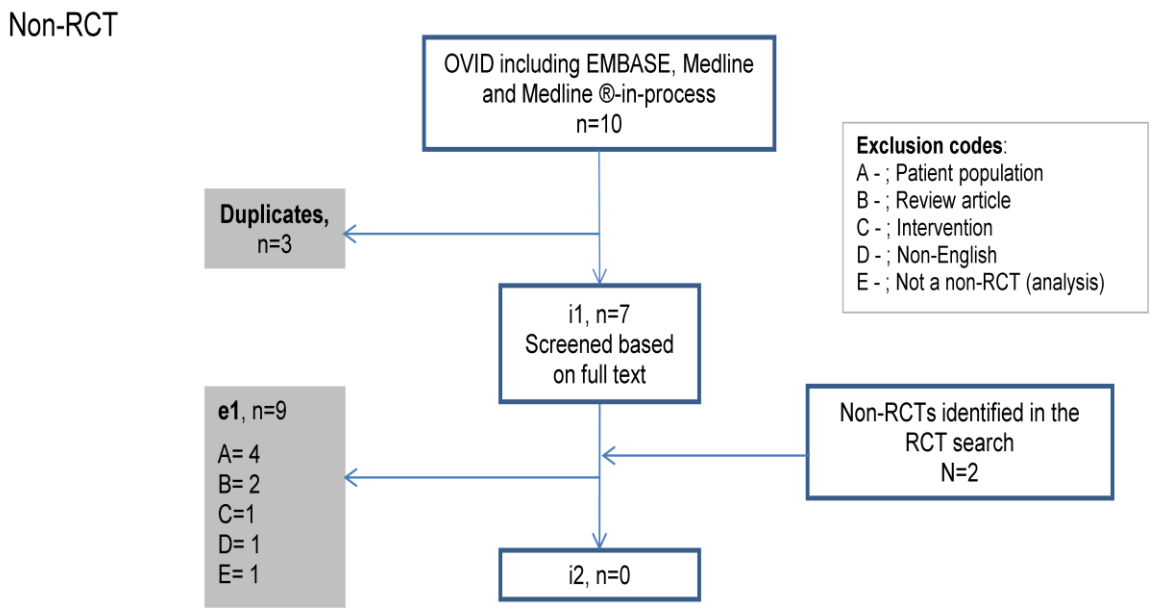
A third systematic literature search was conducted on May 4th 2011, following publication of the final scope, to identify other types of study (non-RCTs) providing effectiveness or safety evidence for ipilimumab in the treatment of unresectable stage III or stage IV malignant melanoma. The search was performed in Medline & Medline In-Process® and Embase using OVID, combining 'disease terms' with 'ipilimumab' and with 'non-RCT terms'. The search was not limited. There were no time limits other than those of the databases themselves (from 1948 for Medline and from 1980 for Embase).

Seven studies were identified for full text screening along with 2 further potentially relevant non-RCTs identified from the second systematic review. None of these studies met the eligibility criteria and were therefore excluded from this review.

No additional non-RCTs were identified through hand searching of conference proceedings or specific journals (see Appendix 2, Section 9.2.5 for further details of the hand searches conducted).

Details of the search strategies are provided in Appendix 6, Section 9.6 and the systematic review schematic is shown in Figure 10.

Figure 10 Schematic for the review of non-RCT evidence



5.9 Adverse events

Summary

The most common drug-related adverse events (AEs) associated with ipilimumab treatment are immune-related in nature, reflecting its immune-based mechanism of action.

- AEs are well characterised and generally medically manageable and usually reversible with topical and/or systemic immunosuppressants.
- There was no evidence that use of systemic steroids altered ipilimumab activity.
- The time to onset for most immune-related AEs is generally between 3-10 weeks from first dose, with most resolving within 2-14 weeks, from first occurrence, depending on the grade of event.
- Patients receiving re-induction treatment experienced similar adverse event profiles to patients receiving induction therapy.
- There was no evidence that concurrent steroid use as AE prophylaxis reduced the rate of diarrhoea ≥ Grade 2.

Trials designed to primarily assess safety

CA184-007 (Weber 2009)

This study was designed primarily to assess the prophylactic effect of budesonide on the rate of grade ≥2 diarrhoea in patients treated with ipilimumab.

This is a randomised, double-blind, phase II study comparing the tolerability of ipilimumab when administered with or without the steroid, budesonide. A 10 mg/kg dose (unlicensed in UK) of ipilimumab was used, therefore this study has been presented in this submission for tolerability data only.

- The addition of budesonide did not affect the rate of grade ≥2 diarrhoea or improve general tolerability in patients treated with ipilimumab
- In each group, the disease control rate was higher in patients with grade 3 to 4 irAEs than in patients with grade 0 to 2 irAEs, although many patients with grade 1 to 2 irAEs experienced clinical benefit.

Summary of methodology of trials designed to primarily assess safety

CA184-007 (Weber 2009) was designed primarily as a tolerability study to assess the prophylactic effect of budesonide on the rate of grade ≥2 diarrhoea on ipilimumab (10mg/kg) (unlicensed in UK dose) therapy. The methodology of this study is described in Section 5.3.

Critical appraisal of trials designed to primarily assess safety

Please refer to Appendix 3.

Results of trials designed to primarily assess safety

Budesonide did not affect the rate of grade ≥2 diarrhoea, which occurred in 32.7% and 35.0% of patients in the ipilimumab + budesonide and ipilimumab (10mg/kg) + placebo groups, respectively. There were no bowel perforations or treatment-related deaths.

The overall tolerability of ipilimumab with and without prophylactic budesonide is shown in Table 14. Ipilimumab side effects were similar in the budesonide and placebo arms. Drug-related AEs were, in general, medically manageable, tolerable, and usually reversible in most patients without known sequelae. There were no gastrointestinal or colonic perforations.

Drug-related AEs of any grade were reported for 52 (90%) of 58 patients in the ipilimumab + budesonide group and 54 (95%) of 57 in the ipilimumab + placebo group. Most drug-related AEs were consistent with immune-related events. Any grade irAEs were reported in 47 (81%) of 58 of patients in the ipilimumab + budesonide group and 48 (84%) of 57 in the ipilimumab + placebo group, and involved the skin in 60% of patients in each group, the gastrointestinal tract in 45%, the liver in 14%, and the endocrine system in 8%. Systemic corticosteroids for the treatment of irAEs were used by 33 (57%) of 58 patients in the ipilimumab + budesonide group and 25 (44%) of 57 in the ipilimumab + placebo group.

Grades 3 and 4 irAEs were seen in 17 (29%) of 58 and 7 (12%) of 58 patients in the ipilimumab + budesonide group and in 15 (26%) of 57 and 7 (12%) of 57 patients in the ipilimumab + placebo group, respectively (Table 14). In decreasing order of frequency, diarrhoea and autoimmune hepatitis were the most common (>5% across both arms). AEs leading to treatment discontinuation were reported for 15 (26%) of 58 patients in the ipilimumab + budesonide group and 18 (32%) of 57 patients in the ipilimumab + placebo group (Table 14).

Table 14: Overall tolerability of ipilimumab with or without prophylactic budesonide (Weber 2009)

	Patients, *n* (%)	
	Ipilimumab + budesonide (*n* = 58)	**Ipilimumab + placebo (*n* = 57)**
AEs leading to discontinuation	15 (26)	18 (32)
Diarrhoea[*†]	7 (12)	5 (9)
Colitis[*†]	2 (3)	3 (5)
Immune-related hepatitis[†]	2 (3)	3 (5)
Drug-related AEs		
Any grade	52 (90)	54 (95)
Grade 3	24 (41)	20 (35)
Grade 4	8 (14)	7 (12)
Serious adverse events		
All	34 (59)	31 (54)
Drug related	26 (45)	21 (37)
irAEs		
Overall irAEs		
Any grade	47 (81)	48 (84)
Grade 3	17 (29)	15 (26)
Grade 4	7 (12)	7 (12)
Gastrointestinal		

	Patients, *n* (%)	
	Ipilimumab + budesonide (*n* = 58)	**Ipilimumab + placebo (*n* = 57)**
Any grade	28 (48)	26 (46)
Grade 3	10 (17)	11 (19)
Grade 4	4 (7)	2 (4)
Liver related		
Any grade	9 (16)	8 (14)
Grade 3	4 (6)	3 (5)
Grade 4	2 (3)	4 (7)
Endocrine		
Any grade	5 (9)	6 (11)
Grade 3	2 (3)	3 (5)
Grade 4	1 (2)	0
Skin		
Any grade	35 (60)	39 (68)
Grade 3	3 (5)	0
Grade 4	0	0
Other		
Any grade	2 (3)	2 (4)
Grade 3	1 (2)	0
Grade 4	0	1 (2)

*All events were considered drug related.
†Only AEs leading to discontinuation in ≥5% of patients in either group are listed; fatal on-study AEs in the ipilimumab +budesonide group A (disease progression in four, lobar pneumonia in one, and arrhythmia in one) and in the ipilimumab +placebo group (disease progression in six, pneumonia aspiration in one, acute renal failure in one, cardiac arrest in one, and hepatic failure in one).

Specifically, the rate of grade ≥2 diarrhoea was similar between treatment arms (ipilimumab + budesonide, 19 (33%) of 58 patients; ipilimumab + placebo group, 20 (35%) of 57 patients (Table 15)). Sixteen (28%) of 58 patients in the ipilimumab + budesonide group and 18 (32%) of 57 in the ipilimumab + placebo group had one event of grade ≥2 diarrhoea; no patient experienced more than two events.

Table 15: Rate of grade ≥2 diarrhoea in patients receiving ipilimumab with or without prophylactic budesonide (Weber 2009)

Patients with grade ≥2 diarrhoea*	**Ipilimumab + budesonide (*n* = 58)**	**Ipilimumab + placebo (*n* = 57)**	**Total (*N* = 115)**
Grade 2, *n* (%)	11 (19.0)	10 (17.5)	21 (18.3)
Grade 3, *n* (%)	6 (10.3)	10 (17.5)	16 (13.9)
Grade 4, *n* (%)	2 (3.4)	0	2 (1.7)
Grade ≥2 diarrhoea rate, *n* (%)	19/58 (32.7)	20/57 (35.0)	39/115 (33.9)
95% CI†	21.0-46.3	22.9-48.8	—
Difference in rate of grade ≥2 diarrhoea, %‡	2.3		
95% CI§	−15.2 to 19.9		

*Patients reporting grade ≥2 diarrhoea inflammatory events regardless of causality before week 24 or first maintenance treatment.
†Clopper and Pearson method.
‡Difference in rates between the budesonide arm and (minus) the placebo arm.
§Estimate and 95% CI for difference in rate of grade ≥2 diarrhoea are computed using the Mantel-Haenszel method, stratified by previous use of immunotherapy (yes versus no) as recorded at randomisation.

Safety results from other relevant studies

Data are provided in this section from the clinical trial reports and the publications of the RCTs of MDX010-20 (Hodi 2010) and CA184-022 (Wolchok 2010).

MDX010-20 (Hodi 2010)

This is the main study concerning the subject of this submission, a large phase III RCT involving 676 patients, using the UK licensed dose of ipilimumab (3mg/kg).

- Overall, ipilimumab, alone or in combination with gp100, was relatively well tolerated in subjects with advanced metastatic melanoma with a generally medically manageable safety profile with no unexpected safety signals.

MDX010-20 (Hodi 2010)

In this study assessing overall survival (OS), a total of 643 patients were treated with ipilimumab + gp100 vaccine (380 patients), ipilimumab monotherapy (131 patients), or gp100 vaccine monotherapy (132 patients). Progressive disease was the most frequent reason for death across treatment groups. Adverse events with an outcome of death were reported for 44 patients, of which 14 were judged by the Investigator to be related to the study drug: 8/380 (2.1%) patients were in the ipilimumab + gp100, 4/131 (3.1%) in the ipilimumab monotherapy and 2/132 (1.5%) in the gp100 monotherapy groups. Seven of the 14 deaths related to the study drug were associated with irAEs: 5 in the ipilimumab + gp100 group (1 patient had grade 3 colitis and septicaemia; 3 patients had bowel perforation–inflammatory colitis, bowel perforation, or multiorgan failure–peritonitis; and 1 patient had Guillain–Barré syndrome, which is considered to be consistent with a neurological irAE) and 2 in the ipilimumab-alone group (1 patient had colic bowel perforation and the other had liver failure).

On-study AEs, severe AEs, and SAEs were reported in a similar proportion of patients across treatment groups, including the gp100 control group.

Study drug-related AEs, regardless of aetiology, were reported for 85.4% of patients, and were severe (≥Grade 3) for 19.5%, 26.0%, and 12.1% of patients treated with ipilimumab + gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively.

Immune-related AEs were the most frequently reported drug-related AEs.

Immune-related AEs (any grade) were reported for 53.3% of patients and were ≥ Grade 3 for 10.7% of patients. The proportion of patients with irAEs was higher in the ipilimumab-treated groups, particularly the ipilimumab monotherapy group, compared to gp100 monotherapy. Across treatment groups, the most frequently (≥ 2%) reported irAEs were skin and subcutaneous tissue disorders and gastrointestinal (GI) disorders and, less commonly, endocrine disorders. The most frequently reported GI irAEs were diarrhoea and colitis. Intestinal perforation was reported for 5 patients in the ipilimumab + gp100 group and 1 patient in the ipilimumab monotherapy group. The most frequently

reported skin irAEs were rash pruritus and urticaria. Toxic epidermal necrolysis was reported for 1 patient in the ipilimumab + gp100 group. The most frequently reported endocrine irAEs were hypothyroidism and hypopituitarism. Hepatic irAEs were infrequent. Hepatic failure leading to death (Grade 5) was reported for 1 patient in the ipilimumab monotherapy group.

Overall, ipilimumab, alone or in combination with gp100, was tolerated in patients with advanced metastatic melanoma with generally medically manageable and usually reversible adverse events which is consistent with the safety profiles demonstrated in previous studies of ipilimumab.

A summary of safety results for all 3 treatment groups is presented in Table 16.

Table 16: Summary of safety in MDX010-20 (Hodi 2010)

	Ipi+gp100 (n=380)	Ipi (n=131)	gp100 (n=132)	Total (n=643)
Subject with any AE (n %)	374 (98.4)	128 (97.7)	128 (97.0)	630 (98.0)
Subjects with any on-study AE[a] (n %)	374 (98.4)	127 (96.9)	128 (97.0)	629 (97.8)
Severe (≥ Grade 3)	194 (51.1)	73 (55.7)	69 (52.3)	336 (52.3)
Serious	156 (41.1)	56 (42.7)	52 (39.4)	264 (41.1)
Related	339 (89.2)	106 (80.9)	104 (78.8)	549 (85.4)
AEs leading to study drug discontinuation	35 (9.2)	17 (13.0)	5 (3.8)	57 (8.9)
AE with outcome of death (n %)	23 (6.1)	13 (9.9)	8 (6.1)	44 (6.8)
Related AE with outcome of death	8 (2.1)	4 (3.1)	2 (1.6)	14 (2.2)
Immune Related Adverse Events (irAE)[b]				
Subjects with irAE (n %)	220 (57.7)	81 (61.8)	42 (32.1)	343 (53.3)
Severe irAE	44 (11.5)	21 (16.0)	4 (3.0)	69 (10.7)
Serious irAE	41 (10.8)	18 (13.7)	1 (0.8)	60 (9.3)
irAE leading to study drug discontinuation	22 (5.8)	11 (8.4)	1 (0.8)	34 (5.3)
Death due to irAE (n %)	4 (1.0)	2 (1.5)	0	6 (0.9)
Gastrointestinal irAEs (any grade)	122 (32.1)	39 (29.8)	19 (14.4)	180 (28.0)
Severe (≥ Grade 3)	25 (6.6)	11 (8.4)	1 (0.8)	37 (5.8)
Hepatic irAEs (any grade)	8 (2.1)	5 (3.8)	6 (4.5)	19 (3.0)
Severe (≥ Grade 3)	4 (1.1)	1 (0.8)	3 (2.3)	8 (1.2)
Endocrine irAEs (any grade)	16 (4.2)	10 (7.6)	2 (1.5)	28 (4.4)
Severe (≥ Grade 3)	4 (1.1)	5 (3.8)	0	9 (1.4)
Skin irAEs (any grade)	152 (40.0)	56 (42.7)	25 (18.9)	233 (36.2)
Severe (≥ Grade 3)	9 (2.4)	2 (1.5)	0	11 (1.7)
Other irAEs (any grade)	15 (3.9)	6 (4.6)	3 (2.3)	24 (3.7)
Severe (≥ Grade 3)	8 (2.1)	3 (2.3)	1 (0.8)	12 (1.9)

AE = adverse event; irAE = immune-related AE

[a] On-study adverse events include all AEs after the first dose and occurring within 70 days of the last dose or any AE related to the study drug.

[b] irAEs are adverse events of unknown aetiology associated with study drug exposure and consistent with an immune phenomenon that were reported by the Investigator to be possibly, probably, or definitely related to study drug or with unknown causality

CA184-022 (Wolchok2010)

This is a randomised, double-blind phase II dose-ranging study comparing 0.3 mg/kg, 3 mg/kg and 10 mg/kg ipilimumab.

- Overall, ipilimumab was relatively well tolerated in subjects with advanced metastatic melanoma with a generally medically manageable safety profile with no unexpected safety signals.

CA184-022 (Wolchok 2010)

Ipilimumab had a manageable safety profile at all three doses (Table 17). The most frequently reported AEs were immune-related; most of these were grade 1–2 and mainly affected the skin and gastrointestinal tract. The frequency of irAEs of any grade rose with increasing dose of ipilimumab. No grade 4 irAEs were recorded in any group and no grade 3–4 events were seen in patients on the 0·3 mg/kg dose. Overall, the incidence of serious irAEs was ≤5% in all treatment groups, except for gastrointestinal irAEs in patients on the10 mg/kg dose.

The most frequent reason for treatment discontinuation or death in all three groups was PD. In the 0·3 mg/kg group, individuals who discontinued reported asthenia and bone pain (grade 3). In the 3 mg/kg group, enteritis (grade 2) and hypopituitarism, hydrocephalus, confusion, respiratory-tract infection, and diarrhoea (grade 3) were noted as reasons for stopping treatment. The most frequent (≥5%) drug-related AE leading to discontinuation from the 10 mg/kg dose was grade 3 diarrhoea (in 6 of 9 patients).

One possible treatment-related death was recorded in the 3 mg/kg group (respiratory infection on day 51). No gastrointestinal perforation was reported, although one patient on 10 mg/kg developed immune colitis with gastrointestinal bleeding requiring colectomy. Diarrhoea and colitis (confirmed on biopsy) were, in general, managed effectively with oral or systemic steroids. Patients maintained their response to ipilimumab when treated with steroids. In the 10 mg/kg group, grade 3–4 diarrhoea resolved or improved (to grade 1 or lower, or baseline grade) after a median of 4·4 weeks (95% CI1·0–6·0) in all ten patients. Grade 3–4 irAEs of the liver (managed with steroids) and of the endocrine system (managed with steroids, hormone replacement therapy, or both) resolved or improved within 30 days of the last ipilimumab dose.

Other irAEs were uncommon and included hypersensitivity, iritis, scleritis, eosinophilia, meningism, and pneumonitis. There was a numerical increase in ‘other’ irAEs in the 10 mg/kg group (7.0%) compared to the 0.3 and3 mg/kg groups (1.4% each).

A summary of safety by treatment groups is presented in Table 17.

Table 17: Summary of safety in CA184-022 (Wolchok 2010)

	Number (%) of Subjects N = 214 Ipilimumab		
	0.3 mg/kg N = 72	3 mg/kg N = 71	10 mg/kg N = 71
Deaths	41 (56.9)	42 (59.2)	32 (45.1)
Within 30 days of last dose of study therapy	9 (12.5)	6 (8.5)[a]	10 (14.1)
Within 70 days of last dose of study therapy	18 (25.0)	18 (25.4)	18 (25.4)
SAEs	26 (36.1)	35 (49.3)	38 (53.5)
Grade 5	15 (20.8)	14 (19.7)	15 (21.1)
Drug-related	6 (8.3)	13 (18.3)	19 (26.8)
Drug-related (Grade 5)	0	0[a]	0
AEs leading to discontinuation	9 (12.5)	7 (9.9)	19 (26.8)
Drug-related (Any Grade)	2 (2.8)	5 (7.0)	11 (15.5)
Drug-related (Grade 3-4)	2 (2.8)	4 (5.6)	9 (12.7)
Drug-related (Grade 5)	0	0	0
AEs	68 (94.4)	69 (97.2)	71 (100.0)
Grade 3-4	21 (29.2)	21 (29.6)	29 (40.8)
Drug-related (Any Grade)	46 (63.9)	55 (77.5)	59 (83.1)
Drug-related (Grade 3-4)	7 (9.7)	10 (14.1)	19 (26.8)
Drug-related (Grade 5)	0	0[a]	0
Overall irAEs	19 (26.4)	46 (64.8)	50 (70.4)
Grade 3-4	0	5 (7.0)	18 (25.4)
GI irAEs	12 (16.7)	23 (32.4)	28 (39.4)
Grade 3-4	0	2 (2.8)	11 (15.5)
Liver irAEs	0	0	2 (2.8)
Grade 3-4	0	0	2 (2.8)
Endocrine irAEs	0	4 (5.6)	3 (4.2)
Grade 3-4	0	2 (2.8)	1 (1.4)
Skin irAEs	9 (12.5)	32 (45.1)	33 (46.5)
Grade 3-4	0	1 (1.4)	3 (4.2)
Other irAEs	1 (1.4)	1 (1.4)	5 (7.0)

[a] One subject died on Day 51, within 30 days of last dose date. This event of death was not captured as a drug-related death in the clinical database before database lock (13-Nov-2007); however BMS' internal safety database indicated that this subject died due to Grade 3 respiratory infection and according to the investigator, the event was possibly related to the study drug.

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. Its incidence is increasing. There are no approved agents for

previously treated advanced malignant melanoma and no agreed-upon standard of care. This results in a high unmet medical need.

Ipilimumab has a well-characterised and generally manageable safety profile mostly defined by mechanism of action-driven irAEs in the following categories: skin, GI, hepatic, endocrine, and neurological. Resolution of irAEs occurs within 2 - 14 weeks from first occurrence through omission or discontinuation of dosing, combined with established diagnosis and management guidelines involving steroid and other immunosuppressants. The use of corticosteroids for treatment of ipilimumab-induced immune-related AEs does not interfere with the ability of ipilimumab to achieve or maintain a clinical response (Weber 2009). Severe complications are rare and are usually bowel perforations/colectomy and liver failure.

In conclusion, ipilimumab has a generally medically manageable and usually reversible toxicity profile, which is different to other agents used to treat advanced melanoma. Ipilimumab offers an exciting and very promising effective treatment for previously treated advanced malignant melanoma where currently very limited options exist.

5.10 Interpretation of clinical evidence

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

Summary

Advanced melanoma is the most aggressive form of skin cancer and is fatal if undetected and untreated. Its incidence is increasing. Up to now, there have been no approved agents for previously treated advanced melanoma and no agreed-upon standard of care. This results in a high unmet medical need.

The patients recruited into the ipilimumab clinical trials were representative of the UK advanced melanoma population, and the data can be considered very applicable to the UK.

It should be emphasised that the survival data shown in the ipilimumab studies are very exciting, and highly remarkable in view of the usual poor prognosis of patients with metastatic melanoma. A meta-analysis of 42 phase II trials with a variety of agents in stage IV melanoma showed a median overall survival of 6.2 months and a 1 year survival rate of 25.5%. These outcomes are similar to that observed with gp100 in the main RCT of this submission (Hodi 2010) but, in contrast, the main RCT showed a 10-10.1 months median overall survival in the ipilimumab arms, and a 43.6-45.6% 1 year survival rate.

Ipilimumab has a well-characterised and generally medically manageable safety profile mostly defined by mechanism of action-driven immune-related adverse events (irAEs). Resolution of irAEs occurs within 2-14 weeks from first occurrence with established medical management, sometimes requiring omission or discontinuation of dosing. Severe complications are rare.

Thus, ipilimumab has a generally medically manageable and usually reversible toxicity profile. Ipilimumab offers an exciting and very promising effective treatment for previously treated advanced malignant melanoma where currently very limited options exist.

Ipilimumab has a new, innovative mode-of-action and should be viewed as a new treatment paradigm in terms of health outcomes, providing a step change in the health benefits it offers advanced malignant melanoma patients, and representing a novel shift from “no effective treatment” to “effective treatment” for previously treated unresectable malignant melanoma.

MDX010-20 (Hodi 2010) provides the main evidence base for this submission and is the pivotal licensing registrational trial, involving 676 patients. This study principally showed that ipilimumab, given with or without a gp100 peptide vaccine, when compared with gp100 vaccine alone, improved the ‘overall survival’ of patients with previously treated, unresectable, stage III or IV malignant melanoma by an additional 3.6-3.7 months, over

and above the 6.4 months achieved among patients receiving gp100 alone. Survival rates at 1 year in the ipilimumab containing arms were 43.6-45.6% of patients compared to 25.3% in the gp100 vaccine alone arm.

The CA184-022 (Wolchok 2010), phase II study confirmed the efficacy of a 3mg/kg dose of ipilimumab in previously treated advanced malignant melanoma patients. The results were similar to the Hodi 2010 study, with survival rates at 1 year of 39.3% of patients in the 3mg/kg ipilimumab arm. The immune-related adverse events were as expected and also consistent with the profile shown in the MDX010-20 (Hodi 2010) study which involved much larger patient numbers.

The CA184-007 (Weber 2009) study has been included in this submission for the safety data, as it was based on an ipilimumab 10mg/kg dose which is not licensed in the UK. The key findings were that irAEs can be managed by appropriate use of systemic steroids and that there was no evidence they altered the activity of ipilimumab. They also showed that concurrent use of prophylactic systemic steroids with ipilimumab did not affect the rate of grade 2 or higher diarrhoea; neither did they improve the general tolerability in patients with diarrhoea.

Ipilimumab's immune-based mechanism of action accounts for the fact that the majority of adverse events are immune-related. These mainly involve the gastrointestinal tract (e.g. diarrhoea), skin (e.g. rash), liver (e.g. raised LFTs), endocrine organs (e.g. hypothyroidism) and the neurological system (e.g. neuropathy). These are all medically manageable with systemic steroids, other systemic immunosuppressants in a minority of cases and sometimes lifelong hormone replacement therapy for endocrine irAEs.

To put the findings in context, the survival data shown by these studies are very remarkable in view of the poor prognosis of patients with metastatic melanoma. The MDX010-20 (Hodi 2010) study (676 patients) showed 10-10.1 months median overall survival in the ipilimumab arms and a 43.6-45.6% 1 year survival rate, whereas, a previous of 42 phase II trials in stage IV melanoma (which included 2100 untreated and previously treated patients with stage IV melanoma) showed a median overall survival of 6.2 months and a 1 year survival rate of 25.5% (Korn et al 2008).

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

MDX010-20 (Hodi 2010)

MDX010-20 (Hodi 2010) was the main evidence base for this submission and the pivotal registrational licensing trial. The strengths of MDX010-20 were that it is a large phase 3, randomised, double-blind, controlled study involving 676 patients. This ensures confidence in its robust set of results. The UK licensed dose (3mg/kg) of ipilimumab was used as well as a patient population of only 'previously treated', unresectable, stage III or IV malignant melanoma patients, therefore being relevant to the subject of this submission. It was a global study, with a large proportion of European patients (257) (which included 55 from the UK). The baseline characteristics and demographics were well balanced among the three arms. The study also ran over a relatively long period of time (5 years) for this disease area.

MDX010-20 (Hodi 2010) also looked at endpoints relevant to both this submission and to current UK clinical practice. Although at the start of the study the primary endpoint was the 'best overall response rate' and this was changed during the study to the even more relevant and useful endpoint, 'overall survival', the preferred ultimate measure of clinical activity. Secondary endpoints included progression-free survival, duration of response and the best overall response rate, which are all relevant to clinical practice and the scope for this submission.

The study had a well designed methodology. All safety information was monitored by an independent data monitoring committee. This ensured patient safety and a comprehensively recorded profile of the adverse events. The study design was robust with clear adverse event based stopping rules.

The main limitation of the MDX010-20 (Hodi 2010) was the gp100 comparator used. Gp100 is a vaccine; it is an unlicensed product and not a standard of care in the UK, although it should be recognised that there is no one standard of best supportive care after single agent chemotherapy has failed. Interestingly, gp100 vaccine alone did show a survival of 6.4 months in this study, which is consistent with meta-analysis survival data of phase II trials in stage IV melanoma (Korn et al 2008) and is in alignment with the current best survival achieved with other chemotherapeutic agents and/or best supportive care (6-9months). These data suggest that gp100 vaccine did act as a suitable comparator, so the demonstration of any survival benefit beyond this, (as seen in this study) is a very positive and exciting outcome for patients with advanced melanoma.

Another possible limitation of MDX010-20 (Hodi 2010) was that through HLA screening of enrolled patients, only HLA positive patients were included in the study (HLA screening was required because of the mechanism of action of the gp100 comparator). However, recent evidence shows that the effectiveness of ipilimumab is not affected by the HLA status of the patient (Wolchok et al 2010b) and as such, this is not considered a limitation.

Finally, all patients included in the MDX010-20 (Hodi 2010) study had previously treated unresectable, stage III or IV malignant melanoma. Patients had received at least 1 course of first-line therapy containing 1 or more of the following: IL-2, dacarbazine, temozolomide, fotemustine or carboplatin, and could not have received prior treatment with an anti-CTLA-4 antibody or any cancer vaccine. Enrolled patients also could not have received prior systemic treatment within 28 days of the first dose of ipilimumab. Although not a limitation in itself, there was no restriction on the number of treatments enrolled patients may have already received.

CA184-022 (Wolchok 2010)

CA184-022 (Wolchok 2010) was a dose ranging comparison study. Of the 12 recruiting countries, 85 patients were included from 5 European countries. One of its strengths was that it included a 3mg/kg (UK licensed dose) treatment arm and is therefore relevant to this submission. It was a randomised, double-blind, phase II study. The patient numbers

were significant for a phase II study, amounting to 72 patients in the 3mg/kg (UK licensed dose) arm. The population of patients studied was relevant to the subject of this submission (i.e. all had previously treated, unresectable, stage III or IV malignant melanoma). The baseline patient characteristics and demographics were well balanced between the arms.

The study ran over a reasonable period of time (1.5 years) relative to the normal expected survival of patients with this prognosis.

All efficacy endpoints (except survival) were based on assessments made by a central independent review committee. Therefore they were useful and relevant to clinical practice.

The study design and methodology was robust ensuring the usefulness of the safety data recorded and presented in this submission for the 3mg/kg (UK licensed dose). The overall adverse event profile of ipilimumab in this study was consistent with previous findings and with the drug's immune-based mechanism of action.

A possible limitation of the CA184-022 (Wolchok 2010) study, as far as this submission is concerned, was that this was a dose-ranging comparison study. In other words, this study was not designed to detect differences in survival between the different dosing arms of ipilimumab. It did, however collect safety data and include a 3mg/kg (UK licensed dose arm), relevant to this submission and presented here.

The initial dosing schedule of ipilimumab used was the same as that licensed for induction dosing (4 doses given 3 weeks apart). This covers the period up to the time point of the primary endpoint (maximum of 24 weeks from the initial dose). From this point onwards, patients who had not progressed received 'maintenance' style dosing, i.e. a single dose every 3 months. This later schedule is not specified in the UK licensed dose schedule. Some of the patients who had progressed at the time of the primary endpoint did not receive any further ipilimumab treatment. This was usually the result of a clinical decision based on the patient's fitness/eligibility to continue to receive ipilimumab or the patient's wish to no longer receive active treatment. Those that were eligible to receive more ipilimumab were crossed over into a separate companion study with a higher dose. However, as this study has only been used for safety data reporting for this submission, this was not a limitation to capture of the safety information for the 72 patients who were originally in the 3mg/kg (UK licensed dose) arm.

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.

MDX010-20 (Hodi 2010)

The baseline characteristics (e.g. previously treated population) and demographics of the included patient population reflect typical advanced melanoma patients who present in UK clinical practice.

As this study was a randomised, double-blind and controlled phase 3 study that included a relatively large number of patients for this disease area, delivery of robust efficacy and safety data was ensured.

As previously mentioned, this study also included a large proportion of European patients (257) with 55 from the UK, supporting the relevance of the outcomes to patients in the UK.

The primary endpoint of this study (overall survival) is deemed a 'gold standard' outcome measure in cancer trials because it is directly relevant to real world patients. As the safety data were captured from a large number of patients, this ensured a good representation of ipilimumab's adverse event profile.

CA184-022 (Wolchok 2010)

This study has been presented in this submission to provide safety data only on the ipilimumab 3mg/kg (UK licensed dose) arm.

The baseline characteristics and demographics of the 3mg/kg treatment arm were closely aligned to patients presenting in UK clinical practice. And as some of these patients were recruited from European countries (28 patients) this increases the relevance of the safety data to UK patients.

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?

MDX010-20 (Hodi 2010)

The baseline characteristics and demographics of patients reflect those of patients presenting in UK clinical practice. The large patient numbers in this study ensured a robust representative sample of previously treated, unresectable, stage III or IV malignant melanoma patients were included, so data generated was robust and applicable.

A large proportion (38%) of included patients was European; 8% of all the patients were from the UK, so the outcomes are applicable to the UK.

The primary endpoint of this study (overall survival) is deemed a 'gold standard' outcome measure in cancer trials because it is directly relevant to 'real world' patients.

The UK licensed dose (3mg/kg) and dosing schedule of ipilimumab was used in this study. The study itself, being a randomised, controlled, double-blind study meant the outcomes were valid and unbiased. The overall survival endpoints for ipilimumab arms

were superior and statistically significant to the comparator arm, meaning that ipilimumab demonstrated a survival benefit of 3.6 months over and above the comparator. Up to now the survival of advanced metastatic melanoma patients on standard of care treatment has been approximately 6 months.

As the safety data were captured from large numbers of patients, a comprehensive and robust representation of ipilimumab's adverse event profile was captured showing immune-related side effects are generally reversible when appropriately managed.

In this study HLA-typing of patients was undertaken as a screening procedure for study eligibility due to the gp100 comparator requiring HLA-A*-0201-positive patients. Although only HLA-positive patients were included in this study, recent evidence (Wolchok 2010b) tells us that the effectiveness of ipilimumab is HLA-status independent, therefore the results for ipilimumab are still applicable to routine clinical practice.

The comparator in this study, gp100 vaccine, was a non-standard comparator as it is not licensed or used in routine clinical practice. It is not a standard of care in the UK. Although, there is no one standard of best supportive care after single agent chemotherapy has failed, gp100 vaccine alone did show a survival of 6.4 months in this study, which is consistent with survival date from a meta-analysis of phase II trials in stage IV melanoma (Korn et al 2008). This survival is in alignment with the current best survival achieved with other chemotherapeutic agents and/or best supportive care (6-9 months). The demonstration of any survival benefit beyond this, as the MDX010-20 (Hodi 2010) study did, is a very positive outcome for patients with this prognosis.

The MDX010-20 (Hodi 2010) study used the licensed dose of ipilimumab given in the Summary of Product Characteristics (SPC).

CA184-022 (Wolchok 2010)

As mentioned previously, this study has only been included in this submission for the ipilimumab safety data, as it was a dose-ranging study with 3 different dosing arms of ipilimumab. Only the 3mg/kg (UK licensed dose) ipilimumab arm with 72 patients was relevant to this submission. For the 3mg/kg arm the dose and dose schedule of ipilimumab up to the timing of the primary endpoint followed the induction dosing schedule in the ipilimumab SPC.

Out of the 12 recruiting countries, 85 patients were included from 5 European countries. The population of patients studied was relevant to the subject of this submission i.e. all had previously treated, unresectable, stage III or IV malignant melanoma. Baseline patient characteristics and demographics were well balanced between the arms.

The study ran over a reasonable period of time (1.5 years) relative to the normal expected survival of patients with this prognosis.

All efficacy endpoints (except survival) were based on assessments made by a central independent review committee. Therefore they were useful and relevant to clinical practice.

The study design and methodology was robust ensuring the usefulness of the safety data recorded and presented in this submission for the 3mg/kg (UK licensed dose). The overall adverse event profile of ipilimumab in this study was consistent with previous findings and with the drug's immune-based mechanism of action.

As this study was a dose-ranging comparison study it was not designed to detect differences in survival between the different dosing arms of ipilimumab. It did, however collect comprehensive and robust safety data for ipilimumab.

Selection of eligible patients in clinical practice.

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 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. For this reason, the ipilimumab clinical trials excluded patients with active autoimmune disease and those on long-term immunosuppressants.

6 Cost-effectiveness

Summary

- Due to the lack of published economic models, a *de novo* economic model has been constructed for ipilimumab.
- The model has patients starting in a baseline disease, and then transitioning to either non-progressed, progressive disease, or death states.
- Ipilimumab greatly increases patient's overall survival (OS) over BSC. The median OS increased from 6.4 months to 10.0 months, and mean OS increased from 12.5 months to 23.1 months, i.e. the median OS benefit of 3.6 months and the mean OS benefit of 10.6 months, respectively.
- Ipilimumab is estimated to increase patient QALYs from 1.01 to 2.38 over a life-time period. Using the unconfirmed list price of £3,750 per 50mg vial, ipilimumab has an ICER of £60,737.
- Probabilistic sensitivity analysis estimates there is a 14% chance that ipilimumab is cost-effective at an ICER of £50,000 per QALY.
- The model is particularly sensitive to the utility used for progressive disease, the choice of curve fit for overall survival for ipilimumab, and the acquisition cost of ipilimumab.

6.1 Published cost-effectiveness evaluations

Identification of studies

A systematic review was conducted on 9 December 2010 in order to identify cost-effectiveness evaluations relating to pre-treated or advanced melanoma. Searches were performed in

- EMBASE 1980-present
- Medline and Medline In Process 1948-present
- Econlit 1961-present
- NHS-EED 1968-present

The search strategies for respective databases are shown in Appendix 10 (Embase Table 71, Medline Table 72, Econlit Table 73, and NHS-EED Table 74). In addition to cost-effectiveness and cost-utility studies, quality of life studies were also searched for, to inform the development of a de novo economic model.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a consultation between the reviewers. Data were extracted from eligible publications into a pre-defined Microsoft Excel® document by a reviewer and additional

Word® tables were created for this report. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

In total, 1,029 studies were identified. Throughout the first stages of review 1,013 studies were excluded according to their title and abstract, shown in Figure 11.

Studies were included if they were economic evaluations that examined any form of treatment for advanced or pre-treated melanoma. Melanoma staging was specified as stage III or IV.

Early stages of melanoma (stage II and earlier) were excluded as they would not examine comparators of relevance for this review. Other reasons for exclusion included duplicate papers, incorrect disease area, and the study not being an economic evaluation.

Diagnostic, screening and surveillance studies were also identified but not included in this review as the focus was on active melanoma treatment. A list of studies identified that cover the above aspects have been reported in Appendix 10: Economic study exclusions.

Sixteen full publications were reviewed to determine their relevance according to the full inclusion criteria. Six of these studies were excluded following review of the full publication (see Appendix 10: Economic study exclusions). The remaining 10 studies are listed in Table 18.

In addition, a rapid review has also been conducted in order to identify any economic studies relevant to ipilimumab. Using the search terms listed below and the databases mentioned above, no suitable articles were identified as of 18 May 2011.

- Ipilimumab cost
- Ipilimumab utility
- Ipilimumab model
- Ipilimumab economic.

Description of identified studies

Although 10 studies were identified as potentially relevant (Table 18), none of the studies identified were both economic models and UK based

Figure 11 Flowchart of economic study inclusions/exclusions

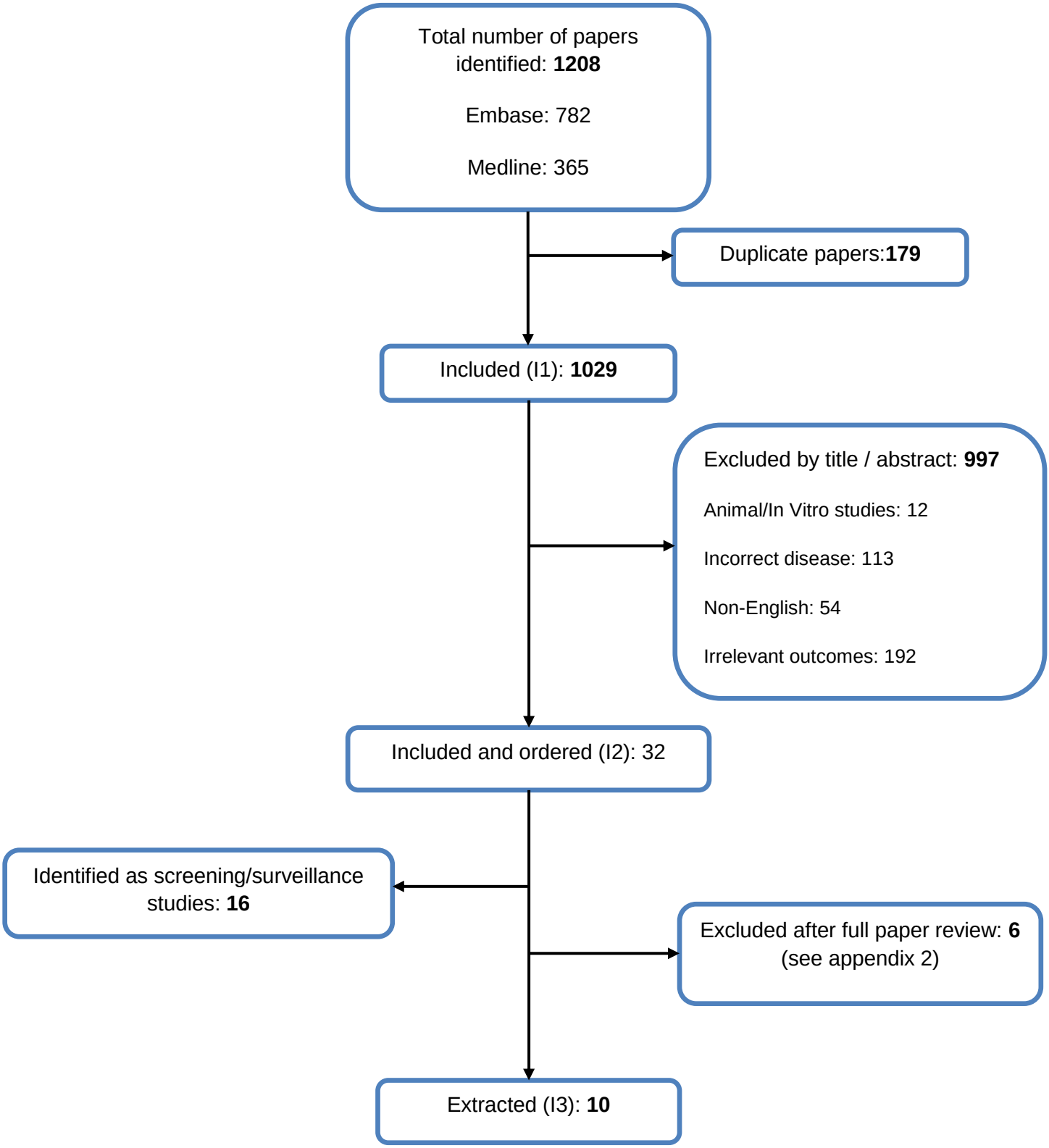


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Table 18: Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Cormier et al.	2007	USA	Markov	50	Not stated, gain of 0.56 QALYs	USD, High dose interferon vs standard of care	$48,129
Crott et al. 2004	2004	Canada	Markov	Not stated	2.62 vs 2.11	Canadian Dollars, High dose interferon vs watchful waiting	$55,090
Dixon et al. 2006	2006	UK	Trial based analysis	51.59	2.40 vs 2.33	GBP, Low dose interferon vs placebo	£41,432
Fader et al. 1998	1998	USA	Case-control cot analysis	50.5, 51.6	n/a	USD, Specialist centre care vs community care	n/a
Gonzalez-Larriba et al. 2000	2000	Spain	Markov	50	n/a – Life Years Gained only	Euros, Interferon vs standard of care	n/a
Hillner et al. 1997	1997	USA	Markov	50	6.06 vs 4.87	USD, Interferon vs no treatment	$15,200
Hillner et al 1998	1998	USA	Markov	50	6.06 vs 4.87	USD, High dose interferon vs no treatment in high risk patients	$15,200
Hillner et al 2000	2000	USA	Markov	58	n/a – Life Years Gained only	USD, Temozolomide vs Dacarbazine	n/a
Messori et al. 1997	1997	Italy	Partitioned survival	Not stated	n/a – Life Years Gained only	Italian Lira, Interferon vs no treatment in high risk patients	n/a
Wilson et al. 2002	2002	USA	Decision tree	Not stated	3.48 vs 3.06	USD, Interferon vs no treatment (testing arms also included)	$28,140

Quality assessment

The only relevant study identified in Section 6.1.2 was by Dixon et al. (2006) published in the British Journal of Cancer, as this was the only study conducted in a UK setting (in terms of both costs and utility values). The study was funded by Roche Pharmaceuticals.

Although a trial based analysis of 674 patients (and therefore not necessarily replicable for the current study), the paper does follow standard UK methodology as per the NICE methods guide (though using the previous from 2004). Utilities were calculated from EQ-5D questionnaires filled in by patients, and then translated using the Dolan (1997) data. Patients were also administered the EORTC questionnaire, though these results are not used to calculate cost per QALY (presumably due to the lack of a mapping algorithm at the time).

While the study is generally of high quality, with a CONSORT diagram of patients in the analysis provided, there are several large omissions from the publication;

- Although costs are said to be taken from standard UK sources, such as PSSRU, the costs used in the analysis are not stated

- The time horizon used in the analysis is 5 years, over which Interferon is estimated to have a gain of 0.07 QALYs (2.40 vs 2.33) and have a cost per QALY of £41,432 compared to observation. However at the end of this 5 year period a difference in survival between the arms of approximately 6% (36% vs 42%) is apparent.

  Had modelling of the estimated patient survival been performed, this would have resulted in a significant change in the ICER, and therefore it can be argued that an insufficient time horizon was used.

- Utility data was said to be taken from EQ-5D questionnaires administered to patients, however the utility values obtained from these questionnaires are not stated in the analysis (only QALYs are reported). This is a large oversight and precludes their use in future modelling.

- The discount rate used in the analysis is not stated - although the text says the analysis was performed in accordance with the NICE Guide to the Methods of Technology Appraisal (2004), the value used is not confirmed.

Summary values such as Life Years and cost per QALY are also not comparable to the analysis performed in this submission, as the patient population is different. The trial analysed by Dixon et al. was a trial in first-line patients, with ipilimumab being studied in second line patients.

6.2 De novo analysis

Patients

The patient groups included in the economic evaluation are patients with advanced (unresectable or ‘metastatic’) melanoma in adults who have received prior therapy. This

is in line with the population defined in NICE final scope, i.e. people with previously treated unresectable stage III or IV malignant melanoma.

Model structure

Model schematic

The economic model projects expected clinical and economic outcomes for patients who are assumed to receive either ipilimumab or a comparator treatment. The model is a cohort model with one cohort receiving ipilimumab and the other receiving a comparator treatment with best supportive care (BSC) being the base-case comparator.

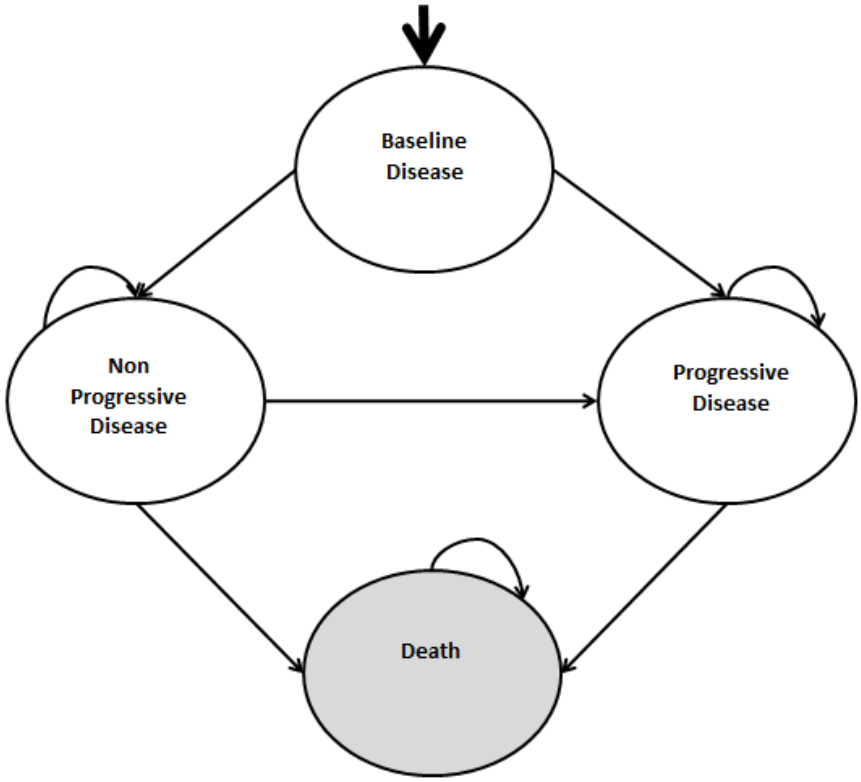
The model is a cost-utility model with outputs of:

- Costs – broken down by cost type
- Life years gained (LYG) – broken down by health state
- Quality adjusted life years (QALYs) – broken down by health state

The modelling approach used in this evaluation may be labelled as a "partitioned-survival" model. The model is characterised by four mutually exclusive health states ("Baseline Disease", "Non Progressive Disease", "Progressive Disease", and "Death"). Following therapy initiation, patients start in "Baseline Disease" and are assumed to move to either the "Non Progressive Disease" health state or the "Progressive Disease" health state. Patients in these health states are at risk of disease progression and/or death over time. Figure 12 shows the model health states.

While residing in a particular health state, patients are assigned a corresponding cost of care as well as a health-state preference weight (i.e., utility value), both of which are assumed to depend upon disease status. The model also includes the impact of adverse events (AEs) on costs. The impact of AEs on utilities is included in the health state utility weights taken from the MDX010-20 (Hodi 2010) trial. The discontinuation rates due to AEs are not considered explicitly in the model as the model takes dose information directly from the MDX010-20 trial, which includes discontinuation due to AE, therefore taking this into account separately would double count the discontinuation rate.

Figure 12 Model Health States



The model is similar to a Markov cohort model; however, unlike a Markov model in which transitions between health states are modelled explicitly using transition probabilities, the partitioned survival model calculates the proportion of patients in each treatment cohort that are expected to be in each health state at any time after treatment initiation.

The proportion of patients in each health states is estimated based on parametric survival curves fitted to empirical data on OS and PFS over time. The proportion of patients in each health state at any given point in time is calculated as follows:

- Non Progressive Disease = proportion of patients in PFS. This is defined as patients who have either shown:
    - Complete response (CR): The disappearance of all lesions by 2 consecutive observations not less than 4 weeks apart, with no evidence of progressive disease.
    - Partial response (PR): A 50% or more decrease in the sum of the products of the longest diameter and the greatest perpendicular diameter of all target lesions compared to baseline, by 2 observations (not necessarily consecutive) not less than 4 weeks apart. There must be no evidence of intercurrent progressive disease between the first measurement showing the 50% decrease and the confirmatory observation.
    - No change (NC) (i.e. Stable disease [SD]): Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease.

- Progressive Disease = proportion of patients in OS – proportion of patients in PFS. This is defined as:
    - An increase of 25% or more in the sum of the products of the longest diameter and the greatest perpendicular diameter of target lesions compared to the smallest recorded sum (nadir) during the study, or appearance of one or more new lesions. A single progressing lesion that does not raise the overall sum of the product of the diameters by 25% will not be considered progressive disease.
- Death = 1 – proportion of patients in OS

Justification of model structure

It was necessary to use a modelling approach in order to project lifetime outcomes and costs for patients. The partitioned survival analysis modelling approach was chosen because it permits projection of the proportion of patients within health states which are defined on the basis of progression and death. This approach is also consistent with clinical outcomes employed in the pivotal clinical trial MDX010-20 trial. In this trial, OS was the primary endpoint, and PFS was a secondary outcome. At completion of the trial, 151 patients were still alive within all treatment arms; also patients are treated in a different manner pre- and post- progression, differences in costs between non-progressive disease health state and progressive disease health state should be expected. Furthermore, OS is necessary for calculation of Quality Adjusted Life Years (QALYs), and PFS is critical for utility estimates. Finally, partitioned survival models have been used in many prior technology assessments of cancer therapies (for example, NICE TA178, 2009; NICE TA202, 2010; NICE TA212, 2010; NICE TA218, 2011), and can be considered to be the standard economic modelling approach in oncology.

The structure of the model accurately reflects an end- stage treatment paradigm (i.e. three mutually exclusive states and non-reversible health states following Baseline Disease: “Non Progressive Disease” following ipilimumab initiation, “Progressive Disease”, following disease progression and “Death”).

Figure 13 shows the standard pathway of care for metastatic melanoma. Dacarbazine is used first-line in the standard pathway as it is the only licensed first-line treatment, although in real life practice patients may be enrolled into a trial for first-line treatment. Ipilimumab is one potential second-line treatment following dacarbazine. As there are currently no licensed second- or third-line treatments, the comparator to ipilimumab and following treatments may be either BSC or a range of active treatments.

Figure 13 Standard Pathway of Care for Metastatic Melanoma Grade III and IV

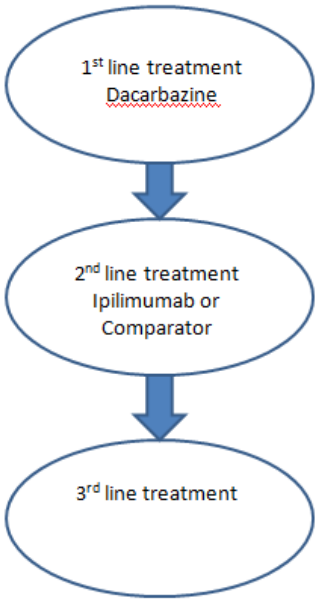


Table 19 shows the proportion of patients receiving different therapies as a second line treatment for unresectable Stage III or Stage IV melanoma according to four different sources. Several datasources have indicated that [redacted] or more patients receive BSC as second line therapy (Middleton et al 2010; [redacted]; A UK-based survey (Collinson and Marples 2010) reported that active treatments are used as frequently as the BSC. Since these patients are likely to be healthier than the average patient and therefore more likely to receive active treatments, therefore this study is most likely to reflect the patient population who may qualify for treatment with ipilimumab... The study also reported that the use of active therapies is wide varying and off-license; the main active therapies are carboplatin with or without paclitaxel.

BSC has been assumed as the base case comparator treatment as no other therapies are currently licensed and [redacted] sources show BSC to be used at least as often as any active therapy (Middleton et al 2010; Collinson and Marples 2010; [redacted]. The assumption of BSC as a comparator treatment is a conservative estimate as most of the active therapies, indicated in the table below, are more costly than BSC in terms of both the drug costs and administration.

Table 19: Current Practice in Second Line Treatment of Stage III or Stage IV Melanoma

Drug	[redacted]	% of Patients - Leeds Survey*	[redacted]	[redacted]
BSC	[redacted]	32%	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	5%	[redacted]	[redacted]
Paclitaxel + Carboplatin	[redacted]	18%	[redacted]	[redacted]
Carboplatin	[redacted]	32%	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]

Drug	[redacted]	% of Patients - Leeds Survey*	[redacted]	[redacted]
Cisplatin + Interferon alfa-2b		5%		
Interferon alfa-2b				
Vindesine		5%		
Treosulfan		5%		
Temozolomide				
Imatinib				

* this relates to the proportion of clinicians giving second-line treatment and not the proportion of patients receiving second-line treatment

Although the base case cost-effectiveness result is given against BSC, the evidence suggests the most appropriate ICER would be for ipilimumab compared with current practice (which may not be effective or cost-effective). Such current practice should include a proportion of active treatments (on average XXX active treatments) as defined by the 4 studies described above.

The proportion of patients receiving active third line treatments outside clinical trials is reported to be [redacted] and [redacted] This indicates that more than [redacted] of patients receive BSC (non-active treatment) as their third line treatment outside clinical trials, therefore in the model it is assumed that all patients receive BSC after second-line treatment.

In the MDX010-20 trial the efficacy of three treatments was monitored:

1. Ipilimumab 3mg/kg every 3 weeks for up to 4 doses

2. Ipilimumab 3mg/kg every 3 weeks for up to 4 doses + gp100 (2mg Peptide A and 2mg Peptide B every weeks up to 4 doses)

3. gp100 (2mg Peptide A and 2mg Peptide B every weeks up to 4 doses)

According to the meta-analysis of over 2000 patients conducted by Korn et al (2008), no treatments for unresectable Stage III or Stage IV melanoma have shown effectiveness (Section 2.1). Therefore, gp100 is assumed to have the same efficacy as that of BSC and the efficacy data of gp100 in the MDX010-020 trial were used as a proxy of efficacy of BSC.

For the same reason, i.e. because of the lack of evidence on efficacy, other therapies are expected to have equivalent effectiveness to GP100 (and therefore BSC).

Definition of health states

The health states in the model are defined as follows:

- Progressive Disease - An increase of 25% or more in the sum of the products of the longest diameter and the greatest perpendicular diameter of target lesions compared to the smallest recorded sum (nadir) during the study, or appearance of one or more new lesions. A single progressing lesion that does not raise the

overall sum of the product of the diameters by 25% will not be considered progressive disease.

- Non Progressive Disease – alive and not in progressive disease. This includes patients with complete response, partial response and stable disease as defined in Section 0.

- Death

PFS was defined as the number of days between the date of randomisation and the date of the progression or the date of death. A subject who died without prior progression was considered to have progressed on the date of death. PFS was assigned a censor in the following cases

1) For subjects who had not progressed and who remained alive, PFS was censored on the date of last assessment.
2) For subjects who remained alive and who had no recorded post-baseline assessment, PFS was censored on the date of randomisation.
3) For subjects who remained alive and who were randomised but not treated, PFS was censored at the date of randomisation (the day of TTP is 1).

The model health states are meant to capture differences in HRQL and costs for progression free and post-progression health states in this patient population. Presence or absence of disease progression is assumed to be a key determinant of medical resource utilisation as discussed in Section 6.2.3.

Context

Prognosis is poor for patients with advanced (unresectable or metastatic) melanoma (Korn et al 2008). For this reason, survival and HRQL are important outcomes, both of which are captured.

In the model, treatment with ipilimumab reflects underlying disease progression. Ipilimumab is administered for 4 doses at initial induction. Re-induction potential is determined according to disease progression status. Subjects who progressed following stable disease (of ≥ 3 months duration beginning at Week 12), or who had experienced an initial objective response (PR or CR) to the initial induction cycle could have been offered additional cycles of treatment with the originally assigned treatment regimen (re-induction) until off-treatment criteria were met, provided they continued to meet re-induction eligibility requirements. No subject was to receive re-induction if they experienced a Grade ≥ 3 gastrointestinal or other selected irAEs. No subject with disease progression following induction was permitted to receive re-induction with the study medication.

Patients who experience disease progression and are not re-inducted (re-induction is discussed in detail in Section 0 – Treatment continuation rules) are assumed to discontinue ipilimumab therapy and receive only BSC. Disease progression is thus also a key determinant of medical resource utilisation.

As noted above, data on PFS and OS (i.e. underlying disease progression and mortality) for patients receiving BSC were not available for patients similar to those in the

MDX010-20 trial. PFS and OS data for patients in the gp100 arm of the MDX010-20 trial were therefore assumed to be an appropriate proxy for underlying disease progression in patients receiving BSC (Section 5).

Key features of the economic evaluation

Table 20: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	30 years	NICE requires life-time horizon; Data modelled from the Kaplan Meier data and exponential curve extension indicate that >99% of patients progressed and 94% patients have died in the ipilimumab arm (in the BSC arm 100% of patients have died) after 30 years.	NICE 2008; MDX010-20
Cycle length	Daily for the first 5 years during trial period; Weekly thereafter	Daily cycle is chosen to allow for the extremely fast progression during the trial period; After this period, a weekly cycle is used to allow for the treatment cycles of potential comparators and to reflect a period short enough to accurately calculate costs and QALYs.	NICE 2008; MDX010-20
Half-cycle correction	Yes	Applied after 5 years when the weekly cycle is started.	NICE 2008
Were health effects measured in QALYs; if not, what was used?	Yes, health effects were measured in QALYs	The QALY reflects the important aspects of this disease, with patients gaining in both quality and duration of life.	NICE 2008
Discount rate	3.5% annually	The 3.5% discount rate specified in the NICE methods guide is used in the base case. The impact of this variable is explored in sensitivity analysis.	NICE 2008
Perspective (NHS/PSS)	NHS	Although some costs would be expected to fall outside the NHS (e.g. carers), the majority of the financial cost in advanced melanoma is borne by the healthcare system.	NICE 2008

Technology

Intervention and comparator

The intervention (ipilimumab) is implemented in the model as per the anticipated marketing authorisation and dose as stated in Appendix 1. Although no changes are anticipated to the regulatory label, any divergence from the proposed indication will be communicated to NICE.

The comparators included in the model are generally used off-licence.

Treatment continuation rule

The continuation rule has been specified in the Summary of Product Characteristics (SmPC) following CHMP positive opinion (see Appendix 1 for SmPC). No additional treatment continuation rule has been assumed in the model beyond those specified in the SmPC.

In the economic evaluation, ipilimumab therapy is assumed to continue until completion of the 4 dose course and any re-inductions, intolerable AEs, disease progression or death (if occurring prior to disease progression). Re-induction and dose completion data has been taken from the MDX010-20 trial and therefore is a direct representation of the patient population upon which the clinical outcomes data is based.

Patients who experience disease progression and discontinue ipilimumab therapy are assumed to receive BSC thereafter, consistent with the absence of other therapies indicated for the treatment of this condition in the UK (Middleton et al 2010). Based on surveys of clinicians and review of the published literature, medical resource utilisation for patients receiving BSC is estimated (Section 6.2.3).

In the clinical trial, 100% of patients treated with ipilimumab began first induction, 38/511 (7%) being re-inducted, and 7/511 (1%) receiving a second re-induction. One patient also received a third induction of ipilimumab. Overall the mean number of doses received was 3.69, as shown in Table 21. The average time from the last re-induction to the last patient follow-up for patients who were re-inducted was almost a year (332 days) and consultation with clinicians has indicated that further re-inductions are unlikely following the trial time period.

Table 21: Clinical trial dosing for all treatments in trial MDX010-20 (Hodi 2010)

Ipilimumab + gp100					
Induction Number	**% of Patients Receiving Induction**	**Number of Patients Receiving Dose**			
		Dose 1	**Dose 2**	**Dose 3**	**Dose 4**
Induction 1	100%	380	350	294	242
Induction 2	8%	29	29	28	26
Induction 3	1%	4	4	3	2
Induction 4	0%	1	1	1	1
Ipilimumab only					
Induction Number	**% of Patients Receiving Induction**	**Number of Patients Receiving Dose**			
		Dose 1	**Dose 2**	**Dose 3**	**Dose 4**
Induction 1	100%	131	121	105	88
Induction 2	7%	9	9	8	7
Induction 3	2%	3	3	3	3
Induction 4	0%	0	0	0	0
Ipilimumab + gp100 and ipilimumab only					
Induction Number	**% of Patients Receiving Induction**	**Number of Patients Receiving Dose**			
		Dose 1	**Dose 2**	**Dose 3**	**Dose 4**

Induction 1	100%	511	471	399	330
Induction 2	7%	38	38	36	33
Induction 3	1%	7	7	6	5
Induction 4	0%	1	1	1	1
gp100					
Induction Number	**% of Patients Receiving Induction**	**Number of Patients Receiving Dose**			
		Dose 1	**Dose 2**	**Dose 3**	**Dose 4**
Induction 1	100%	132	125	99	78
Induction 2	2%	2	2	2	1
Induction 3	0%	0	0	0	0
Induction 4	0%	0	0	0	0

6.3 Clinical parameters and variables

How were clinical data implemented in the model?

PFS and OS

Summary of Approach

Data are available in the MDX010-20 trial for two separate arms containing ipilimumab, and one of gp100 alone.

- Ipilimumab only (n=137)
- Ipilimumab + gp100 (n=403)
- gp100 (n=136)

In the base case analysis, in order to make best use of all available data, the 'ipilimumab alone' and 'ipilimumab + gp100' arms were combined to give the best available estimate of the survival of ipilimumab-treated patients. This is based on the assumption that gp100 does not have significant impact on efficacy, i.e. the efficacy of ipilimumab equals the combined efficacy of ipilimumab and gp100.

It has to be noted that this assumption is conservative and may bias against the estimates of efficacy of ipilimumab. Since in the MDX010-20 trial: the use of gp100 marginally reduces efficacy in terms of PFS and OS (Hodi 2010). Such impact ofgp100 may lead to an underestimate of efficacy of ipilimumab if the combined data of gp100 and ipilimumab, instead of data of ipilimumab alone, is used. As such, the effect on the ICER of using the individual ipilimumab arm of trial MDX010-20 is explored in Section 6.7.9.

Data on PFS and OS for patients receiving BSC were unavailable, therefore this was approximated based on data for subjects in MDX010-20 trial taking gp100 assuming equal efficacy between gp100 and BSC (Korn et al, 2008). This assumption is discussed in Section 6.2.3 and Section 6.2.5.

To calculate measures of effectiveness, the proportion of patients receiving each treatment strategy that is expected to be alive at each time is generated by the model using OS data from the MDX010-20 trial. For each treatment, the proportion of patients alive and post-progression at each time, is calculated based firstly on the number of patients alive, and secondly on the number of patients in the non-progressive disease state. For each treatment, expected PFS and OS equal the area under the curves represented by PFS and OS, while expected post-progression survival (patients in the progressive disease state) represents the area between the PFS and OS curves.

In order to achieve a 'good' curve fit, various strategies were attempted - the method that delivers the best fit (in terms of the Akaike Information Criterion [AIC]) was used for the base case of the model.

Strategy 1: Single curve fit

A variety of parametric curves were fitted to the MDX010-020 trial data, using Weibull, exponential, lognormal, log-logistic and Gompertz functions with the best fitting curve chosen using the minimum AIC.

The AIC is a measure of the relative goodness of fit of a statistical model. Given a set of candidate models for the data, the preferred model is the one with the minimum AIC value. Table 22 shows the AIC for each of the curves, with the best fit, i.e. the curve with the lowest AIC value, for each curve highlighted in bold.

Table 22: AIC for One Curve Parametric Fits

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Ipilimumab OS	1653.34	1655.14	**1607.49**	1609.75	1625.65
Ipilimumab PFS	1614.07	1614.38	1378.98	**1303.06**	1507.87
BSC OS	389.88	388.83	**368.58**	369.34	388.72
BSC PFS	333.15	339.08	254.27	**224.23**	334.70

Graphical representations of best curve fits are shown in Figure 14 and Figure 15. For estimates of OS of both arms, the lognormal function is used; for estimates of PFS of both arms, the log-logistic function is used. It is obvious that visually these so-called 'best-fit' curves do not fit the Kaplan Meier data well, particularly for PFS and for OS near the end of the trial time period, for example at the final time point for ipilimumab OS, the lognormal (the best fitting curve) predicts survival of 9.5% compared to the 15.4% seen in the empirical data (an underestimation of 38%). As such, it would be inappropriate to determine a 'best' fit, given none of the curves fit the data particularly well.

Full details of the individual curve fits and a comparison to the Kaplan Meier data can be found in Appendix 14.

Figure 14 Overall survival – modelled data vs Kaplan Meier data, single curve fit

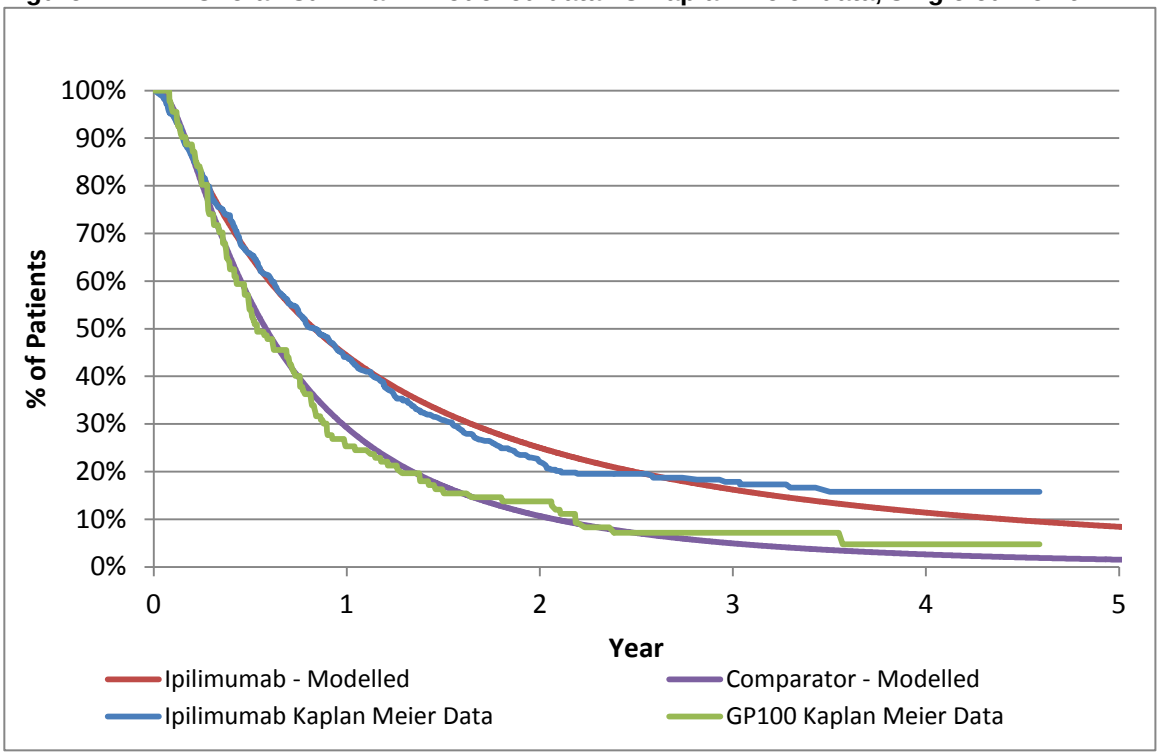
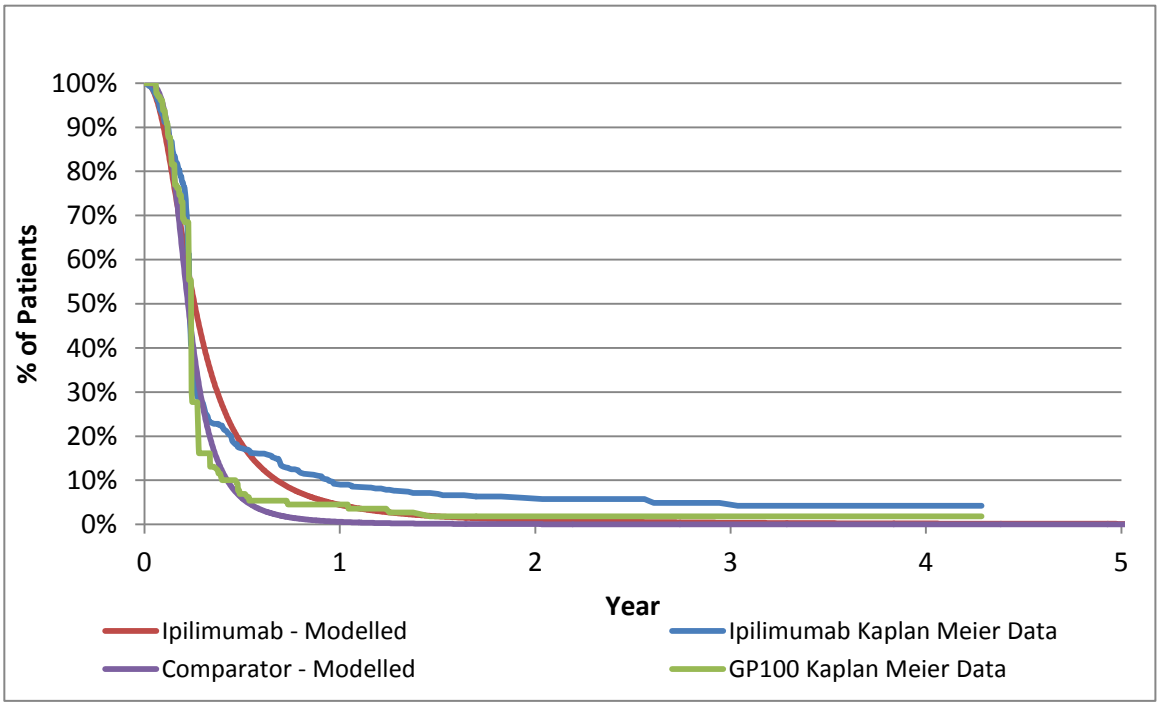


Figure 15 Progression free survival – modelled data vs Kaplan Meier data, single curve fit



Strategy 2: Two Part Curve Fit

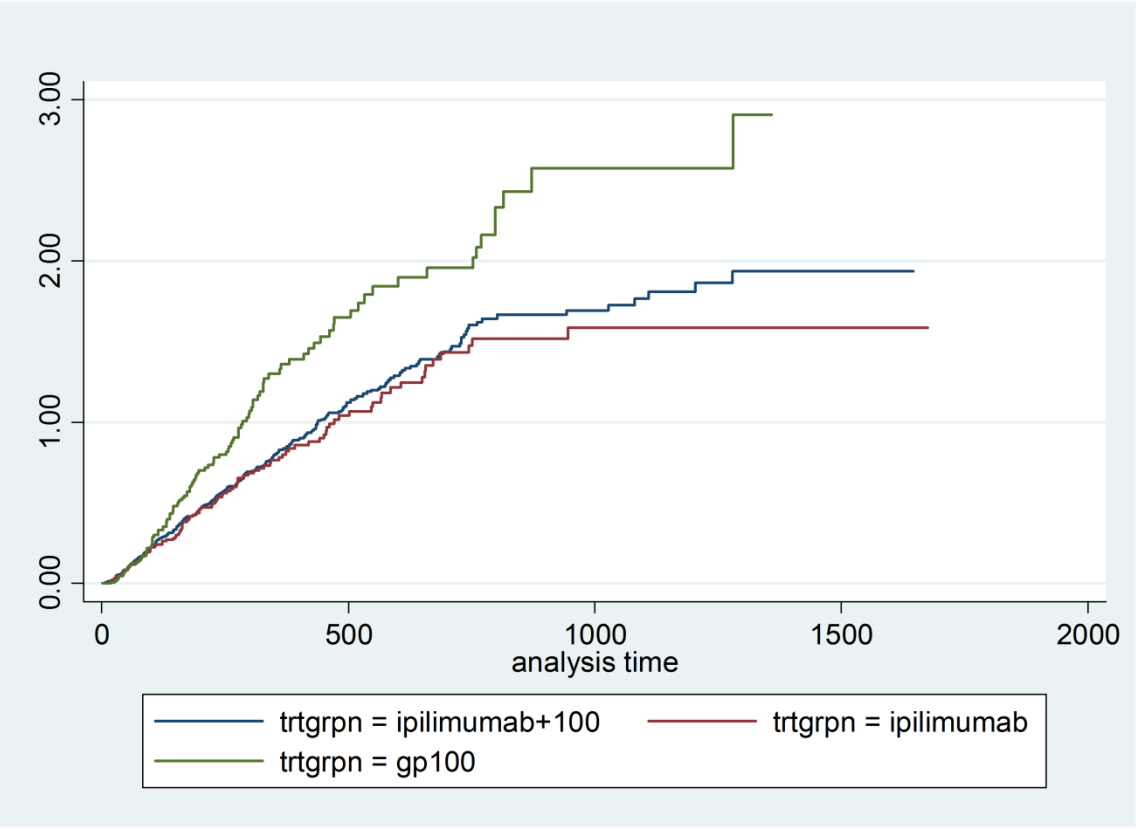
Due to the poor fit of the curves modelled using 'single curve fit' method, a 'two part curve fit' has been constructed for both ipilimumab and BSC. These curve fits use the Kaplan Meier data to 18 months, and a curve fitted to the data from 18 months onwards.

This approach utilises a large proportion of the actual trial data and enables a more representative curve fit to the data for patients during the latter years of the trial.

The 18 month point was chosen to represent the point at which data have started to 'flatten' in both the ipilimumab OS arms, as shown in the Nelson-Aalen cumulative hazard plot (Figure 16). In the plot it can be seen that after approximately 500 days in the ipilimumab alone arm, and 600 days in the ipilimumab + gp100 arm, the hazard flattens. The 18 month timepoint falls between these, at 548 days, and was therefore used in the economic modelling.

This plot also shows that the hazard ratio is not constant in the ipilimumab arms. Therefore, it is inappropriate to use 'hazard ratio' approach in survival modelling for ipilimumab arms.

Figure 16 Nelson-Aalen cumulative hazard estimates for overall survival



However, in the plot above (Figure 16), it is difficult to ascertain exactly if, or when, a change in the hazard rate occurs for gp100 (BSC). For this reason the same timepoint has been used as with the ipilimumab data (18 months). Due to low patient numbers remaining progression-free (n=7, 2.7%) in the BSC arm at 18 months, the curve fit determined for overall survival post 18 months is also used for PFS.

Weibull, exponential, lognormal, log-logistic and Gompertz functions were fitted to the 18-month and onwards data, with the best fitting curve selected and highlighted based on the AIC, i.e. the lowest AIC implies the best fit. Table 23 shows the AIC for each

parametric curve fits from the 18-months onwards data (see Appendix 14 for a full list of parameters and a comparison to the Kaplan-Meier data).

Table 23: AIC for 18-months onwards curve

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Ipilimumab OS	324.39	332.32	316.94	320.31	**314.75**
Ipilimumab PFS	58.27	**57.42**	58.33	58.31	58.71
BSC OS and PFS	54.27	52.29	55.28	**54.18**	54.27

The base-case curve fitting of this 'two part curve' approach in the base case are shown in Figure 17 and Figure 18. These figures are composed by using Kaplan-Meier estimates of PFS and OS upto 18 months, and then the 'best fit' parametric curves (as shown below) to estimate PFS and OS beyond 18 months:

- Exponential for PFS in ipilimumab
- Gompertz for OS in ipilimumab
- Exponential for OS in BSC
- PFS in BSC arm represented by OS arm

Figure 17 Progression Free Survival – Modelled Data vs Kaplan Meier Data, two-part curve fit

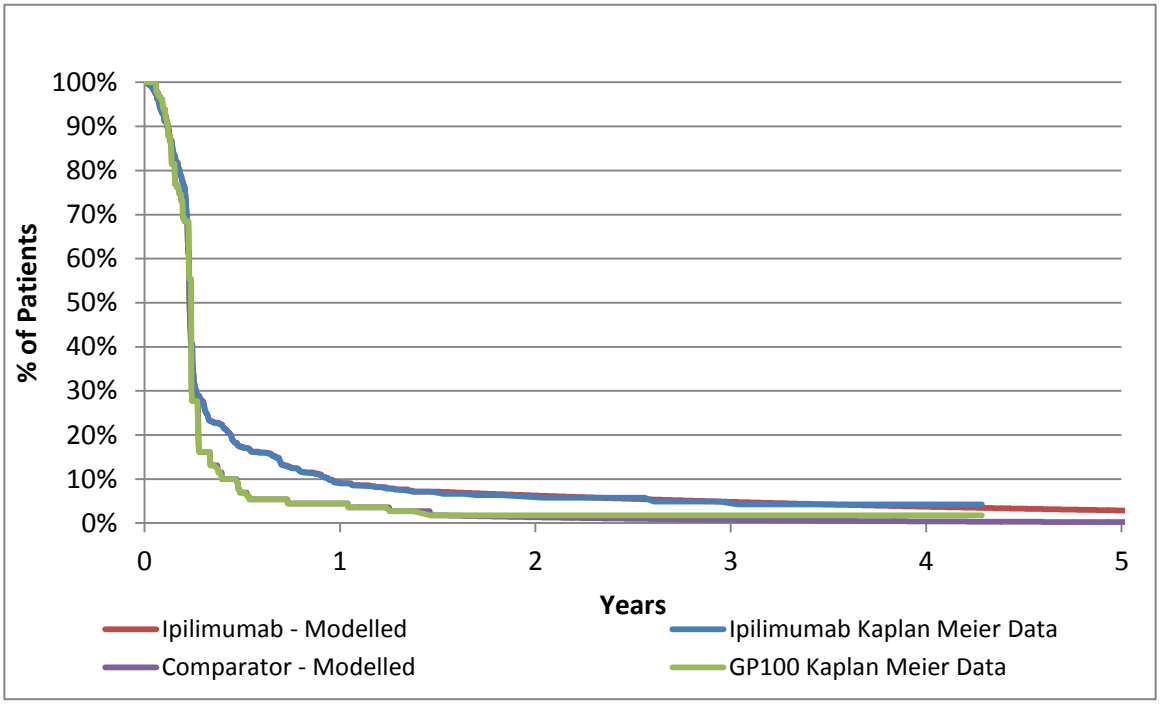
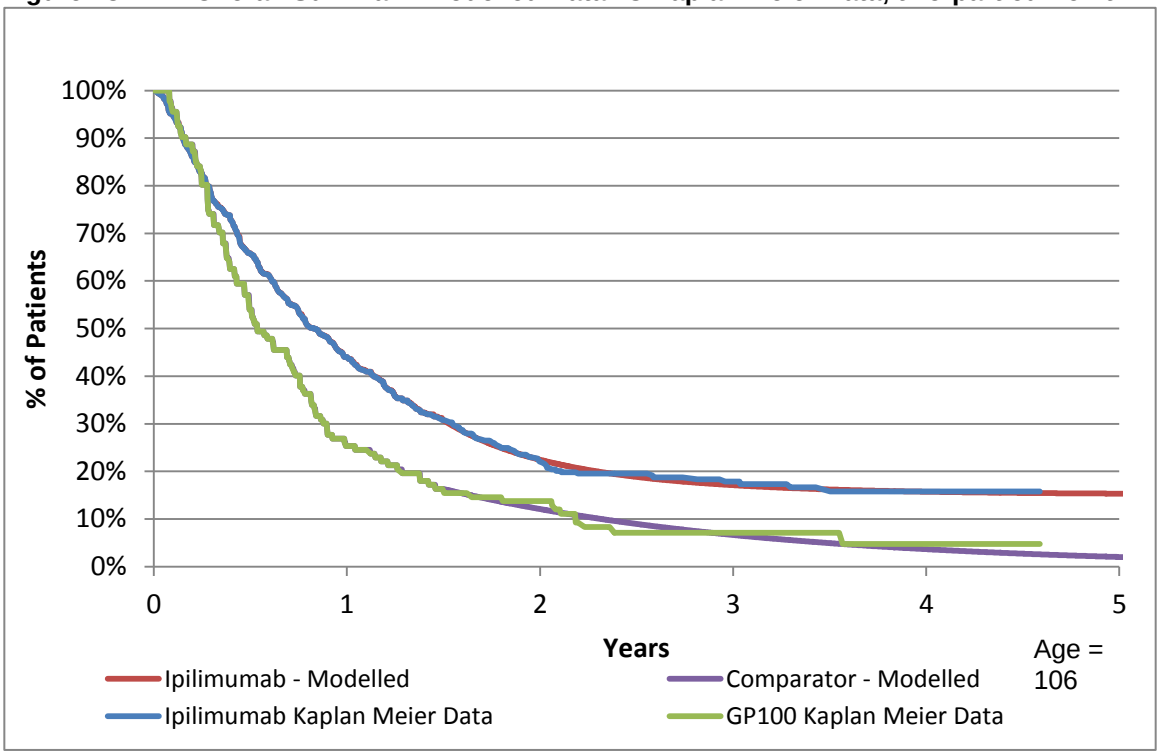


Figure 18 Overall Survival – Modelled Data vs Kaplan Meier Data, two-part curve fit



It can be seen visually in Figure 17 and Figure 18 that these curves provide a good fit to the Kaplan Meier data, which is available for over 4 years for both arms

Adjustment of Overall Survival to Account for Background Mortality

It is noted, however, that OS asymptotes to approximately 15% patients in the ipilimumab arm, whereas in real life background mortality would gradually decrease survival over the latter years of the model. It is therefore appropriate to fit curves to only the period from 18 to 60 months, and include background mortality after 5 years (i.e. the latest date at which trial information is available). The assumption is that patients surviving beyound 60 months (5 years) exhibit long term survival, dying due to natural causes as reflected by Office of National Statistics Interim Life Tables data (ONS, 2011). This assumption is applied to the ipilimumab arm, and also to the BSC arm. Therefore, the curve fits shown in Figure 17 and Figure 18 above have been adjusted to take into account background mortality from year 5 onwards using the three year mortality averages from the Interim Life Tables for 2007 – 2009 (ONS, 2011). This adjustment is based on the MDX020-10 trial observation that patients' average age at the start of the model is 56, and 59% are male patients. The result of this adjustment can be seen in Figure 19 and Figure 20. It is expected that patients would have died before the age of 100; curve fits that generate credible results should show such case. In order to check the face validity of these curve fits, a 50-year time horizon was used in these Figures. However, it should be noted that the time horizon used in the model is 30 years.

Figure 19 Progression Free Survival – Modelled Data vs Kaplan Meier Data, Adjusted for Background Mortality

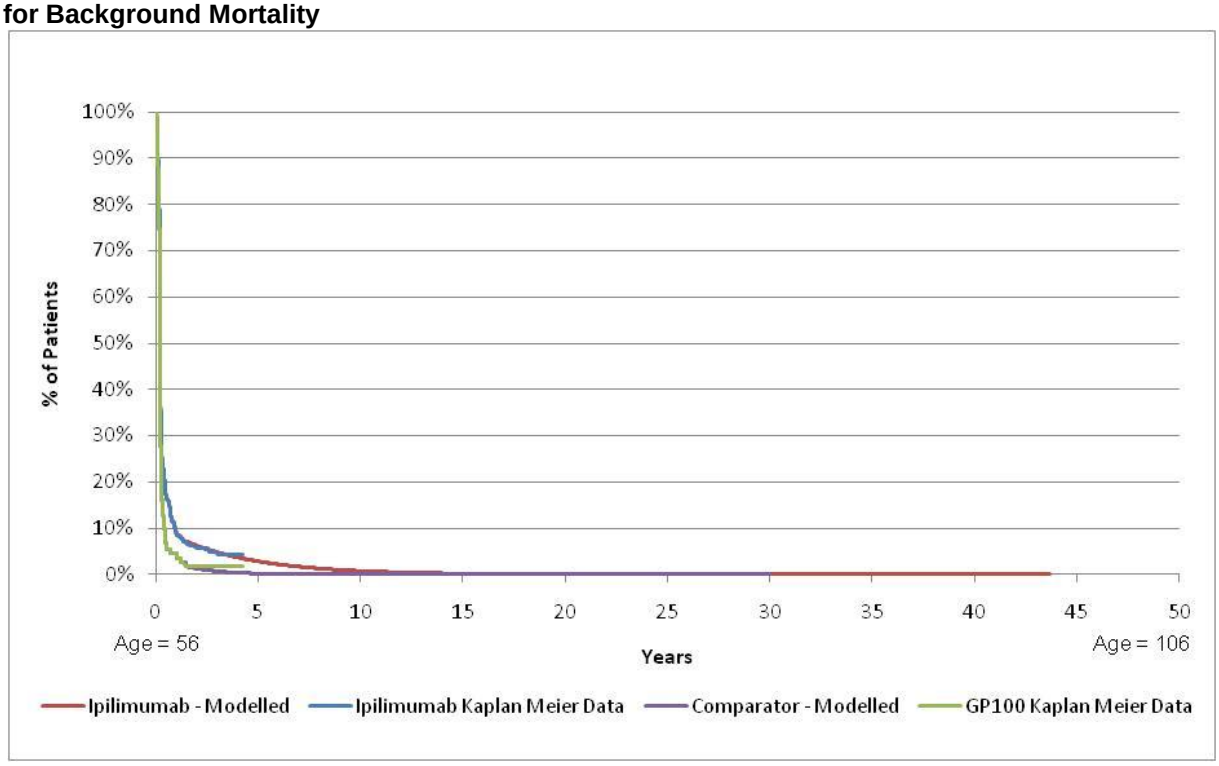
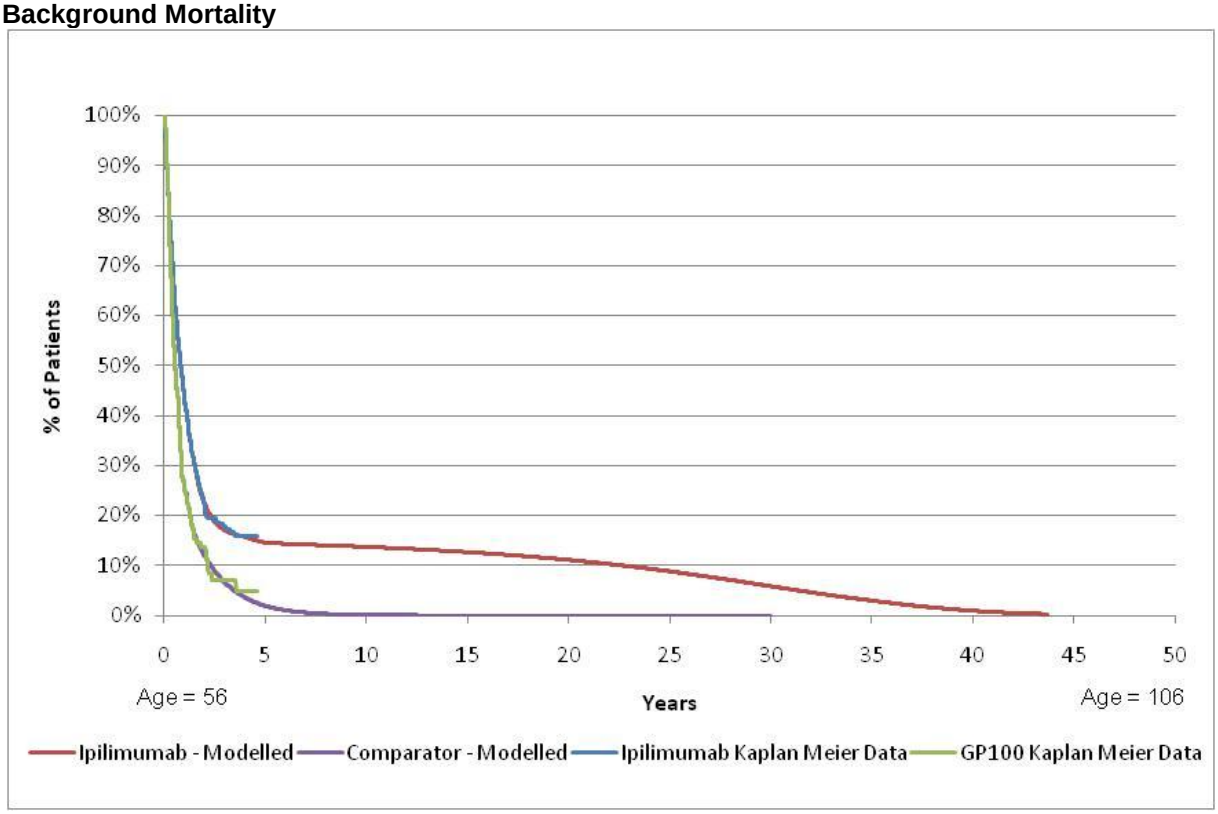


Figure 20 Overall Survival – Modelled Data vs Kaplan Meier Data, Adjusted for Background Mortality



Curve Parameters and Goodness of Fit

Parameters for the survival functions fitted to ipilimumab data are summarised in Table 24. In the model up to 18 months (day 548) the actual Kaplan-Meier data are used for OS and PFS as described in the two part curve fit, utilising a large proportion of the actual trial data, The parameters in Table 24 describe the curves applied to OS and PFS from day 548 (18 months) onwards in the model i.e. taking day 548 to be day 1 when utilising the function.

Table 24: Parameters used to estimate PFS and OS for Ipilimumab and gp100 from 548 days onwards

Treatment	Outcome	Curve fit	Lambda (Scale)		Gamma (Shape)	
			Estimate	SE	Estimate	SE
Ipilimumab	PFS	Exponential	-7.247615	0.3535534		
	OS	Gompertz	-6.080702	0.1997629	-0.00322	0.0008451
BSC (gp100)	PFS*					
	OS	Exponential	-6.414799	0.3015113	-	-

*Assumed to be the same as OS for BSC (gp100)

To assess the goodness of fit of the curves, the median and mean PFS and OS from the empirical (Kaplan-Meier) survival distributions were compared with those from the estimated curves out to the maximum follow-up for each outcome in each group.

Table 25 shows the estimated median values for PFS and OS compared to the Kaplan Meier data. These are the same as actual Kaplan Meier data is used for the first 18 months and for both arms median OS and PFS occur before 18 months.

Table 25: Comparison of Kaplan Meier and estimated median PFS and OS for Ipilimumab and gp100

Treatment	Outcome	Median value – Kaplan Meier	Median Value – Modelled Data
Ipilimumab	PFS	85	85
	OS	303	303
BSC (GP100)	PFS	88	88
	OS	196	196

In order to judge how well the model fits available data, Table 26 shows the estimates of mean survival up to the point where trial data are available (i.e. the first 1,565 days for which empirical information is available for both PFS and OS).The **mean** survival is similar for both the modelled data and the Kaplan Meier data (Table 26), indicating a good fit.

Table 26: Comparison of Kaplan Meier and estimated mean PFS and OS for Ipilimumab and GP100 – trial period data (1565-day horizon)

Treatment	Outcome	Max FU (days)	Days of PFS and OS			
			Empirical	Curve Fit	Abs Diff	% Diff
Ipi + gp100	PFS	1565	166	166	0	0%
	OS	1565	491	485	-6	-1%
Ipi Only	PFS	1565	243	236	-7	-3%
	OS	1565	537	522	-15	-3%
Ipi + gp100 and Ipi Only	PFS	1565	186	184	-2	-1%
	OS	1565	502	493	-9	-2%
BSC (gp100)	PFS	1565	121	111	-9	-8%
	OS	1565	336	332	-4	-1%

Note: Mean calculated over maximum follow-up among all non-responders; mean values may differ from those calculated by Kaplan-Meier method (SAS Proc LIFETEST) which calculate mean out to last failure time only.

In order to assess the curve fitting beyond the trial period, Table 27 shows the comparison of the mean estimates from the model and the mean estimates for the Kaplan Meier data for the entire modelled lifetime (30 years). The differences in mean PFS and OS from the empirical distributions versus the curve fit were relatively small for the BSC arm. This is because by the end of the follow up period fewer than 5% of patients are still alive, giving limited scope for curve fitting to affect the results.

In the ipilimumab arm, there are greater differences in the means predicted using the model and calculated using the Kaplan Meier data to the last observation. This is due to a larger proportion of patients remaining alive at the end of the trial.

Table 27: Comparison of Kaplan Meier and estimated mean PFS and OS for Ipilimumab and GP100 (over 30-year time horizon)

Treatment	Outcome	Max FU (days)	Days of PFS and OS			
			Empirical	Curve Fit	Abs Diff	% Diff
Ipi + gp100	PFS	1565	166	178	12	7%
	OS	1676	514	657	143	28%
Ipi Only	PFS	1565	243	340	97	40%
	OS	1676	569	783	215	38%
Ipi + gp100 and Ipi Only	PFS	1565	186	202	15	8%
	OS	1676	528	703	175	33%
BSC (gp100)	PFS	1565	121	113	-8	-7%
	OS	1676	344	381	37	11%

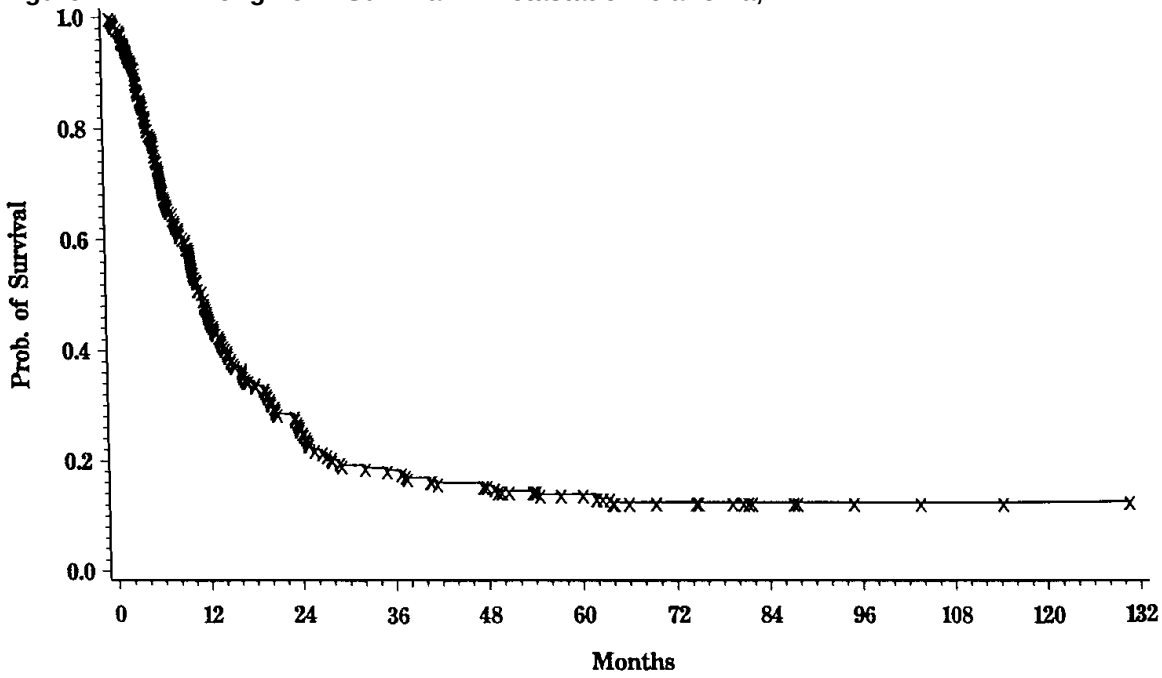
Note: Mean calculated over maximum follow-up among all non-responders; mean values may differ from those calculated by Kaplan-Meier method (SAS Proc LIFETEST) which calculate mean out to last failure time only.

Most importantly, it should be noted that comparing to BSC (GP100), ipilimumab increases in both mean OS (23.1 months [703 days] vs 12.5 months [381 days]) and median OS (10.0 months [303 days] vs 6.4 months [196 days]). Such level of survival benefit is in excess of what is considered significant in terms of NICE 'End of Life' guidance (NICE, 2009).

Validation of survival curve fitting

The modelling above is in line with the survival curves seen in other research into the treatment of metastatic melanoma with IL-2 (also a form of immunotherapy; Atkins, 1999). In this paper, an analysis of 270 patients from 8 separate clinical trials, a steep drop in survival was seen in the initial period, followed by an elongated tail. The majority of patients alive at 2 years remained alive for the 11 years of follow up (see Figure 21).

Figure 21 Long Term Survival in Metastatic Melanoma, IL-2



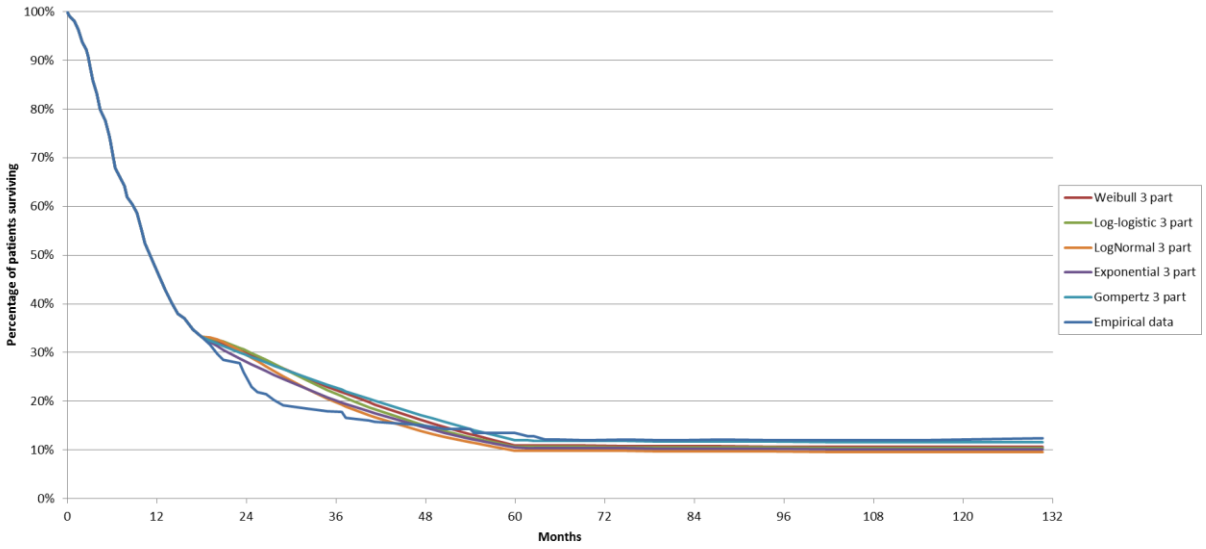
Reproduced from Atkins et al 1999

In order to validate the methodology, the data from Atkins (1999) were digitised using GetData Graph Digitizer (ShareIt! Software, Germany). The methodology used for the ipilimumab data, including the 18 month data split, was used to fit a curve to the IL-2 data including the use of background mortality only from month 60 onwards. The results of the analysis are shown in Figure 22.

In the analysis, the Kaplan-Meier data is used from month 0-18, a curve fitted from the data for months 18-60, and from month 60 onwards, background mortality only is applied (as in the ipilimumab analysis). The data represent a good fit, with the Gompertz curve the best fitting according to the AIC, as is the case with the ipilimumab data which represent further validation of the method.

The use of 11 year data in this disease area validates the methodology, and ensure the hypothesis of long term survival in melanoma patients to be plausible, and the approach taken appropriate to both the underlying biology, and historical data.

Figure 22 Validation of survival curve approach in melanoma applied to Atkins (1999)



Adverse Events

Adverse event (AE) rates for patients receiving ipilimumab in the model were estimated using results from the MDX010-20 trial reported by Hodi et al (2010).

The base-case comparator is BSC. AE rates for BSC were assumed to be the same as those for gp100. This is to reflect the adverse events that patients are likely to experience due to natural progression of the disease.

In the sensitivity analysis, where other active treatments that were considered as comparators AE rates related to these treatments were taken from published literature (see Appendix 15).

The costs associated with AEs are estimated depending on the severity and duration of these AEs. In particular, all Grade 3+ AEs with an incidence of at least 3% among patients treated within the ipilimumab only arm were included. Based on clinical experts' advice, Grade 2 AEs were also included for diarrhoea and colitis due to high treatment costs, but all other Grade 1 and Grade 2 AEs were excluded it is unlikely that they have significant impact on resource use.

The impact of AEs on utilities is included within the model through the use of trial-based utilities which include the impact of adverse events on HRQL. In other words, in order to avoid double-counting, there is no separate consideration of AE-related disutilities in the model.

Estimates of the incidence of AEs among ipilimumab and gp100 patients in the MDX010-20 trial are shown in Table 28.

Table 28: Estimated incidence of AEs among ipilimumab patients and gp100 patients

Adverse Event	% of patients receiving ipilimumab	% of patients receiving gp100
Grade 3+ Fatigue	6.9%	3.0%
Grade 2+ Diarrhoea (not including colitis)	6.1%	18.9%
Grade 2+ Colitis	6.1%	0%
Grade 3+ Dyspnoea	3.9%	4.5%
Grade 3+ Endocrine Disorders	3.8%	0%
Grade 3+ Anaemia	3.1%	8.3%

Utility Information

A systematic review of utility studies was conducted for information on health related quality of life (HRQL) for metastatic melanoma patients. Only one paper (Beusterien et al, 2009) was identified. This study presents estimated utilities for stable, responsive and progressive disease along with utility decrements for various treatment-related adverse events, based upon UK and Australian general population surveys using clinician defined vignettes and standard gamble methods. Table 29 presents the utility values from Beusterien et al for both UK and Australian data. It should be noted that in the sensitivity analysis of this submission, only the UK values have been used, due to the applicability of the data to the UK population.

Table 29: HRQL results, Beusterien et al

Health State	All mean (s.e.)	Australia mean (s.e.)	UK mean (s.e.)
Clinical response status			
Partial response	0.88 (0.01)	0.91 (0.01)	0.85 (0.02)
Stable disease	0.80 (0.01)	0.83 (0.01)	0.77 (0.02)
Progressive disease	0.52 (0.02)	0.47 (0.03)	0.59 (0.02)
Best supportive care	0.52 (0.02)	0.46 (0.03)	0.59 (0.02)
Utility decrement for toxicity states			
Hair loss (grade I/II)	-0.03 (0.01)	-0.03 (0.01)	-0.03 (0.01)
Skin reaction (grade I/II)	-0.06 (0.01)	-0.08 (0.01)	-0.03 (0.01)
Diarrhoea (grade I/II)	-0.09 (0.01)	-0.11 (0.01)	-0.06 (0.01)
Nausea/vomiting (grade I/II)	-0.10 (0.01)	-0.12 (0.01)	-0.07 (0.01)
Flu-like syndrome (grade I/II)	-0.11 (0.01)	-0.13 (0.01)	-0.09 (0.01)
Stomatitis (grade I/II)	-0.13 (0.01)	-0.14 (0.01)	-0.10 (0.02)
1 day in/outpatient stay for severe toxicity (grade III/IV)	-0.13 (0.01)	-0.14 (0.01)	-0.11 (0.02)
Symptomatic melanoma	-0.16 (0.01)	-0.20 (0.02)	-0.11 (0.02)
2-5 day hospitalisation for severe toxicity (grade III/IV)	-0.17 (0.01)	-0.20 (0.02)	-0.13 (0.02)

Information on HRQL was also captured as part of the MDX010-20 trial using the EORTC QLQ-C30 and SF36v2 questionnaires.

MDX010-20 trial-based EORTC QLQ-C30 and mapped EQ-5D scores

EORTC QLQ-C30 values have been mapped from the 971 trial observations using the mapping algorithm 3 defined in Rowen et al. (in press). It is possible that patients who have provided more observations may have increased survival and better health status, in order to avoid bias towards these patients, the average of individual patient readings for the progression and non-progression states is taken before the standard deviations and overall averages are calculated.

The results are split by progression status, and treatment arms, as shown in Table 30. Figure 23 and Figure 24 show a histogram of measured patient utilities over all treatment arms, stratified by progression status.

Table 30: Utility Values Mapped from EORTC QLQ-C30 Trial Data

Treatment Group	Progression Status	Utility	Standard Deviation	n
GP100	progressed	0.719	0.161	68
	not progressed	0.789	0.135	131
Ipilimumab + GP100	progressed	0.760	0.149	185
	not progressed	0.802	0.134	393
Ipilimumab Only	progressed	0.781	0.161	61
	not progressed	0.804	0.141	133
All Treatments	progressed	0.763	0.160	314
	not progressed	0.801	0.138	657

Figure 23 EORTC Utilities For Patients Who Have Not Progressed

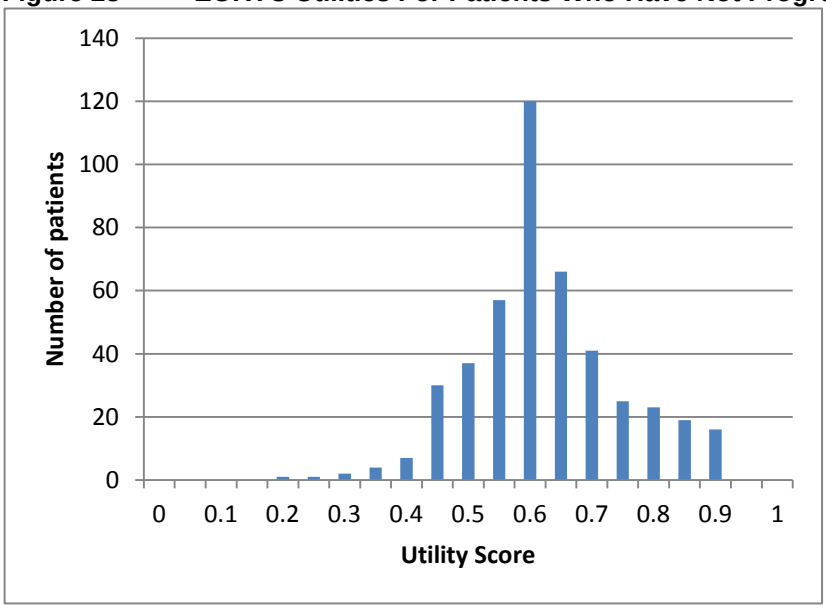
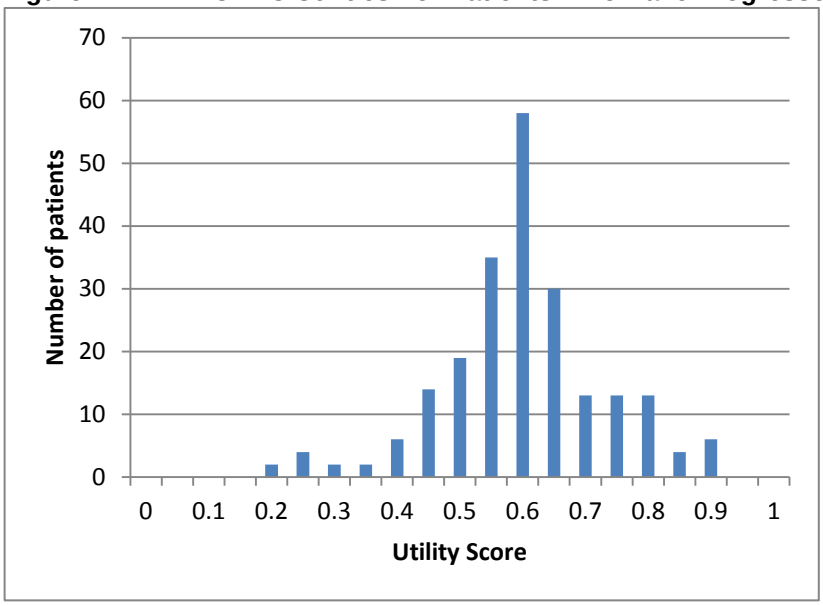


Figure 24 EORTC Utilities For Patients Who Have Progressed



The average utility for patients who have not progressed is similar across all treatments, and consistent with the UK and Australian health state utilities for stable disease found by Beusterien et al (2010). The utilities for progressive disease are also similar across treatments. However, the difference between the EQ-5D utility scores in progressive disease and not progressed states (stable disease) is very small (0.76 versus 0.80, averaging 0.04 lower in progressive state than that in stable disease). The EQ-5D utility in progressive state (0.76) is considerably higher than the utility for progressive disease found in Beusterien et al for UK population (0.59), therefore the Beusterien study has shown a much bigger difference of utility in progressive disease and stable disease (0.59 versus 0.77 for UK population).

For patients who experienced progression the correlation between time from progression and measured utility has been examined in order to determine whether the utilities are unduly influenced by being closer to the time at which progression occurred. The correlation coefficient was 0.19 which indicates that there is no correlation between time elapsed since progression and their utility. Time before progression at which a measurement was taken also did not influence the utility reported (correlation coefficient of 0.18).

According to clinical experts, it is clinically plausible to expect such results, i.e. small utility decrement when patients are progressive disease treated with immunotherapy such as ipilimumab (as discussed in the clinical section). Indeed, these results may be due to the unique kinetics of response associated with treatment with ipilimumab. Saenger et al. (2008) 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).

This response kinetics becomes apparent when looking at long term survival for patients taking the drug. Although follow-up tumour assessments after progression were not

mandated by the protocol, 14 subjects had such additional tumour assessments performed. Of these 14 subjects, 3 demonstrated stable disease (relative to baseline) after Week 24, all in the ipilimumab plus gp100 group. In the absence of uniform follow-up, assessment of response after progressive disease is incomplete and may be underestimated. Long-term survivors include patients with progressive disease according to modified World Health Organization (mWHO) criteria. The average time from progression to the last date of follow-up for long term survivors defined as 'patients still alive at last follow-up who have lived at least 3 years', was 783 days (approximately 26 months).

Patients treated with ipilimumab who are defined as progressed may therefore be expected to have a higher utility than would otherwise be expected. The decrement of utility in progressive disease can be minimal as compared to that in stable disease state.

In the base case of the model, EQ-5D utility scores mapping from the patient-level EORTC QLQ-C30 are used. Since this is most representative of the baseline utilities of the patients within the trial according to clinicians' opinion, and it is consistent with the baseline (non progressed state) utility within the published literature (Beusterien et al), and it is in line with the NICE methods guide (2008). The effects of utilising alternative utility assumptions are tested within sensitivity analysis.

MDX010-20 trial-based SF-36 and mapped SF-6D scores

SF-6D utilities have also been estimated from the SF-36v2 questionnaire included in the trial, using the latest model which weights responses based upon a nonparametric Bayesian method Kharroubi et al (2007). Table 31 shows the utility values mapped from the SF-36 trial data, which has 963 observations, split by health state and treatment arm. As for the EORTC data the average of individual patient readings for the progression and non-progression states is taken before the standard deviations and overall averages are calculated in order to avoid bias towards patients who have provided more observations (as this is likely to be linked to increased survival and therefore better health status).

The average utility for patients pre-progression is much lower using the SF-6D than in either the EORTC mapped values or the Beusterien et al valuations. Similar to the EORTC QLQ-C30 valuation, utilities are similar across all treatments and there is little difference seen following disease progression.

For patients who experienced progression the correlation between time since progression and utility has been examined in order to determine whether the utilities are unduly influenced by being closer to the time at which progression occurred. The correlation coefficient was 0.08 which indicates that there is no correlation between time since progression and their utility. Time before progression also did not influence the utility reported (correlation coefficient of 0.13).

Figure 25 and Figure 26 show the distribution of patient utilities by progression status. These distributions are similar for both states, clustered around a utility of 0.6.

Table 31: Utility Values Mapped from SF-36 Trial Data

Treatment Group	Progression Status	Utility	Standard Deviation	n
GP100	progressed	0.599	0.136	69
	not progressed	0.620	0.108	131
Ipilimumab + GP100	progressed	0.630	0.132	182
	not progressed	0.647	0.122	391
Ipilimumab Only	progressed	0.608	0.114	59
	not progressed	0.649	0.115	131
All Treatments	progressed	0.619	0.130	310
	not progressed	0.640	0.118	653

Figure 25 EORTC Utilities For Patients Who Have Not Progressed

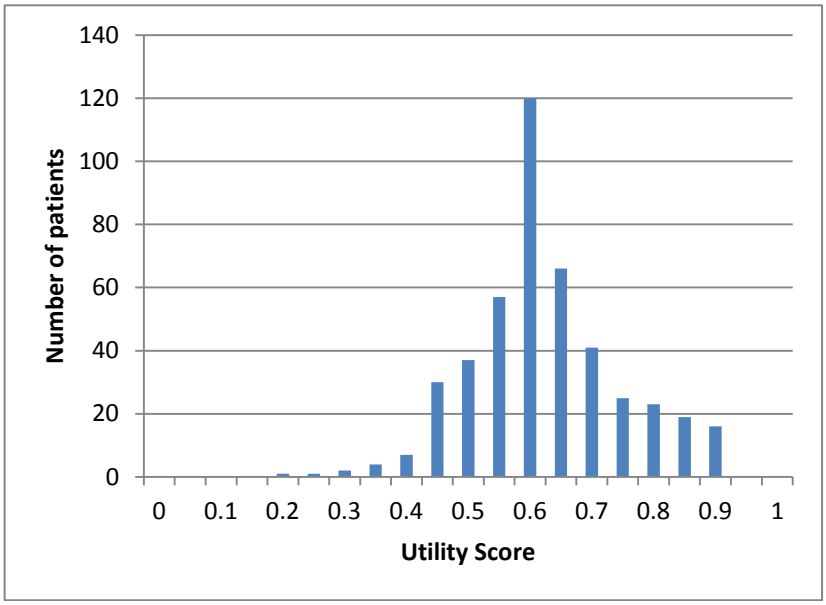
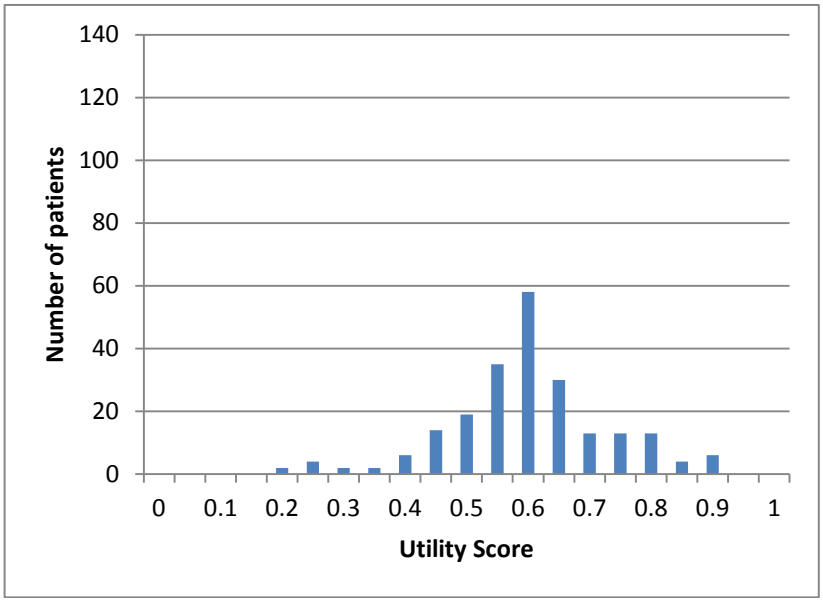


Figure 26 EORTC Utilities For Patients Who Have Progressed



Transition probabilities

As this is a partitioned survival model risks of disease progression and death were allowed to vary over time, consistent with the survival functions as described in Section 6.3.1.

Variation of transition probabilities over time

As this is a partitioned survival model risks of disease progression and death were allowed to vary over time, consistent with the survival functions as described in Section 6.3.1.

Linking intermediate outcome measures to final outcomes

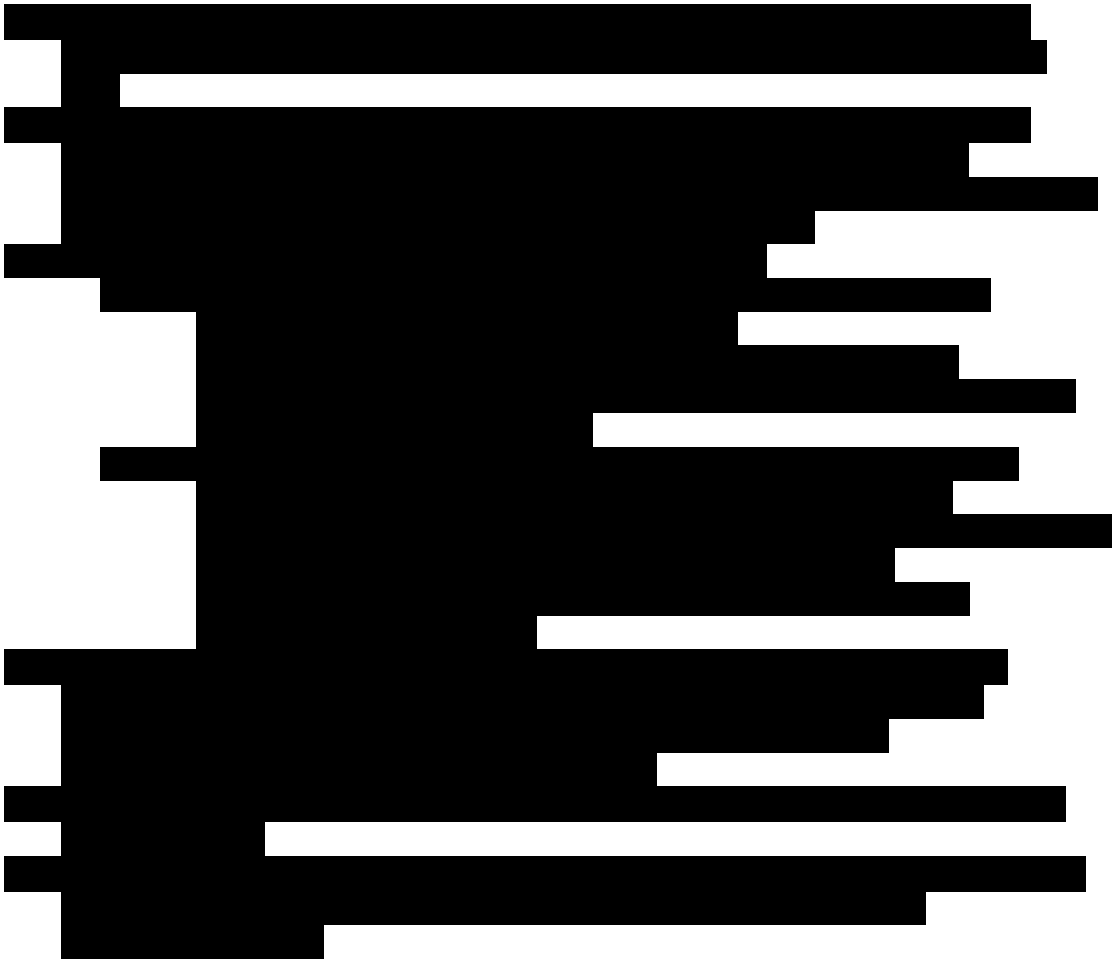
OS in the model was estimated directly and was not linked to PFS. Outcomes for patients receiving BSC from 18 months onwards for PFS were estimated using the curves for OS, as only 7 patients (2.7%) were progression free by this point meaning a curve could not be estimated from available data.

Clinical experts

Expert opinion was used in the following areas of the model

Resource use data are taken from the Oxford Outcomes study (details below):

[redacted]



- Model validation stage 1 - in order to ensure the model has face validity, it was presented to four practising clinicians, independently, with questions and clarifications encouraged. Particular attention was paid to survival curves (and whether these are as would be expected), resource use, patient characteristics, comparators and patient quality of life.

- Model validation stage 2 - A similar approach was used with 6 economic experts (including a former NICE committee member, assessment group members and an SMC economic reviewer), who were consulted in an advisory board on the assumptions and methods used in the final model, with feedback taken in to account and the model strengthened where appropriate.

Summary of selected values

Summary list of variables used

A list of all variables used in the base case economic analysis is provided in Table 32. Parameters used only in the sensitivity analysis relating to comparator treatments can be found in Appendix 15.

Table 32: Summary of variables applied in the economic model

Parameter	Value Used	Distribution	Source
Patient Characteristics			
Average Patient Body Weight (kg)	81.7	Normal – SD 18.1	MDX010-20 – UK patients and compassionate use programme
Patient Starting Age	56	Normal – SD 13.4	MDX010-20
% Male	59%		MDX010-20
Dosing			
Ipilimumab Dose mg/kg	3	N/A	MDX010-20
Average Number of 200mg Vials Required	0.99	N/A	Patient weights from UK patients from MDX010-20 and compassionate use programme
Average Number of 50mg Vials Required	1.24	N/A	
Administrations			
% Receiving Induction 1 Dose 1	100%	Beta – SD	MDX010-20
% Receiving Induction 1 Dose 2	92%	Beta – SD	MDX010-20
% Receiving Induction 1 Dose 3	78%	Beta- SD	MDX010-20
% Receiving Induction 1 Dose 4	65%	Beta – SD	MDX010-20
% Receiving Induction 2 Dose 1	7%	Beta – SD	MDX010-20
% Receiving Induction 2 Dose 2	7%	Beta – SD	MDX010-20
% Receiving Induction 2 Dose 3	7%	Beta – SD	MDX010-20
% Receiving Induction 2 Dose 4	6%	Beta – SD	MDX010-20
% Receiving Induction 3 Dose 1	1%	Beta – SD	MDX010-20
% Receiving Induction 3 Dose 2	1%	Beta – SD	MDX010-20
% Receiving Induction 3 Dose 3	1%	Beta – SD	MDX010-20
% Receiving Induction 3 Dose 4	1%	Beta – SD	MDX010-20
% Receiving Induction 4 Dose 1	0.2%	Beta – SD	MDX010-20
% Receiving Induction 4 Dose 2	0.2%	Beta - SD	MDX010-20
% Receiving Induction 4 Dose 3	0.2%	Beta - SD	MDX010-20
% Receiving Induction 4 Dose 4	0.2%	Beta - SD	MDX010-20
Ipilimumab: Days Between Administrations	21		MDX010-20
Survival			
Ipilimumab PFS Parameter Alpha - second curve	-7.2476	Normal - SE 0.354	MDX010-20 (Section 6.3.1)
Ipilimumab OS Parameter Alpha - second curve	-6.081	Multivariate normal covariance matrix:	MDX010-20 (Section 6.3.1)
Ipilimumab OS Parameter Beta - second curve	-0.0032	*Parameter Constant Gamma* Constant 0.03991 Gamma -0.00012 7.14E-07	MDX010-20 (Section 6.3.1)
BSC PFS Parameter Alpha - second curve	-6.4148	Normal - SE 0.302	MDX010-20 (Section 6.3.1)
BSC OS Parameter Alpha - second curve	-6.4148	Normal - SE 0.302	MDX010-20 (Section 6.3.1)

Parameter	Value Used	Distribution	Source
Unit Costs			
Ipilimumab administration 1st attendance	£271	Normal - SD 124*	NHS Reference Costs 09/10 SB13Z-Outpatient
Ipilimumab administration other attendances	£284	Normal - SD 61*	NHS Reference Costs 09/10 SB15Z-Outpatient
Ipilimumab unit cost	£3,750		BMS, 50mg vial cost
Utilities			
Utility of stable disease	0.81	Beta – SD 0.140	EORTC mapped values from MDX010-20
Utility of progressive disease	0.77	Beta – SD 0.162	
Ipilimumab			
Likelihood of Fatigue	7%		Hodi et al + MDX010-20 for G2 diarrhoea and colitis
Likelihood of Diarrhoea (not including colitis)	6%		
Likelihood of Colitis	6%		
Likelihood of Dyspnoea	4%		
Likelihood of Endocrine disorders	4%		
Likelihood of Anaemia	3%		
Cost of Adverse Events			
Cost of Fatigue	£163	Variation between cost ±30%	Advanced Melanoma Resource Use and Costs in Europe PRELIMINARY DRAFT REPORT
Cost of Diarrhoea	£478		
Cost of Colitis	£919		
Cost of Dyspnoea	£0		
Cost of Endocrine disorders	£527, 6 monthly		
Cost of Anaemia	£740		
Management Costs - Component Parts			
Outpatient visits			
Medical oncologist	£129	Normal - SD 24,*	NHS Reference Costs 2010 370
Radiation oncologist	£82	Normal - SD 5,*	NHS Reference Costs 2010 800
General practitioner	£32	Variation between cost ±30%	PSSRU 2010 without qual, inc direct care staff
Palliative care physician	£254	Normal - SD 154,*	NHS Reference Costs 2010 SD04A/SD05A
Psychologist	£81	Variation between cost ±30%	PSSRU 2010 per hour client contact, assumes 1 hour
Plastic surgeon	£80	Normal - SD 28,*	NHS Reference Costs 2010 160

Parameter	Value Used	Distribution	Source
Inpatient stay			
Oncology/general ward	£204	Normal – SD 89.5*	NHS Reference Costs 2010 Weighted average intermediate skin disorders
Palliative care unit	£235	Normal – SD 295.0*	NHS Reference Costs 2010 SD01A/SD03A
Terminal Care			
Terminal care costs	£5,401	Normal – SD 4,409	Improving choice at end of life, Addicott & Dewer (2008)
Home care			
Palliative care physician	£194	Normal – SD 108.3	PSSRU 2010 medical specialist palliative care attendance
Palliative care nurse	£83	Normal – SD 16.4*	NHS Reference Costs 2010 CN202AF
Home aide visits	£72	Normal – SD 8	PSSRU 2010 outpatient non medical specialist palliative care attendance
Laboratory tests			
Complete blood count (CBC)	£3	Normal – SD 1.48*	NHS Reference Costs 2010 DAP823
Complete metabolic panel (CMP)	£1	Normal – SD 0.3*	NHS Reference Costs 2010 DAP841
Lactate dehydrogenase (LDH)	£1	Normal – SD 0.3*	NHS Reference Costs 2010 DAP841
Radiological exams			
CT scan of abdomen/pelvis	£97	Normal – SD 27*	NHS Reference Costs 2010 RA08Z/RA09Z/RA10Z
CT scan of chest	£97	Normal – SD 27*	NHS Reference Costs 2010 RA08Z/RA09Z/RA10Z
MRI of brain	£194	Normal – SD 50*	NHS Reference Costs 2010 RA01Z/RA02Z/RA03Z
CT scan of brain	£97	Normal – SD 27*	NHS Reference Costs 2010 RA08Z/RA09Z/RA10Z
PET/CT scan	£194	Normal – SD 50*	NHS Reference Costs 2010 RA01Z/RA02Z/RA03Z
Bone scintigraphy	£174	Normal – SD 52*	NHS Reference Costs 2010 RA35Z
Echography	£82	Normal – SD 38*	NHS Reference Costs 2010 DAP823

Parameter	Value Used	Distribution	Source
Chest x-ray	£132	Normal – SD 17.8*	NHS Reference Costs 2010 DAP841
Pain Control			
Morphine - Oral	£10	Variation between cost ±30%	Advanced Melanoma Resource Use and Costs in Europe FINAL REPORT
Morphine - IV	£107		
Transdermal patch	£37		
NSAIDs (Ibuprofen)	£1		
Other: Paracetamol	£4		

* Standard deviations calculated using upper and lower quartile values

Extrapolation of trial outcomes

Costs and clinical outcomes were projected beyond the end of follow-up in the MDX010-20 trial to a 30 year time horizon by fitting survival curves to observed failure time data in the MDX010-20 trial, as described in Section 6.3.1.

Summary of assumptions used

Assumption	Justification
Induction Phase: Ipilimumab dose: 3 mg/kg every 3 weeks x 4 Maintenance: None Re-induction: permitted at the time of progression or relapse in those patients who demonstrated stable disease, partial response or complete response to a previous course of therapy.	This complies with the dosing regimen described in the marketing authorisation and the dosing regimens utilised within MDX010-20. Data on the proportion of patients receiving each dose is taken directly from the MDX010-20 trial.
Patients who discontinue ipilimumab are assumed to receive BSC for the remainder of their lifetime.	This represents the path for the majority of patients. Research carried out in the Advanced Melanoma Resource Use and Costs in Europe report indicates that only 10% of patients receive third line therapy if they have responded to second line and only 7% receive third line therapy if they have not responded.
Outcomes for patients receiving BSC can be approximated based on patients receiving gp100	gp100 was included within the MDX010-20 trial under the assumption that this may be an active treatment for metastatic melanoma, however, the trial showed no improvement in efficacy over BSC. It is therefore reasonable to assume that gp100 has equal efficacy to BSC. This assumption is detailed more fully in Clinical Section 5.10.
PFS and OS with ipilimumab and BSC can be modelled using a 2 part curve as described in Section 6.3.1	Parametric models are widely used in economic evaluations; however, in this case they provide a poor fit to the available data due to the nature of the survival curves. A two part curve fit was therefore felt more appropriate to model the survival seen within the trial and potential long term survival. Similar survival curves have been seen in long term metastatic melanoma studies (Atkins 1999) where the majority of patients alive after 18 months remained alive for the follow up duration of 11 years.
The incidence of adverse events was assumed to reflect the observed incidence in the MDX010-20 trial.	Assumption based on the results of the MDX010-20 trial.

The costs of G2+ diarrhoea and colitis are considered. For all other adverse events only the costs of G3+ AEs which had an incidence of greater than 3% were considered	The costs of G1 and 2 AEs (other than the diarrhoea and colitis) are likely to be minor relative compared to the costs and effects of ipilimumab. The inclusion of these costs therefore likely would not have affected model findings. For example, there were 78 G1-2 AEs among ipilimumab patients in the MDX010-20 trial (less than 1 event per patient). Assuming an average cost of ~£120 per event (~the cost of a clinic visit), and no G1-2 AEs with BSC this would add <£120 to the cost of ipilimumab, an increase of less than 0.01% vs. projected incremental costs without consideration of the cost of such events.
Adverse events impacts are accounted for from the 1st cycle of the model	For all adverse events except endocrine disorders their impacts are taken into account for the event duration assuming they happen from day 1 of the model. This is a conservative assumption which does not discount their impact.
Endocrine disorders last for lifetime and accrue costs every six months	A conservative assumption has been made within the model that all patients experiencing an endocrine disorder will continue to incur regular costs associated with the disorder.
Patients experiencing an adverse event have the same mortality profile as other patients	This is a conservative assumption and has little impact as the costs of adverse events are not a key model driver.
Utilities associated with adverse events are accounted for within the trial-based utilities used within the model	Utility decrements for AEs have not been accounted for separately as these are already taken into account within the trial based information used for the utilities of patients with progressive and non-progressive disease. These include the utilities of any adverse events experienced by patients in these health states. When a sensitivity analysis is conducted with literature data, adverse event utility decrements are included in the model from the same source (Beusterien, 2009).
Utility values conditioned on progression are independent of treatment	Data mapped from the EORTC QLQ-C30 and SF-36 questionnaires show little difference between the utilities of patients between treatments, regardless of progression status. A sensitivity analysis is conducted to explore this hypothesis.
Ipilimumab is assumed to be administered every 21 days for 4 doses in a day case setting	MDX010-20 trial protocol and clinical expert opinion. Assumed costs are described in full in section 6.5.6.
30 years approximates a lifetime time horizon for Stage III/Stage IV melanoma patients	The fitted distributions project that less than 6% of patients receiving ipilimumab and less than 0.1% of patients receiving BSC will be alive at 30 years.
After 5 years background mortality is added to the model to represent death from natural causes	As the projections from the curve fits for overall survival for ipilimumab and BSC both asymptote to a value at around 15 years background mortality has been added into the model from the end of the trial data (5 years) in order to represent the natural rate of mortality within the overall population irrespective of disease progression.

6.4 Measurement and valuation of health effects

Patient experience

Effects of the condition on patients' quality of life

More than most other cancers, melanoma can have either an excellent or poor prognosis depending on the stage at which it is identified and treated. This gives rise to two cohorts with quite distinct trajectories and associated psychosocial concerns: one which, following treatment, will return to usual life with ongoing surveillance and concern regarding increased risk of a recurrence; and a second cohort with metastatic melanoma which needs to balance limited potential benefits from ongoing treatment with likely reductions in HRQL at what may be the end of their life (Boyle 2003). As in the case of other cancers, HRQL has been found to be an important factor in melanoma patients, at least when disease is metastatic.

In a longitudinal study with severely ill patients receiving dacarbazine-vindesine with or without cisplatin, Sigurdadottir et al (1996) reported that at pretreatment there was a relatively low symptom burden, good physical and social functioning, moderate psychological distress (mainly anxiety) and a high overall QOL during the past week. Fatigue and pain were the most frequent symptoms reported followed by dyspnoea, neurological symptoms, sweating, loss of appetite and pain. Nine weeks later there was a significant deterioration in performance status and one-third of the study population already had documented progressive disease or had died an early death. This is a much more pronounced and rapid deterioration than reported from comparable studies of other patient groups with advanced cancer. The observed treatment toxicity was considerable during the first 9 weeks of chemotherapy, with 60% of the patients exhibiting clinical evidence of neuropathy. Severe vomiting, oto- and neurotoxicity were noted in 20% and haematological toxicity in 10% of the patients. A substantial dose reduction was needed early in the course of treatment, whereupon haematological toxicity and nausea/vomiting became less of a problem. Objective documentation of severe alopecia remained stable throughout treatment while neuropathy continued as an increasing clinical problem.

Change in HRQL over time

The results of several studies indicate that there are three distinct periods of HRQL impact during the melanoma experience: diagnosis, treatment and follow-up (Cornish et al 2009). The immediate period following diagnosis (i.e. acute survival phase is 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. Importantly, patients also gave worse evaluations of overall personal health. 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. In the follow-up phase, psychological distress can interfere with screening recommendations and preventive behaviours. Approximately a third of patients in different follow-up regimens suffer from continued significant levels of distress, which is comparable with other cancers (Cornish et al 2009). Patients involved in more aggressive treatments report significantly poorer mental and physical functioning.

HRQL data derived from clinical trials

Description of trial based HRQL data

HRQL data were collected in the MDX010-020 trial using both EORTC QLQ-C30 and SF36v2. EORTC QLQ-C30 has extensive evidence available supporting reliability, validity and responsiveness in different cancer populations. In addition, EORTC QLQ-C30 covers similar domains from the rest of the HRQL questionnaires and is a valid generic HRQL instrument, preferred in oncology clinical trials [redacted]

EORTC QLQ-C30 and SF36 scores were collected at Week1, Week 12, and Week 24; however, most subjects did not complete the Week 24 questionnaires. Both questionnaires have been mapped using validation mapping algorithms in line with the NICE reference case, as described in Section 6.3.1 and Section 6.4.4.

Mapping clinical trial HRQL data

Description of mapping exercise

EORTC QLQ-C30 values have been mapped from the 971 trial observations using mapping algorithm 3 defined by Rowen et al (Rowen et al. in press).

The mapping study utilised factor analysis, Rasch analysis and other psychometric analyses on a clinical trial dataset of 655 patients from the VISTA trial with multiple myeloma who completed the EORTC-QLQ questionnaire at each of 1-9 cycles of treatment. Using this data a health state classification system was derived amenable to valuation with a valuation study conducted on 350 members of the UK general population using time trade-off. This mapping algorithm uses a validation dataset using a mid-cycle treatment point with 471 responses.

The mapping uses mapping algorithm 3 from the Rowen et al paper. This algorithm is chosen as it has:

1. A low mean absolute error (0.046)
2. No inconsistencies within the model
3. The lowest number of large errors (>5 or 10% out)

In addition it is recommended by the authors as it more appropriately deals with TTO values for worse than death health states.

Following mapping of individual patient observations the average for each patient for the progressed and not progressed states is calculated and the averages for the overall health states are calculated based upon the individual patient averages in order to avoid bias towards patients with more observations.

963 SF-36 observations have been mapped using the SF-6D algorithm which is based upon 3,518 observed SG valuations from the UK general population across 249 health states using a non parametric Bayesian model. The root mean square error of this model is 0.088 and the model was validated using 3 datasets (Kharroubi et al).

Following mapping of individual patient observations the average for each patient for the progressed and not progressed states is calculated and the averages for the overall health states are calculated based upon the individual patient averages in order to avoid bias towards patients with more observations.

When the values produced by these mapping algorithms are compared to the only available published literature (Beusterien et al) the progression free disease estimates produced by the EORTC-QLQ mapping algorithm are similar (0.80 compared to 0.77) whereas those produced by the SF-6D algorithm are significantly lower (0.64 compared to 0.77).

Neither the EORTC QLQ-C30 mapping or SF-6D mappings decrease markedly on disease progression however - EORTC QLQ-C30 decreases from 0.80 to 0.76 (-4.7%), and SF-6D from 0.64 to 0.62 (-3.3%). This is in contrast to the Beusterien et al data which shows a decrease from 0.77 to 0.59 (-30.5%).

This difference may be due to the unique kinetics of ipilimumab, and that the fact that long-term survivors include patients with progressive disease (PD) according to modified World Health Organization (mWHO) criteria (Maio et al 2010).

HRQL studies

Literature search to identify HRQL studies

The literature search the identify HRQL data is described in Section 6.1.

HRQL studies identified

The systematic review identified one study which included HRQL data for advanced metastatic melanoma patients (Beusterien et al 2009). This study was conducted for a total of 140 participants; 77 from Australia and 63 from the United Kingdom.

A cross-sectional study was conducted for advanced melanoma health states among, as recommended by the UK National Institute for Clinical Excellence, members of the general public (NICE, 2004) using the standard gamble technique and based upon pre-defined health states. The mean respondent age was 45±14 years, and 48% were male.

Four melanoma treatment-related response states, one symptomatic melanoma state, and nine toxicity-related health states were developed on the basis of published literature. Specifically, treatment response status was described on the basis of the World Health Organisation's definition for all cancers (WHO, 1979).

Partial response state was based on a >50% decrease in lesion mass; stable disease was based on a <25% decrease or increase in lesion mass; and PD was based on the appearance of new lesions or increase by >25% in lesion mass. In addition, a best supportive care (BSC) state represented no indicated or desired cancer treatment, and a symptomatic melanoma health state represented symptoms experienced in advanced melanoma.

Toxicity health states were selected on the basis of common grade I/II toxicities (occurring in ≥10% of treated patients) from published and unpublished literature, and

product inserts for ipilimumab, dacarbazine, temozolomide, interleukin-2, fotemustine, and IFN-α. Grade III/IV toxicities were described in two health states: one involving outpatient treatment for 1–2 days and the other involving hospitalisation for 2–5 days. Toxicity health state descriptions were developed using the CTCAE (Cancer Therapy Evaluation Program, 2006).

The health states were described as being treated for cancer (melanoma was not specified), whether or not treatment is working, and changes in tumour size, pain levels, appetite, effort required to perform daily activities, and fatigue. Each of the toxicity descriptions was described in association with partial response so that the respective utility decrements for toxicities could be calculated by subtracting the utility for partial response from the utility of the toxicity state. All health states were labelled with symbols to avoid imposing a predetermined hierarchical order on the states. The descriptions were developed in layperson terms, and health states were refined after an iterative review by five clinical experts, two oncology nurses, three quality-of-life researchers, and a pilot test with individuals from the general public.

Table 33 presents the results from the Beusterien et al study, complete with standard errors.

Table 33: HRQL Results, Beusterien et al

Health State	**All mean (s.e.)**	**Australia mean (s.e.)**	**UK mean (s.e.)**
Clinical response status			
Partial response	0.88 (0.01)	0.91 (0.01)	0.85 (0.02)
Stable disease	0.80 (0.01)	0.83 (0.01)	0.77 (0.02)
Progressive disease	0.52 (0.02)	0.47 (0.03)	0.59 (0.02)
Best supportive care	0.52 (0.02)	0.46 (0.03)	0.59 (0.02)
Utility decrement for toxicity states			
Hair loss (grade I/II)	-0.03 (0.01)	-0.03 (0.01)	-0.03 (0.01)
Skin reaction (grade I/II)	-0.06 (0.01)	-0.08 (0.01)	-0.03 (0.01)
Diarrhoea (grade I/II)	-0.09 (0.01)	-0.11 (0.01)	-0.06 (0.01)
Nausea/vomiting (grade I/II)	-0.10 (0.01)	-0.12 (0.01)	-0.07 (0.01)
Flu-like syndrome (grade I/II)	-0.11 (0.01)	-0.13 (0.01)	-0.09 (0.01)
Stomatitis (grade I/II)	-0.13 (0.01)	-0.14 (0.01)	-0.10 (0.02)
1 day in/outpatient stay for severe toxicity (grade III/IV)	-0.13 (0.01)	-0.14 (0.01)	-0.11 (0.02)
Symptomatic melanoma	-0.16 (0.01)	-0.20 (0.02)	-0.11 (0.02)
2-5 day hospitalisation for severe toxicity (grade III/IV)	-0.17 (0.01)	-0.20 (0.02)	-0.13 (0.02)

The Beusterien et al study uses direct valuation techniques and was carried out in representative sample of the UK population with ‘full health’ as the upper anchor; however, time trade-off methods were not used.

The NICE reference case states:

"When EQ-5D data are not available, methods can be used to estimate EQ-5D utility data by mapping (also known as 'cross-walking') EQ-5D utility data from other HRQL measures included in the relevant clinical trial(s). This can be done if an adequate mapping function can be demonstrated and validated. Mapping should be based on empirical data and the statistical properties of the mapping function should be clearly described.

When EQ-5D utility data are not available, direct valuations of descriptions of health states based on standardised and validated HRQL measures included in the relevant clinical trial(s) may be submitted. In these cases, the valuation of descriptions should use the time trade-off method in a representative sample of the UK population, with 'full health' as the upper anchor, to retain methodological consistency with the methods used to value the EQ-5D."

For this reason in the base case EORTC QLQ-C30 values have been used for non-progressive and progressive disease. Utility decrements for AEs have not been accounted for separately as these are already taken into account within the trial based information used for the utilities of patients with progressive and non-progressive disease. These include the utilities of any adverse events experienced by patients in these health states.

It should be noted that the utility of patients does not fall as far on progression when treated with ipilimumab, when compared with GP100. Additionally patient utility is higher in the pre-progression state (though the model is treatment independent in the base case). It is therefore unlikely that ipilimumab is linked to a decrease in HRQL due to AEs, and in fact, the effect of treatment is likely to be positive towards the patient experience.

Comparison of HRQL data

The key difference between the values in the Beusterien et al paper and the mapped values is the utility ascribed to PD and BSC (which is much lower in Beusterien et al). Section 6.4.4 discusses these differences more fully, and provides a possible explanation for the observed differences.

The SF-6D mapped values are significantly lower than the EORTC-QLQ values for both progressive and progression free disease, with a similar decrement in utility between the health states when compared to the EORTC QLQ-C30 data. These differences are discussed more fully in Section 6.4.4.

The differences in utility data are explored in Sensitivity analysis, and presented in Section 6.7.9.

Adverse events

The impact of adverse events on HRQL

Section 6.4.6 provides a description of the impact of common AEs on HRQL. Utility decrements for AEs have not been accounted for separately in the model as these are already taken into account within the trial based information used for the utilities of patients with progressive and non-progressive disease. These include the utilities of any AEs experienced by patients in these health states.

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

Summary of HRQL values used

Based upon the data available in the base case, the EORTC-QLQ-C30 trial data have been utilised as these are the data which most closely meet the NICE reference case and are relatively consistent with the Beusterien et al values.

Table 34: Summary of quality of life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference to section in submission	Justification
Progression Free Disease	0.80	[0.53, 0.97] Beta distribution	6.3.1, 6.4.4 and 6.4.9	Use of closest trial data to NICE reference case
Progressive Disease	0.76	[0.46, 0.97] Beta distribution	6.4.4, 6.4.6 and 6.4.9	Use of closest trial data to NICE reference case

HRQL has been age adjusted taking the baseline spread of ages from the MDX010-20 trial using the values from Kind et al shown in Table 35; as the average age of patients increases a utility decrement is applied to both health state utilities to reflect the natural decrease in utility associated with increasing age.

Table 35: Kind et al Utilities by Age Band

	Male Utility	Female Utility	Average Utility	% of Patients at Year 1
Under 25	0.94	0.94	0.94	1%
25-34	0.93	0.93	0.93	6%
35-44	0.91	0.91	0.91	14%
45-54	0.84	0.85	0.84	17%
55-64	0.78	0.81	0.79	30%
65-74	0.78	0.78	0.78	25%
75+	0.75	0.71	0.73	6%

Input from clinical experts

Four leading clinical experts were approached in order to validate the economic model during individual face-to-face informal 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.

HRQL experienced in each health state

Patients are assumed to experience a constant health related quality of life in the two health states based upon the available trial information.

Health effects excluded from the analysis

No health effects were excluded from the analysis.

Baseline HRQL

The baseline quality of life assumed is 'non progressive disease' which is consistent with the health states.

Changes in HRQL over time

HRQL in health states is assumed to remain constant over time. However, the mean utility decreases over time due to disease progression and death (both disease specific and background mortality).

Have the values in Sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No values have been amended.

6.5 Resource identification, measurement and valuation

NHS costs

How is the clinical management of the condition currently costed in the NHS?

The clinical management of patients with metastatic melanoma includes routine monitoring and follow-up as well as treatment of complications associated with the condition. Such treatment may include inpatient, day case, and outpatient treatments that would fall under a variety of HRG codes. HRG codes and corresponding reference costs used in the model are described in the following sections.

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

There are no HRG and PbR codes specific to ipilimumab. Ipilimumab is administered as a 90 minute i.v. infusion and therefore requires a clinic visit for each administration. Because of the infusion time, it was assumed that ipilimumab would be administered on a day case basis.

Administration costs for ipilimumab were therefore based on NHS reference costs for day case administration of chemotherapy (HRG SB13Z Deliver more complex Parenteral Chemotherapy at first attendance (£271), and HRG SB15Z (£284) - Deliver subsequent elements of a chemotherapy cycle). These were used in the calculation of the costs of ipilimumab administration.

Resource identification, measurement and valuation studies

Literature search to identify resource data

A broad search identified no papers relating to the costs of resource use relating to ipilimumab. This is likely due to its current unlicensed status, and limited clinical experience. The search strategy is described in Appendix 12.

In order to provide assumptions to power the model, the MELODY study was commissioned, as described in Section 6.2.3 and 6.3.5.

Input from clinical experts

Resource use costings are based on a survey of five UK clinicians carried out as part of the Advanced Melanoma Resource Use and Costs in Europe study.

The population of interest was all individuals in the UK diagnosed with unresectable stage III or stage IV melanoma who received active treatment with systemic therapy, outside of a clinical trial, or who received any form of supportive care. In MELODY, the majority of health resource utilisation variables were only recorded for this population, so broader eligibility criteria were not considered.

[redacted]

Intervention and comparators' costs

Costs of ipilimumab treatment are presented in Table 36. Ipilimumab was assumed to be administered as an intravenous infusions as an outpatient visit. As per the dosage schedule in MDX010-20, the dosing is assumed to be 3mg/kg for every 21 days for 4 doses. Patients were eligible for reinduction if:

- They have progressed and in response to treatment cycle 1 they had evidence for stable disease of ≥ 3 months duration (beginning Week 12) or they had an initial objective response (PR or CR) to the first cycle of therapy
- They had not experienced a Grade 3 non-skin irAE, except for endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy or any related Grade 4 toxicity of any organ.

Product wastage (i.e. no vial-sharing) is considered in the model and in the base case the model rounds up patient administrations to the nearest vial. This is a conservative assumption. Vial-sharing scenarios (i.e. reduced/no product wastage) are built into the model, for example, we can choose to use methods such as 'cost per mg' or 'round cost up or down to the nearest vial'. It has to be noted that if the vial sharing is allowed which is highly likely in the NHS accordingly to oncologists, the ICER will be reduced significantly (e.g. from £60,737 to £55,824).

Patient level analysis of the weight of UK clinical trial patients in MDX010-20 (n=55), and the weight of UK patients in the ipilimumab compassionate use program (n=258), from these weights, the mean number of vials required (assuming no vial sharing) is calculated. Summary results of this analysis are presented in Table 36, with the full calculations presented in the economic model (tab 'Weight Data').

Average weights do not vary significantly over the various available data sources. The average weight for all patients in the MDX010-20 trial was 80.1 kg, compared to the average weight for UK patients in the trial of 81.7 kg and the average weight from the named patient programme of 77.8kg.

It was assumed that no vial sharing was allowed and that doses were always rounded up to the nearest full vial in the base case. This assumption and the assumption on patient weight are varied in sensitivity analysis (Section 6.7.9).

Table 36: Unit costs associated with the technology in the economic model – vials of ipilimumab required (assuming dose of 3 mg/kg)

	MDX010-20 Trial UK Patients	Compassionate Use Programme Patients	Total
3 x 50mg	3 (5%)	3 (1%)	6 (2%)
1 x 200mg	9 (16%)	58 (22%)	67 (21%)
1 x 200mg + 1 x 50mg	19 (35%)	108 (42%)	127 (41%)
1 x 200mg + 2 x 50mg	14 (25%)	69 (27%)	83 (27%)
1 x 200mg + 3 x 50mg	9 (16%)	17 (7%)	26 (8%)
2 x 200mg	1 (2%)	3 (1%)	4 (1%)
Average Vials Used	**1.51 x 50mg + 0.96 x 200mg**	**1.19 x 50mg + 1 x 200mg**	**1.24 x 50mg + 0.99 x 200mg**

The confirmed list price of ipilimumab is £3,750 per 50mg vial and £15,000 per 200mg vial. The costs of administration of ipilimumab were based on NHS reference costs (NHS Reference Costs, 2010).

Health state costs

The costs of disease management were estimated using a micro costing approach for 5 different categories:

- On Initiation of Treatment – one-off
- On Treatment Pre Progression – monthly
- BSC Cost - monthly
- On Progression Cost – one-off
- Palliative Care Off Treatment – monthly
- Terminal Care – one-off

Routine care pre-progression is costed for both ipilimumab arm using the 'on treatment pre progression cost' and routine care post progression and for BSC was costed using the BSC cost. A one-off cost was applied for ipilimumab patients on treatment initiation and for all patients on progression and also for terminal care upon death (taken from recent research funded by Marie Curie Cancer Care; Addicott & Dewer, 2008). The cost of palliative care (£838 per month) is applied for both arms for 4 months prior to death.

The monthly cost of BSC is assumed to be the same as for patients on treatment except that patients do not receive a monthly cost for administration of treatment (the HRG code) and instead carry out visits to the medical oncologist as defined within the Oxford Outcomes clinician survey (2011).

These costs were derived from the resource use estimates from the Oxford Outcomes clinician survey (2011) and the application of appropriate HRG codes and PSSRU information to cost each resource use element. Costs are summarised in Table 37; standard deviations are presented where these were available from the source or have been calculated from available upper and lower quartile information (NHS Reference cost data).

These costs have been utilised as they are the most accurate costs currently available for the various stages of metastatic melanoma. The costs of medical oncologist and radiation oncologist at initiation of treatment and during treatment are assumed to be included in the administration HRG codes in the ipilimumab arm.

Table 37: Disease management microcosting information

Treatment Type	Unit	Cost	SD	Code	Source		% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use
							On Initiation of First Line Treatment		On Treatment Pre Progression - Monthly		BSC - Monthly		On Progression Cost - One Off		Palliative Care - Monthly		Terminal Care - On Death	
Outpatient visits																		
Medical oncologist	Visit	£129	£24	370	NHS Reference Costs 2010						86%	1.9	75%	2.40	63%	0.90		
Radiation oncologist	Visit	£82	£5	800	NHS Reference Costs 2010						6%	1	6%	1.50	6%	1.50		
General practitioner	Visit	£32		NA	PSSRU 2010	without qual, inc direct care staff	4%	2	4%	2	4%	2	3%	2	78%	1.90		
Palliative care physician	Visit	£254	£154	SD04A/SD05A	NHS Reference Costs 2010								15%	1	29%	1.20		
Psychologist	Visit	£81		NA	PSSRU 2010	per hour client contact, assumes 1 hour									4%	3		
Plastic surgeon	Visit	£80	£30	160	NHS Reference Costs 2010		2%	1.50	2%	1.50	2%	1.50	2%	1.50				
Inpatient stay																		
Oncology/general ward	Day	£204	£89.53	Weighted average intermediate skin disorders	NHS Reference Costs 2010		6%	2.80	5%	1.30	5%	1.30	17%	3.40	14%	3.60		
Palliative care unit	Day	£235	£295	SD01A/SD03A	NHS Reference Costs 2010										26%	4		
Terminal Care																		
Terminal Care	Patient	£5,401	£4,409		Improving choice at end of life, Kings Fund, 2008 Inflated to 2010 costs using PSSRU 2010												100 %	1
Home care																		
Palliative care physician	Visit	£194	£108	NA	PSSRU 2010	medical specialist palliative care attendance									24%	1		
Palliative care nurse	Visit	£83	£16.40	CN202AF	NHS Reference Costs 2010										58%	1.40		

Treatment Type	Unit	Cost	SD	Code	Source		% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use
							On Initiation of First Line Treatment		On Treatment Pre Progression - Monthly		BSC - Monthly		On Progression Cost - One Off		Palliative Care - Monthly		Terminal Care - On Death	
Home aide visits	Visit	£72	£8	NA	PSSRU 2010	outpatient non medical specialist palliative care attendance									22%	7.30		
Laboratory tests																		
Complete blood count (CBC)	Test	£3	£1.48	DAP823	NHS Reference Costs 2010		100%	1.20	100%	1.30	100%	1.30	90%	1.80				
Complete metabolic panel (CMP)	Test	£1	£0.30	DAP841	NHS Reference Costs 2010		100%	1.20	95%	1.30	95%	1.30	90%	1.80				
Lactate dehydrogenase (LDH)	Test	£1	£0.30	DAP841	NHS Reference Costs 2010		100%	1.20	95%	1.30	95%	1.30	90%	1.80				
Radiological exams																		
CT scan of abdomen/pelvis	Test	£97	£27.29	RA08Z - RA10Z	NHS Reference Costs 2010		100%	1	96%	0.40	96%	0.40	76%	1.10				
CT scan of chest	Test	£97	£27.08	RA08Z - RA10Z	NHS Reference Costs 2010		100%	1	96%	0.40	96%	0.40	76%	1.10				
MRI of brain	Test	£194	£50.13	RA01Z/RA02Z/RA03Z	NHS Reference Costs 2010		6%	1	21%	0.30	21%	0.30	22%	0.70				
CT scan of brain	Test	£97	£26.87	RA08Z/RA09Z/RA10Z	NHS Reference Costs 2010		41%	1	11%	0.20	11%	0.20	29%	1.10				
PET/CT scan	Test	£194	£49.93	RA01Z/RA02Z/RA03Z	NHS Reference Costs 2010		5%	1	2%	0.40	2%	0.40	2%	0.70				
Bone scintigraphy	Test	£174	£51.90	RA35Z	NHS Reference Costs 2010		19%	1	1%	0.30	1%	0.30	2%	0.70				
Echography	Test	£82	£37.62	RA23Z - RA27Z	NHS Reference Costs 2010		6%	1	12%	0.30	12%	0.30	12%	0.30				
Chest x-ray	Test	£132	£17.80	RA16Z	NHS Reference Costs 2010		20%	1	30%	1.10	30%	1.10	10%	0.70				
Pain Control																		
[redacted]																		
[redacted]																		
[redacted]																		

Treatment Type	Unit	Cost	SD	Code	Source	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use
						On Initiation of First Line Treatment		On Treatment Pre Progression - Monthly		BSC - Monthly		On Progression Cost - One Off		Palliative Care - Monthly		Terminal Care - On Death	
[redacted]																	
[redacted]																	

Datasource: [redacted]

Improving choice at end of life, Kings Fund, 2008

Table 38: Unit costs associated with the technology in the economic model

Items	Intervention (confidence interval)	Reference to section in submission	Comparator 1 (confidence interval)	Reference to section in submission
Drug costs	£3,750 for 50mg vial £15,000 for 200mg vial	Section 1.10 and 1.11	£0 - BSC assumed no drug costs	Section 6.5.5
Treatment initiation cost	£365 (£191, £538)	Section 6.5.5	£0 - BSC assumed no treatment initiation	Section 6.5.5
Drug administration costs	£271 (£67 - £474) 1st administration £284 (£184 - £384) subsequent administrations	Section 6.5.2	£0 - BSC assumed no drug administration	Section 6.5.2
Monthly cost of routine treatment pre progression	£162 (£92, £231)	Section 6.5.5	£378 (£244, £511)	Section 6.5.5
Cost on progression	£648 (£338, £958)	Section 6.5.5	£648 (£338, £958)	Section 6.5.5
Monthly cost of treatment post progression prior to palliative care	£378 (£244, £511)	Section 6.5.5	£378 (£244, £511)	Section 6.5.5
Monthly cost of palliative care (4 months)	£838 (£295, £1642)	Section 6.5.5	£838 (£295, £1642)	Section 6.5.5
Terminal care cost	£5,401 (£0, £13,752)	Section 6.5.5	£5,401 (£0, £13,752)	Section 6.5.5

Datasource: Oxford Outcomes (2011), Improving choice at end of life, King's Fund (2008)

As described in Section 6.5.5 costs are assigned to each health state according to the treatment given and shown in Table 39.

Table 39: List of health states and associated costs in the economic model

Health states	Items	Value	Reference to section in submission
Progression Free Disease	Drug Costs	Ipilimumab - £19,565 per dose BSC – £0	6.5.5
	One off Treatment Initiation Cost	Ipilimumab - £365 BSC – £0	6.5.5
	Drug Administration	Ipilimumab - £271 first admin, £284 per admin thereafter BSC – £0	6.5.5
	Routine Treatment per month	Ipilimumab - £162 BSC – £378	6.5.5
Progressive Disease	One off Cost on Progression	£648	6.5.5
	Routine Treatment per month	£378	6.5.5

Health states	Items	Value	Reference to section in submission
	Palliative Care per month (4 months before death)	£838	6.5.5
Death	One off Terminal Care Cost	£5,401	6.5.5

Adverse-event costs

The costs utilised for adverse events have been taken from research conducted by Oxford Outcomes with five UK clinicians (Advanced Melanoma Resource Use and Costs in Europe, Oxford Outcomes). The costs are based upon a microcosting approach which estimates the proportion of patients treated as inpatients versus outpatients for each condition and assigns a cost to each type of treatment.

The costs for endocrine disorders are assumed to be incurred every six months as this is a lifetime condition; all other adverse events are only assumed to incur costs once at the start of the model.

Table 40 provides a summary of the adverse events costs used in the model. All costs presented below are per patient per episode.

Table 40: List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference to section in submission
Fatigue	Inpatient Cost & %	[redacted]	
	Outpatient Cost & %	[redacted]	
	Average Cost per Patient	[redacted]	
Diarrhoea	Inpatient Cost & %	[redacted]	
	Outpatient Cost & %	[redacted]	
	Average Cost per Patient	[redacted]	
Colitis	Inpatient Cost & %	[redacted]	
	Average Cost per Patient	[redacted]	
Dyspnoea	Average Cost per Patient	[redacted]	
Anaemia	Inpatient Cost & %	[redacted]	

Adverse events	Items	Value	Reference to section in submission
	Outpatient Cost & %	[redacted]	
	Average Cost per Patient	[redacted]	
Endocrine Disorders	Inpatient Cost & %	[redacted]	
	Average Cost per Patient	[redacted]	

Miscellaneous costs

There are no additional costs in the model that have not already been described. Personal and social service costs have not been considered but are not expected to be significant, as the majority of the financial burden in advanced melanoma falls on the NHS.

6.6 Sensitivity analysis

Uncertainty around structural assumptions

A list of alternative scenarios is presented in Table 41.

Table 41: Comprehensive list of analyses presented

Scenario number	Rationale
1	Discount rate 0%
2	Revised comparator to Current Practice or suggested alternative comparators This takes into account the current mix of treatments utilised for 2nd line treatment of metastatic melanoma
3	Impact of changing the source of the utilities in the model This scenario explores the impact of utility using the Beusterien et al values for both non progressive and progressive disease (worst case) and the SF-6D values for non progressive and progressive disease (best case) This section also presents the impact of using drug specific utilities and the impact of age adjusting the utility values
4	Effect of dosing assumptions All patients receive all 4 doses; setting the mean ipilimumab dose to be equal to the maximum ipilimumab dose i.e. all patients continue to receive treatment regardless of disease progression or death. This is a conservative analysis, in order to ascertain the maximum possible cost of ipilimumab therapy to the NHS. Increased or decreased reinduction: this explores the impact of reinduction upon the ICER
5	Impact of curve fit assumptions; the key assumption in this model is the curve fit used for overall survival and progression free survival This takes into account the impact of the type of curve used to model the second half of the broken curve, Weibull curve has been used for all curves as a comparator, and the impact of including general population mortality after year 5. This also takes into account the impact of utilising a one curve fit on the ICER (for both arms and just the BSC arm) using the curves with the best AIC and also a Weibull curve

6	Impact of source of ipilimumab data; this explores the impact of using data from the individual arms of the MDX010-20 trial rather than using the combined data from the two arms. In both cases the two part curves with the best AICs have been selected following the procedure used in the base case.
7	Impact of time horizon; the impact of the utilisation of a variety of time horizons from 15 years to lifetime.
8	Impact of source of weight data; this explores the impact of using weight data from the two different available sources: the compassionate use programme and the UK patient data from the MDX010-20 trial.

Deterministic sensitivity analysis

Deterministic analysis was conducted for the following key variables using the 5% and 95% confidence intervals for the variables except where it is indicated otherwise:

- Overall survival curve coefficients
- Progression free survival curve coefficients
- Patient starting age – this uses the minimum and maximum ages from the published randomised controlled trials in the disease area analysed in the systematic reviews (47 and 64 years)
- Proportion of patients who are male - this uses the minimum and maximum from the published randomised controlled trials in the disease area analysed in the systematic reviews (43 and 71%)
- Patient body weight
- Price of ipilimumab – variation ±25%
- Administration cost of ipilimumab
- Cost of treatment initiation
- Cost of progression
- Monthly cost pre progression
- Monthly cost of BSC
- Costs of terminal care
- Costs of adverse events
- Utilities of stable and progressive disease
- Utility decrements for adverse events
- Proportion of patients receiving each dose of ipilimumab

The only parameter omitted from sensitivity analysis was the dose in mg/kg of ipilimumab (as this is fixed).

Probabilistic sensitivity analysis

Given the uncertainty in this evaluation, and the differing impact of structural changes on not only the ICER, but probability of cost-effectiveness and shape of the cost-effectiveness acceptability curve, a thorough PSA been conducted which includes the uncertainty around all variables except for the patient age, proportion of males and bodyweight (as these are stable at a population level), with the variability between patients already accounted for in wastage calculations), and cost and dose in mg/kg of ipilimumab (as this is fixed).

PSA was conducted by repeated sampling from the distributions specified in Section 6.3.6. For the PSA, 1,000 Monte-Carlo simulations were performed as this should provide sufficient runs to allow PSA results to stabilise (Batty & Paulden, 2010).

6.7 Results

Clinical outcomes from the model

Summary of clinical outcomes from the model

Table 42 presents the results of the economic model and clinical trial for the outcomes achieved in MDX010-20 for ipilimumab patients and BSC patients (assumed to correspond to gp100 treated patients).

The mean overall survival that is modelled for ipilimumab is higher than the mean overall survival in the clinical trial, as at the end of the clinical trial 16% of the patients who had not been censored were still alive. This means that their actual overall survival time is not taken into account in the clinical trial results. This is not the case for BSC where only 5% of patients were still alive at the end of the trial, and explains why the difference in the mean model results is much smaller for BSC than it is for ipilimumab.

See Section 6.3.1 for a comparison of the model fit based solely upon the timeframe for which clinical data are available.

Table 42: Summary of model results compared with clinical data - days

Outcome	Mean clinical trial result	Mean model result	Median result clinical trial	Median result model
Ipilimumab PFS	186	202	85	85
Ipilimumab post-progression survival	341	501	218	218
Ipilimumab OS	528	703	303	303
BSC PFS	121	113	88	88
BSC post-progression survival	223	268	108	108
BSC overall survival	344	381	196	196

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.

Not applicable.

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.

QALYs are generated in the model based on the estimated proportion of patients in each health state (pre-progression, post-progression) on a per day basis.

The proportion of patients in each health state is estimated through a two part curve fit, based on curves calculated from patient level data (see the process detailed in Section 6.3.1).

Life years and QALYs accrued for each clinical outcome

Table 43 illustrates model outputs, broken down by clinical outcome and treatment.

Table 43: Model outputs by clinical outcomes and treatment arm - discounted

Outcome	LY	QALY	Cost (£)
Ipilimumab PFS	0.60	0.48	£78,739
Ipilimumab post progression	2.58	1.90	£17,449
Ipilimumab OS	3.19	2.38	£96,188
BSC PFS	0.31	0.25	£1,908
BSC post progression	1.02	0.76	£10,929
BSC OS	1.33	1.01	£12,837

Disaggregated incremental QALYs and costs

Table 44, Table 45 and Table 46 provide disaggregated results for the estimated incremental costs and benefits of ipilimumab.

Table 44: Summary of QALY gain by health state - discounted

Health state	QALY Intervention (X)	QALY Comparator (Y)	Increment	Absolute increment	% absolute increment
Progression free	0.48	0.25	0.23	0.23	17%
Post progression	1.90	0.76	1.14	1.14	83%
Total	2.38	1.01	1.37	1.37	100%

Table 45: Summary of costs by health state - discounted

Health state	Cost Intervention (X)	Cost Comparator (Y)	Increment	Absolute increment	% absolute increment
Progression free	£78,739	£1,908	£76,831	£76,831	92%
Post progression	£17,449	£10,929	£6,520	£6,520	8%

Health state	Cost Intervention (X)	Cost Comparator (Y)	Increment	Absolute increment	% absolute increment
Total	£96,188	£12,837	£83,351	£83,351	100%

Table 46: Summary of predicted resource use by category of cost - discounted

Item	Cost Intervention (X)	Cost Comparator (Y)	Increment	Absolute increment	% absolute increment
Technology cost	£72,171	£0	£72,171	£72,171	85.59%
Administration cost	£1,035	£0	£1,035	£1,035	1.23%
Pre-progression cost	£3,801	£1,751	£2,050	£2,050	2.43%
Progression cost	£12,278	£5,271	£7,007	£7,007	8.31%
Terminal care cost	£5,171	£5,658	-£487	£487	0.58%
Adverse event cost	£1,732	£157	£1,575	£1,575	1.87%
Total	**£96,188**	**£12,837**	**£83,351**	**£84,325**	**100%**

Base-case analysis

Summary of results

Base case results are presented in Table 47.

Table 47: Base-case results

Technology	Total			Incremental			ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£12,837	1.33	1.01				
Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737

The committee should also be mindful that the list price or the product has not been confirmed at this stage, and is therefore explored further in Section 6.7.7 as BMS look to work with NICE in order to make this innovative medicine available to patients.

Despite ipilimumab having a large net QALY benefit (an increase of 135%), the cost of the treatment takes it above traditionally accepted NICE thresholds of £20,000 to £30,000 per QALY. This however should be considered in the context of the innovative nature of the technology, and the life-extending properties of ipilimumab – the estimated gain in excess of 1 QALY places ipilimumab amongst the some of the most significant breakthrough technologies assessed by NICE such as trastuzumab, sunitinib and rituximab, with the survival gains seen with ipilimumab qualifying the product under the NICE 'End of Life' criteria (NICE, 2009).

The innovative nature of the product is discussed further in Section 2.

Sensitivity analyses

Deterministic sensitivity analysis

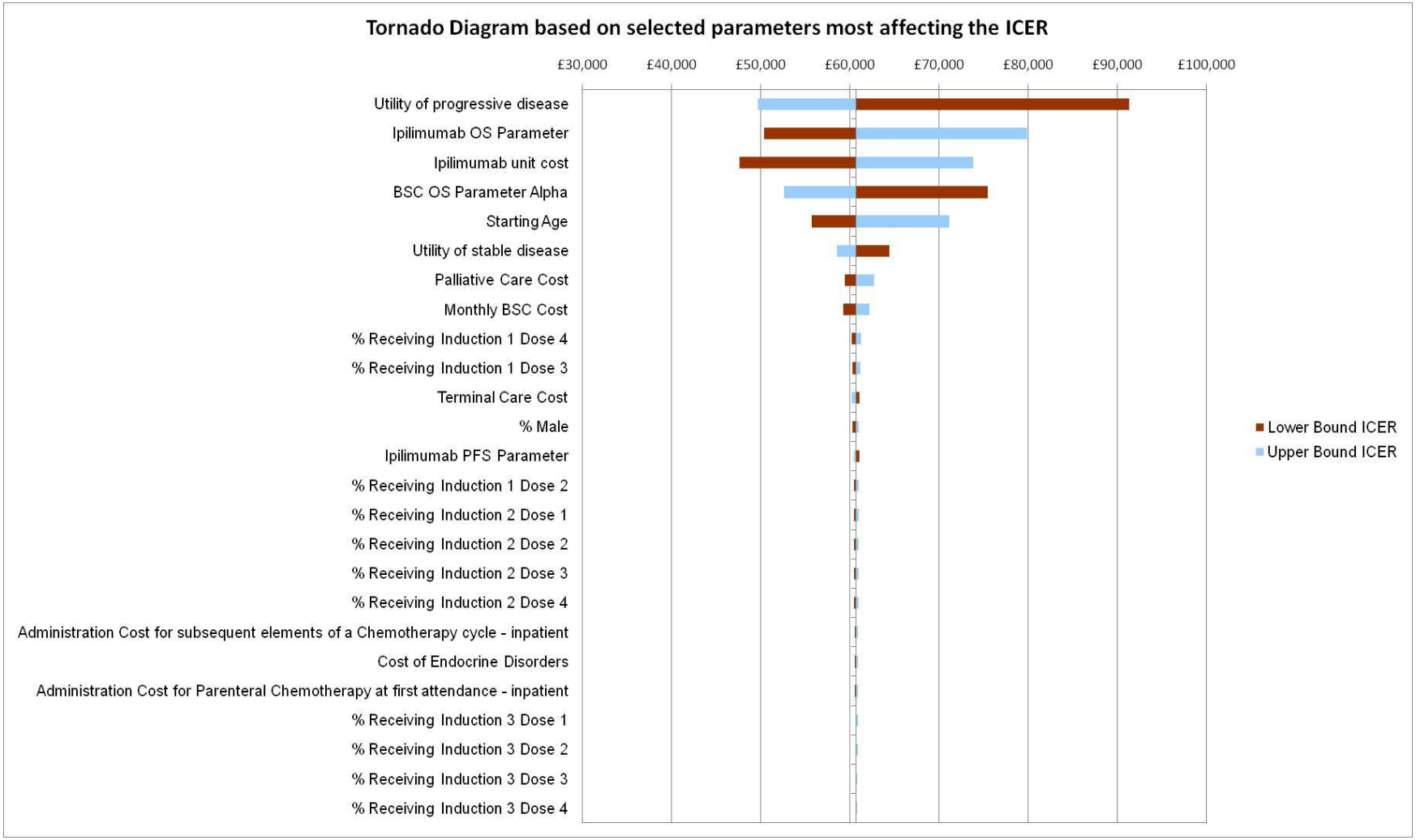
Figure 27 shows the results of the deterministic sensitivity analysis for all variables that produced a change of greater than or equal to £200 in the ICER.

The input which most affects the ICER is the utility assumed for PD. An increase in the utility assumed for progressive disease reduces the ICER (as patients live longer in progressive disease in the ipilimumab arm) and conversely a reduction in the utility assumed for progressive disease increases the ICER.

Other variables which significantly affect the ICER are:

- The curve fit parameters assumed for overall survival for ipilimumab - as the majority of the benefits associated with ipilimumab come from increased survival over BSC
- The cost of ipilimumab – as this forms a high proportion of the total costs on the ipilimumab arm
- The curve fit parameters assumed for overall survival for BSC - as the majority of the benefits associated with ipilimumab come from increased survival over BSC
- The patient's starting age – as this affects the rate at which patients suffer all-cause mortality and therefore the length of time over which the overall survival benefits associated with ipilimumab can be accrued

Figure 27 Tornado diagram presenting results of sensitivity analysis for all variables that cause a change of ≥ ± £200



In addition deterministic sensitivity analysis is shown separately in Table 48 to Table 50 for key variables:

- Numbers of vials required per patient and vial sharing assumptions
- Utility of progressive disease

In each table the base case assumption is highlighted in bold text.

The dose of ipilimumab given per patient per induction also has a large impact on the ICER with the minimum dose given in the trial and compassionate use programme resulting in an ICER of £38,387 and the maximum dose given resulting in an ICER of £88,788. The risk surrounding the dose is evenly distributed between upside and downside risk. Vial sharing has the potential to reduce the ICER by approximately £4,900 and the use of the closest vial size has the potential to reduce the ICER by approximately £4,800 – this may happen in normal clinical practice.

Using a lower utility for progressive disease increases the ICER. In the worst likely case the ICER increases by approximately £13,100. The assumption with the model for the utility of progressive disease contains more downside than upside risk; however, the utility used meets the NICE reference case and has been validated by clinicians.

Table 48: Impact of Vial Sharing Assumptions

Vial Sharing Assumptions with Average Dose	ICER
No Vial Sharing - Round Up	**£60,737**
No Vial Sharing - Round to Nearest	£55,939
Vial Sharing Allowed	£55,824

Table 49: Impact of Dose Required

Number of Vials	ICER
3 x 50mg	£38,387
1 x 200mg	£48,467
1 x 200mg + 1 x 50mg	£58,548
1.24 x 50mg + 0.99 x 200mg	**£60,737**
1 x 200mg + 2 x 50mg	£68,628
1 x 200mg + 3 x 50mg	£78,708
2 x 200mg	£88,788

Table 50: Impact of the Utility of Progressive Disease

Utility of Progressive Disease	ICER
0.6	£73,854
0.625	£71,491
0.65	£69,275
0.675	£67,192
0.7	£65,231
0.725	£63,381
0.75	£61,633

Utility of Progressive Disease	ICER
0.771	**£60,737**
0.775	£59,979
0.8	£58,411

Probabilistic sensitivity analysis

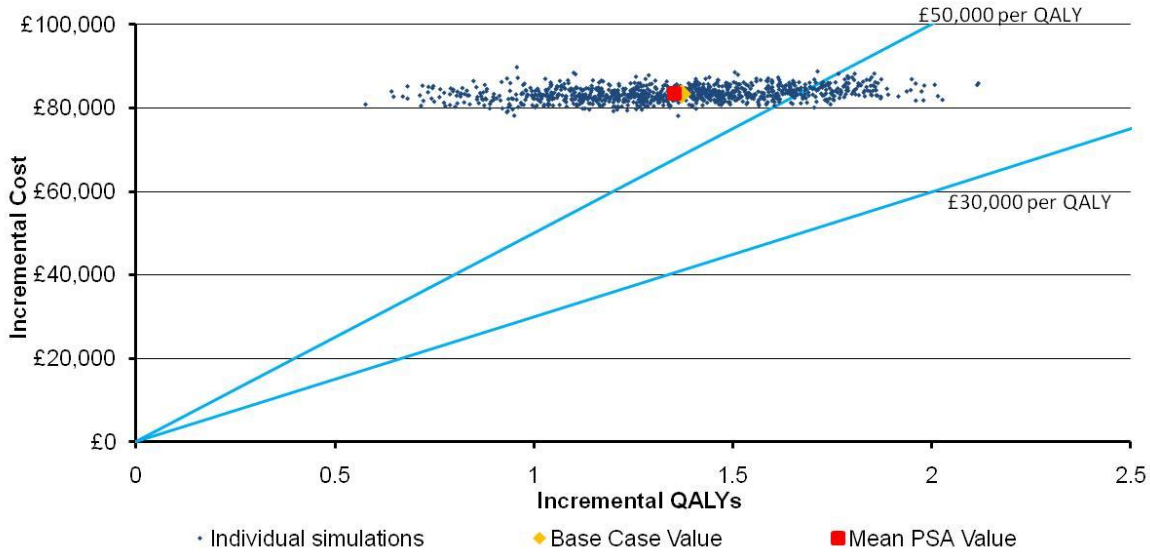
A scatter plot of PSA results is shown in Figure 28. The main source of variance in the model is in the QALYs gained between the two treatment arms. This is consistent with the key sources of uncertainty identified in the deterministic sensitivity analysis (relating to the efficacy of treatment).

The mean PSA value lies very close to the model's base case value (as can be seen below) indicating that model uncertainty is relatively evenly distributed (the ICER is equally as likely to be below the base case value as above it).

The cost effectiveness acceptability curve (CEAC) shows that at the £50,000 per QALY threshold, there is an approximately 14% chance ipilimumab is cost-effective with a median ICER of £61,338.

These figures should be considered when appraising the life-extending nature of ipilimumab in advanced melanoma. In all cases the QALY difference between the two arms is in favour of ipilimumab.

Figure 28 Scatterplot of PSA results (1,000 simulations)



Scenario analysis

Table 51 to Table 58 present the results of the structural sensitivity analysis and scenario analysis.

Table 51 shows that decreasing the discount rate reduces the ICER – as the benefits of ipilimumab in the longer term in the base case are discounted to a large degree, while

costs are incurred within the first year of the model, and therefore are unaffected by discounting.

Table 51: No discounting, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
Discount 0%	BSC	£14,329	1.63	1.22					
	Ipilimumab	£102,534	4.44	3.28	£88,205	2.81	2.06	£42,871	£42,871

Table 52 shows the ICERs when comparing to the various different estimates of current practice and the suggested alternative comparators of paclitaxel, paclitaxel + carboplatin and carboplatin. In all cases the ICER is reduced as Korn et al (2008) indicates than none of the current potential comparators have an efficacy greater than BSC, therefore the use of an alternative comparator increases the cost associated with treatment in the comparator arm without increasing efficacy. Assumptions relating to comparator treatments (such as costs and adverse events profiles) can be found in Appendix 15.

Table 52: Scenario 2: Alternative comparators, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
Collinson	Current Practice	£20,204	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£75,984	1.86	1.37	£55,369	£55,369
IMS	Current Practice	£14,519	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£81,668	1.86	1.37	£59,511	£59,511
MELODY	Current Practice	£14,121	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£82,067	1.86	1.37	£59,802	£59,802
Oxford Outcomes	Current Practice	£16,322	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£79,866	1.86	1.37	£58,198	£58,198
Paclitaxel	Paclitaxel	£24,513	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£71,674	1.86	1.37	£52,229	£52,229
Paclitaxel + Carboplatin	Paclitaxel + Carboplatin	£36,915	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£59,273	1.86	1.37	£43,192	£43,192
Carboplatin	Carboplatin	£19,063	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£77,125	1.86	1.37	£56,201	£56,201

Table 53 presents the differences in the ICER dependent on the source of utilities used. Use of the utilities from the SF-6D and Beusterien et al increases the ICER by approximately £14,350 and £15,600, respectively. It can be seen that the use of drug

specific utilities would decrease the ICER by approximately £3,200 (as utilities are marginally higher for ipilimumab patients) and the effect of adjusting the utilities for age (or not) is relatively small.

Table 53: Alternative utility estimates, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
Beusterien et al UK Utilities	BSC	£12,837	1.33	0.82					
	Ipilimumab	£96,188	3.19	1.92	£83,351	1.86	1.09	£76,340	£76,340
SF-6D Utilities	BSC	£12,837	1.33	0.81					
	Ipilimumab	£96,188	3.19	1.92	£83,351	1.86	1.11	£75,098	£75,098
Drug Specific EORTC Utilities	BSC	£12,837	1.33	0.96					
	Ipilimumab	£96,188	3.19	2.41	£83,351	1.86	1.45	£57,502	£57,502
EORTC Utilities unadjusted for age	BSC	£12,837	1.33	1.03					
	Ipilimumab	£96,188	3.19	2.46	£83,351	1.86	1.43	£58,310	£58,310

Table 54 presents the differences in the ICER if all patients receive all 4 doses of ipilimumab during the first induction. This represents a scenario of maximum dosing beyond what would be expected in clinical practice (due to AE dropouts, disease progression, and death). The ICER does not increase substantially, while increasing or decreasing the proportion of patients receiving re-induction also does not affect the ICER substantially.

Table 54: Scenario 4: Maximum dosing assumption, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
Patients Receive all 4 Doses of Ipilimumab	BSC	£12,837	1.33	1.01					
	Ipilimumab	£109,122	3.19	2.38	£96,285	1.86	1.37	£70,163	£70,163
50% more patients receive each reinduction	BSC	£12,837	1.33	1.01					
	Ipilimumab	£99,567	3.19	2.38	£86,730	1.86	1.37	£63,200	£63,200
50% less patients receive each reinduction	BSC	£12,837	1.33	1.01					
	Ipilimumab	£92,808	3.19	2.38	£79,971	1.86	1.37	£58,275	£58,275

Table 55 presents the ICERs associated with various possible curve fits. It can be seen that curve fit does have a substantial effect on the ICER, particularly in the case of utilising the one part curve fit in the ipilimumab arm (which as discussed in Section 6.3.1 does not fit the trial data well).

Using a one part curve fit for the BSC arm reduces the ICER by approximately £16,000 – a result which is not substantially impacted by the curve type selected and indeed may be appropriate as seen in Section 6.3.1 and Appendix 14.

The use of background mortality to model survival after 5 years also has a large impact – the use of different curve fits without background mortality can either reduce the ICER (in the case of the curves with the best AIC) or substantially increase the ICER (in the case of the use of Weibull curves).

The curve fit used for overall survival for ipilimumab as part of the two part curve fit does not have a substantial impact on the ICER when mortality is included within the model, using a Weibull curve rather than the best fitting curve increases the ICER by approximately £8,300. The curve fit with the best fit to the data (using AIC) has been chosen as the model base case which is detailed in Section 6.3.1.

Removing the assumption that patients living to 60 months (5 years) experience long term survival within the BSC arm (this assumption is maintained on the ipilimumab arm) decreases the ICER by approximately £9,300 when the best fitting curves are selected (Table 55).

Table 55: Scenario 5: Alternative curve fits, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
One Curve Fit Both Arms – Best AIC without Background Mortality	BSC	£11,036	0.92	0.71					
	Ipilimumab	£88,480	1.70	1.30	£77,444	0.78	0.59	£131,783	£131,783
One Curve Fit Both Arms – Weibull without Background Mortality	BSC	£10,840	0.89	0.69					
	Ipilimumab	£87,085	1.40	1.08	£76,245	0.51	0.39	£194,895	£194,895
One Curve Fit BSC Arm – Best AIC without Background Mortality	BSC	£11,036	0.92	0.71					
	Ipilimumab	£97,708	3.58	2.66	£86,673	2.66	1.95	£44,535	£44,535
One Curve Fit BSC Arm – Weibull without Background Mortality	BSC	£10,840	0.89	0.69					
	Ipilimumab	£97,708	3.58	2.66	£86,868	2.69	1.97	£44,119	£44,119

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Two Part Curve Fit – Best AIC without Background Mortality	BSC	£11,201	0.94	0.73					
	Ipilimumab	£97,708	3.58	2.66	£86,507	2.64	1.93	£44,825	£44,825
Two Part Curve Fit – Weibull without Background Mortality	BSC	£11,181	0.94	0.73					
	Ipilimumab	£91,157	1.86	1.43	£79,975	0.93	0.71	£113,211	£113,211
Two Part Curve Fit – Weibull Background Mortality Only After 5 Years Both Arms	BSC	£12,775	1.31	1.00					
	Ipilimumab	£95,699	2.93	2.20	£82,925	1.62	1.20	£69,071	£69,071
Two Part Curve Fit – Best AIC Background Mortality Only After 5 Years Ipi Only	BSC	£11,191	0.94	0.73					
	Ipilimumab	£96,188	3.19	2.38	£84,996	2.25	1.65	£51,445	£51,445
Two Part Curve Fit – Weibull Background Mortality Only After 5 Years Ipi Only	BSC	£11,173	0.94	0.72					
	Ipilimumab	£95,699	2.93	2.20	£84,527	1.99	1.47	£57,383	£57,383

Table 56 presents the ICERs using data from the individual ipilimumab trial arms as opposed to the combined data used in the base case. The use of ipilimumab data alone reduces the ICER as greater efficacy was seen in the ipilimumab only arm.

Table 56: Scenario 6: Use of alternative data for ipilimumab

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
Data for Ipilimumab only arm	BSC	£12,837	1.33	1.01					
	Ipilimumab	£104,393	3.72	2.81	£91,556	2.39	1.80	£50,934	£50,934
Data for Ipilimumab + gp100 arm	BSC	£12,837	1.33	1.01					
	Ipilimumab	£93,916	2.83	2.12	£81,079	1.50	1.11	£72,914	£72,914

Table 57 shows the impact of the use of alternative time horizons on the ICER. As expected reducing the time horizon increases the ICER as one of the benefits of ipilimumab is increased long term survival. Reducing the time horizon to 15 years increases the ICER to £82,324 at which time approximately 13% of ipilimumab patients are expected to still be alive.

Table 57: Scenario 7: Use of alternative time horizons

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Base Case – 30 years	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
Lifetime for all patients	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,736	3.29	2.45	£83,899	1.96	1.44	£58,241	£58,241
15 years	BSC	£12,028	1.16	0.89					
	Ipilimumab	£92,655	2.46	1.87	£80,627	1.30	0.98	£82,324	£82,324
20 years	BSC	£12,398	1.24	0.94					
	Ipilimumab	£94,278	2.80	2.11	£81,880	1.56	1.17	£70,282	£70,282
25 years	BSC	£12,665	1.29	0.98					
	Ipilimumab	£95,441	3.04	2.28	£82,776	1.74	1.29	£63,984	£63,984

Table 58 shows that the source of the weight data used in the model has little effect upon the ICER.

Table 58: Scenario 8: Use of alternative weight data

Scenario	Technologies	Total			Incremental			ICER (£)	ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Base Case	BSC	£12,837	1.33	1.01					
	Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737	£60,737
UK Patients from MDX010-20 trial only	BSC	£12,837	1.33	1.01					
	Ipilimumab	£98,213	3.19	2.38	£85,376	1.86	1.37	£62,229	£62,229
Compassionate use programme patients only	BSC	£12,837	1.33	1.01					
	Ipilimumab	£95,756	3.19	2.38	£82,919	1.86	1.37	£60,420	£60,420

Summary of main findings from sensitivity analysis

The probabilistic sensitivity analysis shows that the model has relatively equal levels of upside and downside risk with the majority of the uncertainty in the model being associated with the model outcomes rather than costs. There is a 22% probability of ipilimumab being cost effective at a £50,000 threshold.

The scenario analysis shows that the key structural sensitivities in the model surround the curve fit chosen. The utilisation of comparators other than BSC reduces the ICER as these comparators add additional costs without increasing efficacy.

Key drivers of the cost-effectiveness results

The key drivers of the cost-effectiveness results as shown in the sensitivity analyses are:

- The curve type selected – as many of the potential curve fits do not fit the trial data well

- The utility assumed for progressive disease – as this affects the QALY gain seen for ipilimumab over BSC, where the vast majority of patients will have died

- The patient's starting age – as this affects the length of time over which the survival associated with ipilimumab can be accrued

The curve fit parameters assumed for overall survival for ipilimumab and BSC - as the majority of the benefits associated with ipilimumab come from increased survival over BSC.

6.8 Validation

A number of steps were taken to validate the model.

First, estimates of PFS and OS from the final model were checked against values calculated in a separate spreadsheet – results were the same.

Secondly, extensive one-way sensitivity analyses were conducted on all model inputs and results were reviewed to ensure that changes in cost and effectiveness measures were consistent with expectations, given model specifications.

Thirdly, random checks were made on model inputs compared with source data.

Finally, in terms of internal validity, as noted above the survival functions used to generate estimates of PFS and OS for ipilimumab are very close to those obtained based on the empirical (Kaplan-Meier) survival distributions (see Section 6.3.1).

After the creation of the model, it was presented to 4 practicing clinicians who are currently treating melanoma patients in the UK in order to ensure the model has face validity, and matches clinical practice. The key issues around the economic modelling such as time horizon, comparator, survival analysis, adverse events, and utility measures were discussed with the experts using a face to face run through of each of the inputs to the draft model [redacted]

Following this stage, the model was presented to an advisory board of 6 leading UK health economists with extensive experience in UK HTA processes including a former NICE committee member, a former Technology Assessment Review Group lead and a current SMC Economic reviewer. Following a day of discussion, changes and clarifications were made to the model and the base case analysis, as well as to the submission in order to justify assumptions used, and further support the methodology applied.

As a last step in the model validation process, the model was reviewed by a senior health economist not involved with the project, using the Drummond checklist and Glasgow checklist, as well as a proprietary internal checklist (BresMed Health Solutions

2011, [redacted]. Following this review a report was produced, with discussions held and changes made to the model and documentation accordingly

6.9 Subgroup analysis

Rationale for subgroup analysis

N/A

Subgroup patient characteristics

N/A

Please describe how the statistical analysis was undertaken.

N/A

Results of subgroup analyses

N/A

Relevant subgroups not considered

There are no obvious subgroups.

6.10 Interpretation of economic evidence

Comparison with published economic literature

As there is no published cost-effectiveness analysis of ipilimumab, it is not possible to compare the results from this study.

Relevance of the economic evaluation to all patient groups

The economic analysis is relevant to all patients described in the MAA, and as laid out in the final scope by NICE.

In the United States, ipilimumab has a broader licence approved by the FDA, but this patient population is not considered in this submission due to both ethical and legal issues arising from unlicensed patient populations.

Strengths and weaknesses of the evaluation

The analysis performed is highly robust and makes use of the best available data in this disease area – either directly from clinical trials, published literature, or where not available through synthesis (e.g. utility mappings). Extensive sensitivity analyses are also provided in order to allow an understanding of the key variables.

The weaknesses of the analysis relate to the data upon which the model is constructed - underlying uncertainty around the appropriate comparator for the UK remains due to the lack of a clear treatment pathway at this disease stage. Data from Collinson & Marples (2010) as well as other data included in the submission do go some way to bridging this gap.

Equally the effectiveness of comparator treatments has not been demonstrated, meaning patients are potentially being treated with chemotherapy (with associated side effects) that has little to no benefit (as shown in Korn et al. 2008). This is the key area of uncertainty relating to the modelling approach.

Further information of HRQL could also be beneficial, as it would be important to understand patient utility throughout the disease course, particularly relating to the extended survival seen with immunotherapy, as this is a key driver of cost-effectiveness. Analysis has been performed on the EORTC and SF-36 data from trial MDX010-20 (as shown in Section 6.3.1) which indicates no relationship between time before (or after) progression and HRQL (correlation coefficients <0.20), however this is limited by the number of observations in the extended survival period, and the length of the trial.

The final limitation relates to the data for ipilimumab, for which only 5 years of follow up data is available, with 15% of patients remaining alive at this time point. As the data becomes increasingly mature, the uncertainty relating to survival benefits will reduce accordingly. In order to demonstrate however that long term survival is plausible in melanoma, data from Atkins (1999) which has 11 years of data from patients treated with IL-2, has been used to support the methodology used in (detailed in Section 6.3.1).

Further analyses

BMS are unaware of any further analyses which could be performed with the existing datasets to inform the current economic modelling approach. However should any further analysis be required, we would like to enter in to a discussion of how this can best be achieved.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 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.

In 2010, there were an estimated 11,800 cases of melanoma in the UK (Cancer Research UK, 2011) with around 16% of these patients being Stage IV & IIIc (Mitra et al., 2008). 21% of these patients will progress to 2nd line treatment (IMS Oncoanalyser, 2011). This proportion is not expected to increase between 2011 and 2015 as no major changes have been made to 1st line treatment, in addition due to the toxicity of ipilimumab it is only expected to be used for fitter patients who have already received 1st line therapy, the numbers of which are unlikely to increase in the short – medium term.

Presently Melanoma diagnoses are estimated to be growing at a rate of 3.5% per year (Gricks et al., 2006), bringing the total number of Stage IV and IIIc melanoma patients in 2011 to 1,954 (rising to 2,240 by 2015). The projected number of eligible patients for the next 5 years is presented in Table 59.

Table 59: Estimated patient numbers, 2011 - 2015

Year	2011	2012	2013	2014	2015
Melanoma diagnoses	12,213	12,640	13,082	13,539	14,012
Stage IIIc & IV	1,954	2,022	2,092	2,165	2,240
% of patients progressing to 2nd line treatment	21%	21%	21%	21%	21%
Number of 2nd line patients	414	429	444	459	475

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

It is assumed that in a treatment course, all patients receive four doses of ipilimumab, and that 5% of all treated patients are re-inducted for a further treatment course.

The dosage assumption used were the same as those in the economic model (detailed in Section 6.5.5), using individual patient weights for UK patients from clinical trial MDX020-10 and the UK Ipilimumab compassionate use program to calculate the mean number of vials required (including wastage) per administration. This equates to 0.99 200mg vials, and 1.24 50mg vials per patient. Patients were assumed to receive the licensed dose of 3mg/kg.

A further assumption was made that all patients would receive a complete course of ipilimumab (4 doses) when assigned to treatment. This was made as a conservative assumption, and in the interests of transparency of calculations.

Table 60: Estimated treated patients, 2011 - 2015

Year	2011	2012	2013	2014	2015
Melanoma Incidence	12,213	12,640	13,082	13,539	14,012
Stage IIIc & IV	1,954	2,022	2,092	2,165	2,240
% of patients progressing to 2nd line treatment	21%	21%	21%	21%	21%
Number of 2nd line patients	414	429	444	459	475
Ipilimumab market share	5%	10%	15%	20%	25%
Patients treated	21	43	67	92	119
Patients reinducted	1	2	3	5	6
Total treatments	22	45	70	97	125

7.3 What assumption(s) were made about market share (when relevant)?

Market share assumptions are presented in Section 7.2.

7.4 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).

Commissioners should also consider the impact of administration, which although not significant relative to other oncology therapies (the mean number of cycles received in MDX020-10 by all ipilimumab patients was 3.69) does need to be accounted for both in budgets and clinical resource.

Commissioners should also consider the cost of having more patients experiencing long term survival; however there is significant uncertainty surrounding the medical resource required by these patients

7.5 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?

The unit cost of one 50mg vial of ipilimumab was assumed to be £3,750, and the cost of one 200mg vial of ipilimumab was assumed to be £15,000.

NHS Reference Costs 09/10 for day case chemotherapy were used for administration costs. It was assumed that the first cycle in a treatment course cost £271, using SB13Z- day case, for delivery of more complex parenteral chemotherapy at first attendance. Subsequent cycles of chemotherapy within the course were assumed to cost £284, using SB15Z- day case, for delivery of subsequent elements of a chemotherapy cycle. The same costs were used for patient reinduction.

7.6 Were there any estimates of resource savings? If so, what were they?

There is expected to be a slight offset in other chemotherapy cost which would seldom be used as a result of ipilimumab becoming available, however is used frequently at present (Collinson & Marples, 2011; [redacted]

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated budget impact for the NHS is presented in Table 60. Costs are expected to rise to approximately £9.9 million in 2015 should ipilimumab receive NICE approval at the proposed list price.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

With patients experiencing long term survival, there is also the potential of patients returning to work; however this has not been included in the model due to a lack of direct evidence

Table 61: Estimated budget impact in England & Wales, 2011 - 2015

Year	2011	2012	2013	2014	2015
Melanoma Incidence	12,213	12,640	13,082	13,539	14,012
Stage IIIc & IV	1,954	2,022	2,092	2,165	2,240
% of patients progressing to 2nd line treatment	21%	21%	21%	21%	21%
Number of 2nd line patients	414	429	444	459	475
Ipilimumab market share	5%	10%	15%	20%	25%
Patients treated	21	43	67	92	119
Patients reinducted	1	2	3	5	6
Total treatments	22	45	70	97	125
Vials of ipilimumab required per patient (200mg / 50mg)	(0.99 / 1.24)	(0.99 / 1.24)	(0.99 / 1.24)	(0.99 / 1.24)	(0.99 / 1.24)
Drug cost	£ 1,725,606	£ 3,533,384	£ 5,505,506	£ 7,559,799	£ 9,778,435
Administration cost	£ 24,762	£ 50,703	£ 79,003	£ 108,482	£ 140,319
Total Budget Impact	£ 1,750,368	£ 3,584,088	£ 5,584,509	£ 7,668,281	£ 9,918,754

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9 Appendices

9.1 Appendix 1

SPC:

Final Summary of Product Characteristics (SPC) has been issued on 13th July. Please refer to the reference: Bristol-Myers Squibb. Yervoy (ipilimumab), Summary of Product Characteristics (SPC), 13th July 2011. This reference is submitted in the updated STA dossier on 26th July 2011

9.2 Appendix 2: Search strategy for Section 5.1 (Identification of studies)

Databases searched

First systematic review

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

EMBASE (Ovid)

The Cochrane Library (systematic reviews, DARE, CCRT)

Second systematic review

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

EMBASE (Ovid)

The Cochrane Library

Date on which the search was conducted

First systematic review

The searches in Datastar were conducted on 8th April 2010. The searches in Cochrane were conducted on the 26th March 2010.

Second systematic review

Searches in OVID were conducted on the 6th May 2011.

Date span of the search

First systematic review

Ovid MEDLINE(R) 1950 to 8th April 2010

EMBASE (Ovid), 1980 to 8th April 2010

The Cochrane Library, to 26th March 2010

Second systematic review

Ovid MEDLINE(R) 1950 to 6thMay 2011

EMBASE (Ovid), 1980 to 6thMay 2011

The Cochrane Library, to 6thMay 2011

Search strategy

All the following searches were combined and inclusion/exclusion criteria applied.

First systematic review

Table 62 Search strategy/history in Datastar - performed on 8th April, 2010

No.	Database	Search terms	Info added	Results
1	MEZZ	SKIN-NEOPLASMS#.DE.	unrestricted	79924
2	MEZZ	MELANOMA#.W..DE.	unrestricted	60876
3	MEZZ	SKIN ADJ NEOPLASM$1 OR SKIN ADJ CANCER$1 OR SKIN ADJ TUMOUR$1 OR SKIN ADJ TUMOR$1 OR SKIN ADJ CARCINOMA$1 OR SKIN ADJ ADENOCARCINOMA$1 OR (SKIN ADJ SARCOMA$1).TI,AB.	unrestricted	82493
4	MEZZ	1 OR 2 OR 3	unrestricted	123595
5	MEZZ	(ADVANCED OR METASTA$3 OR RECURR$5 OR UNRESECT$ OR NON-RESECT$ OR DISSEMINATED OR STAGE ADJ '3' OR STAGE ADJ III OR STAGE ADJ IIIC OR STAGE ADJ 3C OR STAGE ADJ '4' OR STAGE ADJ IV).TI,AB.	unrestricted	690838
6	MEZZ	4 AND 5	unrestricted	28601
7	MEZZ	IPILIMUMAB OR MDX-010 OR BEVACIZUMAB OR CTLA-4 OR CTLA4 OR MDX-CTLA4 OR PLX4032 OR PLX-4032 OR PLEXXICON.TI,AB.	unrestricted	4828
8	MEZZ	OBLIMERSEN OR INTERFERON ADJ ALFA$2 OR INTRON ADJ A OR IFN-A OR IFN ADJ A OR PROLEUKIN OR INTERLEUKIN ADJ '2' OR (IL ADJ '2').TI,AB.	unrestricted	72124
9	MEZZ	DACARBAZINE OR DTIC OR IMIDAZOLE ADJ CARBOXAMIDE OR IMIDAZOLE ADJ '4' ADJ CARBOXAMIDE OR TEMOZOLOMIDE OR TEMOZOLAMIDE OR CISPLATIN OR VINBLASTINE OR CARMUSTINE OR LOMUSTINE OR DOCETAXEL OR PACLITAXEL OR CARBOPLATIN OR LENALIDOMIDE OR AMIFOSTINE OR TREMELIMUMAB OR TAXANE$1.TI,AB.	unrestricted	83817
10	MEZZ	FOTEMUSTINE OR FOTOMUSTINE OR NITROSOUREA$1 OR ALKYLATING ADJ AJD ADJ AGENT OR VINCRESTINE OR VINDESINE OR (VINCA ADJ ALKOIDS ADJ AB).TI.	unrestricted	9734
11	MEZZ	VACCINE$1 OR THERACCINE OR ONCOPHAGE OR ABRAXANE.TI,AB.	unrestricted	184013
12	MEZZ	EXPERIMENTAL ADJ THERAP$3 OR MONOCLONAL ADJ ANTIBOD$3 OR GENE ADJ THERAP$3 OR CELLULAR ADJ THERAP$3 OR ADOPTIVE ADJ IMMUNOTHERAP$3 OR IMMUNOTHERAP$3 OR CELL ADJ THERAP$3 OR BIOCHEMOTHERAP$3 OR BIOTHERAP$3 OR CHEMOIMMUNOTHERAP$3 OR (ANTIANGIOGENIC ADJ AGENT$1).TI,AB.	unrestricted	246807
13	MEZZ	7 OR 8 OR 9 OR 10 OR 11 OR 12	unrestricted	558217
14	MEZZ	((RANDOMIZED OR RANDOM OR RCT OR DOUBLE ADJ BLIND ADJ METHOD OR SINGLE ADJ BLIND ADJ METHOD OR PLACEBO OR RANDOMLY OR RANDOMISED OR CROSS ADJ OVER OR CROSSOVER OR TRIAL) ADJ AB).TI.	unrestricted	2
15	MEZZ	RANDOMIZED-CONTROLLED-TRIAL.DE. OR CLINICAL-TRIAL.DE. OR CONTROLLEDCLINICAL- TRIAL.DE. OR DOUBLE-BLINDPROCEDURE. DE. OR CONTROLLEDCLINICAL- TRIAL.DE. OR RANDOMALLOCATION#. DE. OR RANDOMIZEDCONTROLLED- TRIAL#.DE. OR PLACEBOS#.W..DE.	unrestricted	95520
16	MEZZ	RETRACTED-PUBLICATION.DE.	unrestricted	0
17	MEZZ	PT=EDITORIAL OR PT=PRACTICE-GUIDELINE OR PT=REVIEW	unrestricted	1770158
18	MEZZ	CASE ADJ REPORT OR PT=CASE-REPORTS OR PT=LETTER OR LETTER#.W..DE.	unrestricted	2043057
19	MEZZ	(14 OR 15 OR 16) NOT (17 OR 18)	unrestricted	90944
20	MEZZ	6 AND 13 AND 19 AND LA=EN	unrestricted	0
21	MEZZ	ANIMAL=YES	unrestricted	4523989
22	MEZZ	HUMAN=YES	unrestricted	11102340
23	MEZZ	21 NOT 22	unrestricted	336982

				3
24	MEZZ	20 NOT 23	unrestricted	0
25	MEZZ	6 AND 13	unrestricted	5707
26	MEZZ	25 AND 19	unrestricted	38
27	MEZZ	26 NOT 23	unrestricted	33
28	MEZZ	(RANDOMIZED OR RANDOM OR RCT OR DOUBLE ADJ BLIND ADJ METHOD OR SINGLE ADJ BLIND ADJ METHOD OR PLACEBO OR RANDOMLY OR RANDOMISED OR CROSS ADJ OVER OR CROSSOVER OR TRIAL).AB,TI.	unrestricted	824661
29	MEZZ	(28 OR 15 OR 16) NOT (17 OR 18)	unrestricted	728132
30	MEZZ	25 AND 29 AND LA=EN	unrestricted	0
31	MEZZ	6 AND 13 AND 29	unrestricted	1007
32	MEZZ	31 NOT 23 AND LG=EN	unrestricted	938
33	EMZZ	SKIN-TUMOR#.W..DE. OR MELANOMA#.W..DE. OR SKIN ADJ CANCER$1 OR SKIN ADJ CARCINOMA OR SKIN ADJ TUMOR$1 OR SKIN ADJ TUMOUR$1 OR MELANOMA	unrestricted	204164
34	EMZZ	METASTA$3 OR ADVANCED OR RECURR$5 OR UNRESECT$ OR STAGE ADJ III OR STAGE ADJ IIIC OR STAGE ADJ IV OR STAGE ADJ '3' OR STAGE ADJ 3C OR STAGE ADJ '4'	unrestricted	918733
35	EMZZ	33 AND 34	unrestricted	53861
36	EMZZ	IPILIMUMAB OR MDX-010 OR BEVACIZUMAB OR CTLA-4 OR CTLA4 OR MDX-CTLA4 OR PLX4032 OR PLX-4032 OR PLEXXICON.TI,AB.	unrestricted	13148
37	EMZZ	OBLIMERSEN OR INTERFERON ADJ ALFA$2 OR INTRON ADJ A OR IFN-A OR IFN ADJ A OR PROLEUKIN OR INTERLEUKIN ADJ '2' OR (IL ADJ '2').TI,AB.	unrestricted	89186
38	EMZZ	DACARBAZINE OR DTIC OR IMIDAZOLE ADJ CARBOXAMIDE OR IMIDAZOLE ADJ '4' ADJ CARBOXAMIDE OR TEMOZOLOMIDE OR TEMOZOLAMIDE OR CISPLATIN OR VINBLASTINE OR CARMUSTINE OR LOMUSTINE OR DOCETAXEL OR PACLITAXEL OR CARBOPLATIN OR LENALIDOMIDE OR AMIFOSTINE OR TREMELIMUMAB OR TAXANE$1.TI,AB.	unrestricted	170689
39	EMZZ	FOTEMUSTINE OR FOTOMUSTINE OR NITROSOUREA$1 OR ALKYLATING ADJ AJD ADJ AGENT OR VINCRESTINE OR VINDESINE OR (VINCA ADJ ALKOIDS ADJ AB).TI.	unrestricted	16151
40	EMZZ	EXPERIMENTAL ADJ THERAP$3 OR MONOCLONAL ADJ ANTIBOD$3 OR GENE ADJ THERAP$3 OR CELLULAR ADJ THERAP$3 OR ADOPTIVE ADJ IMMUNOTHERAP$3 OR IMMUNOTHERAP$3 OR CELL ADJ THERAP$3 OR BIOCHEMOTHERAP$3 OR BIOTHERAP$3 OR CHEMOIMMUNOTHERAP$3 OR (ANTIANGIOGENIC ADJ AGENT$1).TI,AB.	unrestricted	344431
41	EMZZ	VACCINE$1 OR THERACCINE OR ONCOPHAGE OR ABRAXANE.TI,AB.	unrestricted	210656
42	EMZZ	36 OR 37 OR 38 OR 39 OR 40 OR 41	unrestricted	757354
43	EMZZ	(RANDOMIZED OR RANDOM OR RCT OR DOUBLE ADJ BLIND ADJ METHOD OR SINGLE ADJ BLIND ADJ METHOD OR PLACEBO OR RANDOMLY OR RANDOMISED OR CROSS ADJ OVER OR CROSSOVER OR TRIAL).AB,TI.	unrestricted	919274
44	EMZZ	CONTROLLED-CLINICAL-TRIAL#.DE. OR RANDOMIZED-CONTROLLED-TRIAL.DE.	unrestricted	280820
45	EMZZ	RETRACTED-ARTICLE.DE.	unrestricted	4502
46	EMZZ	PT=EDITORIAL OR PT=LETTER OR PT=PRESS-RELEASE OR PT=REVIEW	unrestricted	2593706
47	EMZZ	(43 OR 44 OR 45) NOT 46	unrestricted	847612
48	EMZZ	35 AND 42 AND 47 AND LG=EN	unrestricted	1788
49	EMZZ	ANIMAL=YES	unrestricted	4008822
50	EMZZ	HUMAN=YES	unrestricted	11489954
51	EMZZ	49 NOT 50	unrestricted	3352884
52	EMZZ	48 NOT 51	unrestricted	1722

53	MEIP	SKIN ADJ CANCER$1 OR SKIN ADJ CARCINOMA OR SKIN ADJ TUMOR$1 OR SKIN ADJ TUMOUR$1 OR MELANOMA	unrestricted	1406
54	MEIP	METASTA$3 OR ADVANCED OR RECURR$5 OR UNRESECT$ OR STAGE ADJ III OR STAGE ADJ IIIC OR STAGE ADJ IV OR STAGE ADJ '3' OR STAGE ADJ 3C OR STAGE ADJ '4'	unrestricted	17043
55	MEIP	53 AND 54	unrestricted	455
56	MEIP	IPILIMUMAB OR MDX-010 OR BEVACIZUMAB OR CTLA-4 OR CTLA4 OR MDX-CTLA4 OR PLX4032 OR PLX-4032 OR PLEXXICON.TI,AB.	unrestricted	367
57	MEIP	OBLIMERSEN OR INTERFERON ADJ ALFA$2 OR INTRON ADJ A OR IFN-A OR IFN ADJ A OR PROLEUKIN OR INTERLEUKIN ADJ '2' OR (IL ADJ '2').TI,AB.	unrestricted	610
58	MEIP	DACARBAZINE OR DTIC OR IMIDAZOLE ADJ CARBOXAMIDE OR IMIDAZOLE ADJ '4' ADJ CARBOXAMIDE OR TEMOZOLOMIDE OR TEMOZOLAMIDE OR CISPLATIN OR VINBLASTINE OR CARMUSTINE OR LOMUSTINE OR DOCETAXEL OR PACLITAXEL OR CARBOPLATIN OR LENALIDOMIDE OR AMIFOSTINE OR TREMELIMUMAB OR TAXANE$1.TI,AB.	unrestricted	1592
59	MEIP	FOTEMUSTINE OR FOTOMUSTINE OR NITROSOUREA$1 OR ALKYLATING ADJ AJD ADJ AGENT OR VINCRESTINE OR VINDESINE OR (VINCA ADJ ALKOIDS ADJ AB).TI.	unrestricted	55
60	MEIP	VACCINE$1 OR THERACCINE OR ONCOPHAGE OR ABRAXANE.TI,AB.	unrestricted	3407
61	MEIP	EXPERIMENTAL ADJ THERAP$3 OR MONOCLONAL ADJ ANTIBOD$3 OR GENE ADJ THERAP$3 OR CELLULAR ADJ THERAP$3 OR ADOPTIVE ADJ IMMUNOTHERAP$3 OR IMMUNOTHERAP$3 OR CELL ADJ THERAP$3 OR BIOCHEMOTHERAP$3 OR BIOTHERAP$3 OR CHEMOIMMUNOTHERAP$3 OR (ANTIANGIOGENIC ADJ AGENT$1).TI,AB.	unrestricted	3514
62	MEIP	56 OR 57 OR 58 OR 59 OR 60 OR 61	unrestricted	8939
63	MEIP	(RANDOMIZED OR RANDOM OR RCT OR DOUBLE ADJ BLIND ADJ METHOD OR SINGLE ADJ BLIND ADJ METHOD OR PLACEBO OR RANDOMLY OR RANDOMISED OR CROSS ADJ OVER OR CROSSOVER OR TRIAL).AB,TI.	unrestricted	21626
64	MEIP	55 AND 62 AND 63	unrestricted	29
65	MEZZ EMZZ MEIP	combined sets 32, 52, 64	unrestricted	2689
66	MEZZ EMZZ MEIP	dropped duplicates from 65	unrestricted	884
67	MEZZ EMZZ MEIP	unique records from 65	unrestricted	1805

Comment: MEDLINE - 1949 todate (MEZZ); EMBASE - 1974 to date (EMZZ); MEDLINE In-Process - latest 8 weeks (MEIP)

Table 63 Search strategy/history in the Cochrane Library - performed on 26th March, 2010

No	Search terms	Results
1	Cochrane SKIN-NEOPLASMS (MESH Term explode all trees)	889
2	MELANOMA (MESH Term explode all trees)	850
3	SKIN NEXT NEOPLASM* OR SKIN NEXT CANCER* OR SKIN NEXT TUMOUR* OR SKIN NEXT TUMOR* OR SKIN NEXT CARCINOMA* OR SKIN NEXT ADENOCARCINOMA* OR SKIN NEXT SARCOMA*.TI,AB, KW.	1062
4	1 OR 2 OR 3	1475
5	(ADVANCED OR METASTA* OR RECURR* OR UNRESECT* OR NON-RESECT* OR DISSEMINATED OR STAGE NEXT 3 OR STAGE NEXT III OR STAGE NEXT IIIC OR STAGE NEXT 3C OR STAGE NEXT 4 OR STAGE NEXT IV).TI,AB,KW.	47490
6	4 AND 5	669
7	IPILIMUMAB OR MDX-010 OR BEVACIZUMAB OR CTLA-4 OR CTLA4 OR MDX-CTLA4 OR PLX4032 OR PLX-4032 OR PLEXXICON.TI,AB,KW	251
8	OBLIMERSEN OR INTERFERON NEXT ALFA* OR INTRON NEXT A OR IFN-A OR IFN	3884

	NEXT A OR PROLEUKIN OR INTERLEUKIN NEXT 2 OR IL NEXT 2.TI,AB,KW	
9	DACARBAZINE OR DTIC OR IMIDAZOLE NEXT CARBOXAMIDE OR IMIDAZOLE NEXT '4' NEXT CARBOXAMIDE OR TEMOZOLOMIDE OR TEMOZOLAMIDE OR CISPLATIN OR VINBLASTINE OR CARMUSTINE OR LOMUSTINE OR DOCETAXEL OR PACLITAXEL OR CARBOPLATIN OR LENALIDOMIDE OR AMIFOSTINE OR TREMELIMUMAB OR TAXANE*.TI,AB,KW	9956
10	FOTEMUSTINE OR FOTOMUSTINE OR NITROSOUREA* OR ALKYLATING NEXT AGENT OR VINCRESTINE OR VINDESINE OR VINCA NEXT ALKOIDS. TI,AB, KW	1024
11	VACCINE* OR THERACCINE OR ONCOPHAGE OR ABRAXANE.TI,AB,KW	8128
12	EXPERIMENTAL NEXT THERAP* OR MONOCLONAL NEXT ANTIBOD* OR GENE NEXT THERAP* OR CELLULAR NEXT THERAP* OR ADOPTIVE NEXT IMMUNOTHERAP* OR IMMUNOTHERAP* OR CELL NEXT THERAP* OR BIOCHEMOTHERAP* OR BIOTHERAP* OR CHEMOIMMUNOTHERAP* OR ANTI-ANGIOGENIC NEXT AGENT*.TI,AB,KW	5221
13	7 OR 8 OR 9 OR 10 OR 11 OR 12	26023
14	RANDOMIZED OR RANDOM OR RCT OR DOUBLE NEXT BLIND NEXT METHOD OR SINGLE NEXT BLIND NEXT METHOD OR PLACEBO OR RANDOMLY OR RANDOMISED OR CROSS NEXT OVER OR CROSSOVER OR TRIAL.TI,AB,KW	397388
15	RANDOMIZED-CONTROLLED-TRIAL as TOPIC (MESH Term explode all trees)	13738
16	CONTROLLED CLINICAL TRIALS as TOPIC (MESH Term explode all trees)	14000
17	DOUBLE-BLIND METHOD (MESH Term explode all trees)	87819
18	RANDOM-ALLOCATION (MESH Term explode all trees)	20312
19	PLACEBOS (MESH Term explode all trees)	19353
20	RETRACTED PUBLICATION:PT	55
21	Retraction of Publication as Topic (MESH Term explode all trees)	0
22	EDITORIAL OR (PRACTICE GUIDELINE) OR REVIEW OR LETTER:PT	7901
23	CASE NEXT REPORT:TI,AB,KW	881
24	(14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20) NOT (21 OR 22)	392318
25	6 AND 13 AND 24	295
26	#25 and Clinical Trials	287

Second systemic review

Table 64 Search strategy/history in EMBASE 1980 to 2011 Week 17 - performed on 6th May 2011

	Searches	Results
1	skin neoplasms.mp. or exp skin tumor/	150690
2	melanoma.mp. or exp MELANOMA/	95832
3	((skin adj1 neoplasm*) or (skin adj1 cancer*) or (skin adj1 tumo?r*) or (skin adj1 carcinoma*) or (skin adj1 adenocarcinoma*) or (skin adj1 sarcoma*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	61461
4	1 or 2 or 3	231441
5	(malignan* or advanc* or metasta* or recurr* or unresect* or non-resect* or disseminat* or stage III or stage 3 or stage IIIc or stage 3c or stage IV or stage 4).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1528321
6	4 and 5	95780
7	ipilimumab.mp. or exp IPILIMUMAB/	649
8	(MDX010 or MDX-010 or MDX101 or MDX-101 or yervoy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	212
9	((best adj1 supportive adj1 care) or BSC).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	2276
10	dacarbazine.mp. or exp DACARBAZINE/	12442

11	(DTIC or dimethyl triazeno imidazole carboxamide or imidazole carboxamide or imidazole carboxamidedimethyltriazene or WR-139007 or WR139007).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1221
12	temozolomide.mp. or exp TEMOZOLOMIDE/	7057
13	(temodar or temodal or TMZ).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1587
14	(aldesleukin or proleukin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1001
15	carboplatin.mp. or exp CARBOPLATIN/	33546
16	(Paraplatin or Paraplatin-AQ or ParaplatinAQ or (platinum adj3 chemo*) or (platinum adj3 therap*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	6210
17	exp palliative therapy/ or palliative radiation.mp.	46021
18	Clinical trial/	831653
19	Randomised controlled trial/	294424
20	Randomisation/	54082
21	Single blind procedure/	14221
22	Double blind procedure/	102906
23	Crossover procedure/	30771
24	Placebo/	179431
25	Randomi?ed controlled trial$.tw.	61708
26	Rct.tw.	6841
27	Random allocation.tw.	1032
28	Randomly allocated.tw.	15496
29	Allocated randomly.tw.	1704
30	(allocated adj2 random).tw.	687
31	Single blind$.tw.	10989
32	Double blind$.tw.	118048
33	((treble or triple) adj blind$).tw.	240
34	Placebo$.tw.	158402
35	Prospective study/	168312
36	or/18-35	1136368
37	Case study/	11796
38	Case report.tw.	199824
39	Abstract report/ or letter/	778710
40	or/37-39	986532
41	36 not 40	1103622
42	or/7-17	101254
43	6 and 42	6082
44	41 and 43	2084
45	limit 44 to yr="2010 -Current"	325

Table 65: Search strategy/history in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present - performed on 6th May 2011

	Searches	Results
1	skin neoplasms.mp. or exp Skin Neoplasms/	84218
2	exp Melanoma/ or melanoma.mp.	79180
3	((skin adj1 neoplasm*) or (skin adj1 cancer*) or (skin adj1 tumo?r*) or (skin adj1 carcinoma*) or (skin adj1 adenocarcinoma*) or (skin adj1 sarcoma*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	86542
4	1 or 2 or 3	142223

5	(malignan* or advanc* or metasta* or recurr* or unresect* or non-resect* or disseminat* or 'stage III' or 'stage 3' or 'stage IIIc' or 'stage 3c' or 'stage IV' or 'stage 4').mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	1313431
6	4 and 5	62731
7	(ipilimumab or MDX010 or MDX-010 or MDX101 or MDX-101 or yervoy).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	144
8	((best adj1 supportive adj1 care) or BSC).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	1857
9	dacarbazine.mp. or exp Dacarbazine/	4641
10	(DTIC or dimethyl triazeno imidazole carboxamide or imidazole carboxamide or imidazole carboxamidedimethyltriazene or WR-139007 or WR139007).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	1112
11	(temozolomide or temodar or temodal or TMZ).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	2418
12	(aldesleukin or proleukin).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	135
13	carboplatin.mp. or exp Carboplatin/	10302
14	(Paraplatin or Paraplatin-AQ or ParaplatinAQ or (platinum adj3 chemo*) or (platinum adj3 therap*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	3759
15	exp Palliative Care/ or palliative radiation.mp.	34107
16	or/7-15	54534
17	6 and 16	2027
18	Randomised controlled trials as Topic/	72681
19	Randomised controlled trial/	305697
20	Random allocation/	71251
21	Double blind method/	109596
22	Single blind method/	14866
23	Clinical trial/	462177
24	exp Clinical Trials as Topic/	240326
25	or/18-24	771730
26	(clinic$ adj trial$1).tw.	161084
27	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	109840
28	Placebos/	29537
29	Placebo$.tw.	132136
30	Randomly allocated.tw.	13046
31	(allocated adj2 random).tw.	673
32	or/26-31	334665
33	25 or 32	880952
34	Case report.tw.	166778
35	Letter/	728161
36	Historical article/	273973
37	Review of reported cases.pt.	0
38	Review, multicase.pt.	0

39	or/34-38	1159025
40	33 not 39	855906
41	17 and 40	613
42	limit 41 to yr="2010 -Current"	39

Table 66: Search strategy/history in Cochrane Wiley – performed on 6th May 2011

ID	Search	Hits
#1	MeSH descriptor Skin Neoplasms explode all trees	987
#2	MeSH descriptor Melanoma explode all trees	919
#3	SKIN NEXT NEOPLASM* OR SKIN NEXT CANCER* OR SKIN NEXT TUMOUR* OR SKIN NEXT TUMOR* OR SKIN NEXT CARCINOMA* OR SKIN NEXT ADENOCARCINOMA* OR SKIN NEXT SARCOMA*	1270
#4	(#1 OR #2 OR #3)	1699
#5	Malignan* OR ADVANC* OR METASTA* OR RECURR* OR UNRESECT* OR NON-RESECT* OR DISSEMINATED OR STAGE NEXT 3 OR STAGE NEXT III OR STAGE NEXT IIIC OR STAGE NEXT 3C OR STAGE NEXT 4 OR STAGE NEXT IV	63401
#6	(#4 AND #5)	938
#7	ipilimumab or MDX-010 or MDX010 or MDX-101 or MDX101 or yervoy	17
#8	MeSH descriptor Dacarbazine explode all trees	366
#9	DTIC or (dimethyl triazeno imidazole carboxamide) or (imidazole carboxamide) or (imidazole carboxamidedimethyltriazene) or WR-139007 or WR139007	245
#10	(best NEXT supportive NEXT care) or BSC	398
#11	temozolomide or temodar or temodal or TMZ	176
#12	aldesleukin or proleukin	14
#13	MeSH descriptor Carboplatin explode all trees	809
#14	(platinum NEAR chemo*) or (platinum NEAR therap*)	681
#15	MeSH descriptor Palliative Care explode all trees	1303
#16	(palliative radiation)	350
#17	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR 16)	81175
#18	(#6 AND #17)	304
#19	(#18), from 2010 to 2011	29
	Cochrane Reviews [17] | Other Reviews [1] | Clinical Trials [10] | Methods Studies [0] | Technology Assessments [0] | Economic Evaluations [0] | Cochrane Groups [1]	

Additional searches

First systematic review

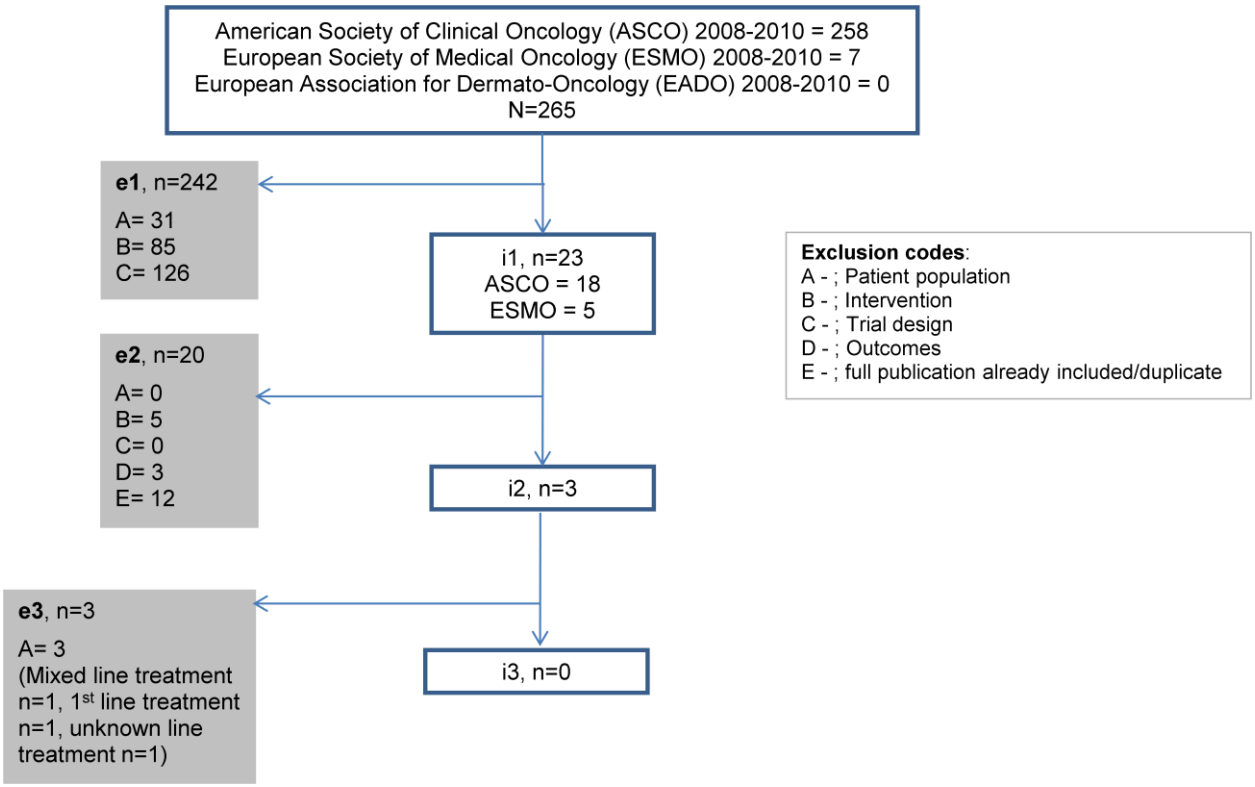
Additional studies were identified by hand searching the following resources in the first systematic review:

- American Society of Clinical Oncology (ASCO) 2008-2010
- European Society of Medical Oncology (ESMO) 2008-2010

- European Association for Dermato-Oncology (EADO) 2008-2010

The searches were performed on March 26th 2010 and identified studies were assessed for relevance based on criteria outlined in Section 5.2. No studies of relevance were identified during these searches. The systematic review schematic for this search is shown in Figure 29.

Figure 29 Schematic for hand-searching conference proceedings (2008-2010)



Abbreviations: i1, studies included at first pass; i2, studies included at second pass; i3, studies included at third and final pass; e1 studies excluded during first pass; e2, studies excluded during second pass; e3, studies excluded during third pass.

Second systematic review

During the second systematic review, the following resources were searched in order to identify any further relevant studies. This includes updated searches of the previously included conference proceedings. The hand searches were carried out on 26th May 2011 and were assessed according to the eligibility criteria outlined in Section 5.2. Both RCT evidence and non-RCT evidence was included.

Hand searches – conference proceedings and specific journals

A hand search of conference proceedings from the following organisations was performed, to identify abstracts of recent evidence:

- The American Society of Clinical Oncology (ASCO) 2010
- The European Association of Dermato-Oncology (EADO) 2011
- The European Society of Medical Oncology (ESMO) 2011
- Perspectives in Melanoma (2008-2011)
- Annual International Congress of the Society for Melanoma Research (2008-2011)

The following journals were specifically searched:

- Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society (Pigment Cell Res) (up to 2007 when the journal was no longer available)
- Pigment cell and melanoma research (Pigment Cell Melanoma Res) (from the earliest date available, 2008 onwards)
- Melanoma research (Melanoma Res) (from 1991 on)

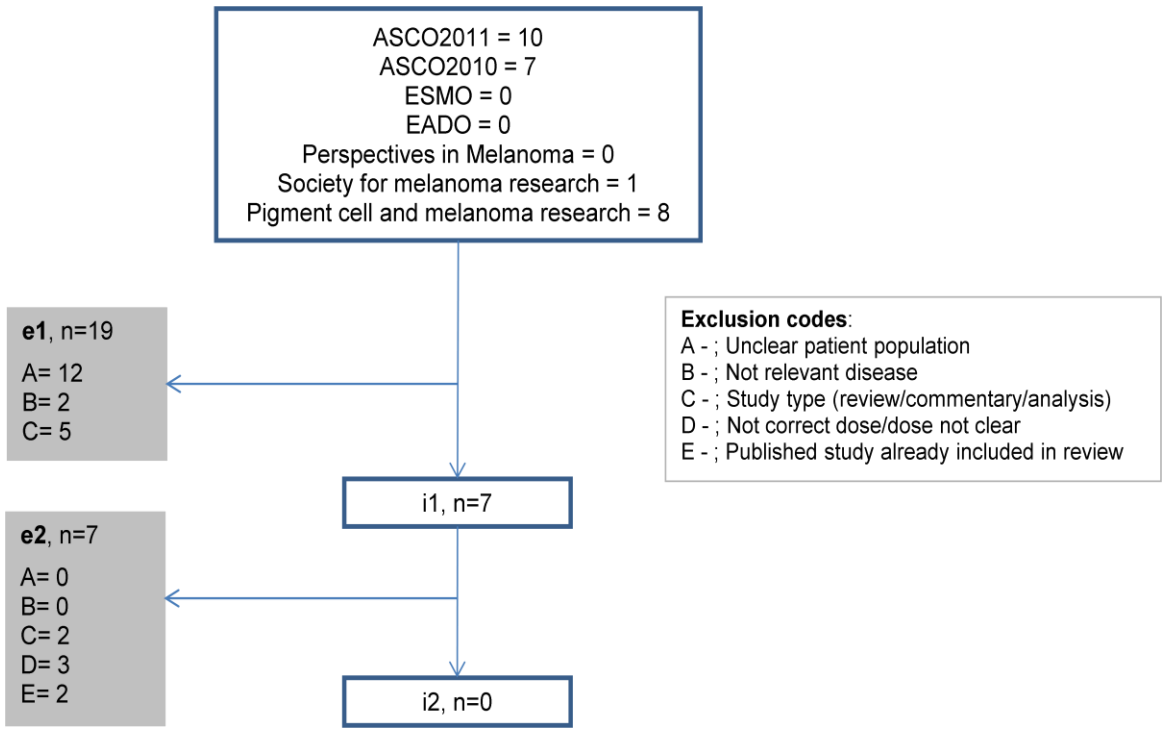
These searches resulted in the identification of seven potentially relevant studies (Jospeh et al 2011, Kotapati et al 2011, Saenger and Wolchok 2009, Hersey 2010, Wolchok 2009, O'Day 2010, and Hodi 2010). These studies did not meet the eligibility criteria for the review and were therefore excluded. Table 67 outlines the studies identified and reasons for exclusion. The schematic for these searches is presented in Figure 30.

Table 67: Studies identified through hand searching – reasons for exclusion

Study	Reason for exclusion
Jedd D. Wolchok, MD, PhD Correlative Immunologic Results of Compassionate-use Trial of Ipilimumab in Advanced Melanoma at MSKCC Memorial Sloan-Kettering Cancer Center (MSKCC) Annual International Congress of the Society for Melanoma Research (2009)	Excluded due to dose. Study reports on an unlicensed dose
Saengar YM, and Wolchok JD. The heterogeneity of the kinetics of response to ipilimumab in metastatic melanoma: patient cases. Cancer Immunity, 2008; 8:1-7	Excluded due to dose. Doses reported unclear. Only one case with a clear licensed dose is reported.

Hersey P et al. Impact of HLA-A2 status on the efficacy and safety of ipilimumab in previously treated patients with advanced melanoma. Pigment cell and melanoma research 2010; 23: 6: 956	Excluded due to study type. Reporting of an analysis and is therefore not a RCT or non-RCT
O'Day et al. A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma. 2010. J Clin Oncol 28:18s (suppl; abstr 4). Presented at 2010 ASCO Annual Meeting.	Excluded as full publication is already included in the review of RCTs (Hodi et al 2010).
Hodi 2010 Re-induction with ipilimumab, gp100 peptide vaccine, or a combination of both from a phase III, randomized, double-blind, multicenter study of previously treated patients with unresectable stage III or IV melanoma. 2010. J Clin Oncol 28:15s, (suppl; abstr 8509). Presented at 2010 ASCO Annual Meeting.	Excluded as full publication containing updated data from this analysis is already included in the review of RCTs (Hodi et al 2010).
Kotapatti et al. Overall survival (OS) in the management of pretreated patients with unresectable stage III/IV melanoma: A systematic literature review and meta-analysis. 2011. J Clin Oncol 29: (suppl; abstr 8580). Presented at 2011 ASCO Annual Meeting.	Excluded due to study type. This is a review not a RCT or non-RCT.
Joseph et al. Clinical benefit of ipilimumab in patients with metastatic melanoma who progress on high-dose IL-2. J Clin Oncol 29: 2011 (suppl; abstr 8537). Presented at Presented at 2011 ASCO Annual Meeting.	Excluded due to dose. It is unclear if the study reports on a licensed dose.

Figure 30 Schematic for updated conference proceeding and specific journal searches



Abbreviations: i1, studies included at first pass; i2, studies included at second and final pass; e1 studies excluded during first pass; e2, studies excluded during second pass.

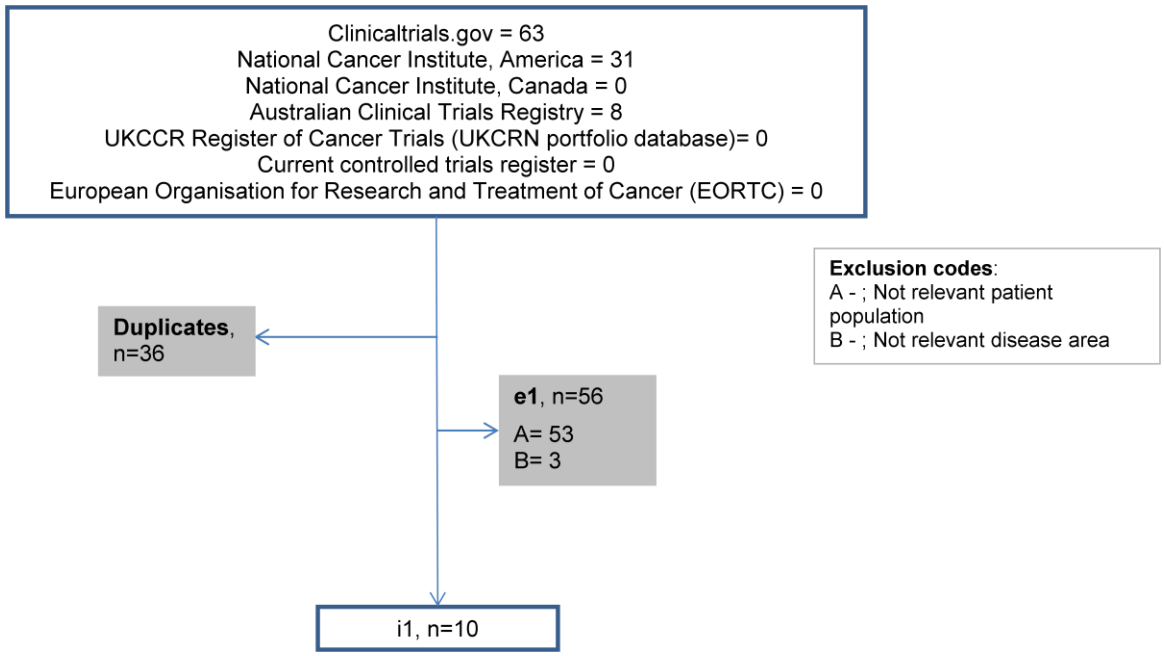
Identification of ongoing research

To identify unpublished, ongoing research, the following databases were searched:

- clinicaltrials.gov (http://www.clinicaltrials.gov)
- National Cancer Institute, America (http://www.cancer.gov/clinicaltrials/)
- National Cancer Institute, Canada (http://http://www.ctg.queensu.ca/public/Clinical_Trials/clinical_trials.html)
- Australian Clinical Trials Registry (http://www.actr.org.au/)
- UKCCR Register of Cancer Trials (UKCRN portfolio database)
- Current controlled trials register (http://www.controlled-trials.com) including *meta*Register (*m*RCT) of Controlled Trials, and ISRCTN register, UK Clinical Trials Gateway (http://controlled-trials.com/ukctr/)
- European Organisation for Research and Treatment of Cancer (EORTC) (http://www.eortc.be)

Ten ongoing trials were identified as shown in the schematic below. Details of the ten identified studies can be found in Table 68.

Figure 31 Schematic for ongoing research identification



Abbreviations: i1, studies included at first and final pass; e1 studies excluded during first pass.

Table 68: Ongoing trials identified

Database	Relevant abstracts and/or details of the search
Clinicaltrials.gov	MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients With Melanoma Conditions: Melanoma; Metastases Study Design: Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator); Primary Purpose: Treatment ID: NCT00094653
Clinicaltrials.gov	Study of Ipilimumab (MDX-010) Monotherapy in Patients With Previously Treated Unresectable Stage III or IV Melanoma Condition: Melanoma Study Design: Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment ID: NCT00289640
Clinicaltrials.gov	A Single Arm Study of Ipilimumab Monotherapy in Patients With Previously Treated Unresectable Stage III or IV Melanoma Condition: Melanoma Study Design: Allocation: Non-Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking:

Database	Relevant abstracts and/or details of the search
	Open Label; Primary Purpose: Treatment ID: NCT00289627
Clinicaltrials.gov	Ipilimumab in Patients With Advanced Melanoma and Spontaneous Preexisting Immune Response to NY-ESO-1 Condition: Metastatic Melanoma Study Design: Allocation: Non-Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment ID: NCT01216696
Clinicaltrials.gov	Autologous TriMix-DC Therapeutic Vaccine in Combination With Ipilimumab in Patients With Previously Treated Unresectable Stage III or IV Melanoma Conditions: Malignant Melanoma Stage III; Malignant Melanoma Stage IV Study Design: Allocation: Non-Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment ID: NCT01302496
Clinicaltrials.gov	Compassionate Use Trial for Unresectable Melanoma With Ipilimumab; A Multicenter Treatment Protocol for Compassionate Use of Ipilimumab in Subjects With Unresectable Stage III or IV Melanoma Condition: Melanoma Intervention: Drug: Ipilimumab ID: NCT00495066
Clinicaltrials.gov	A Study of MDX-010 (BMS-734016) Administered With or Without Prophylactic Oral Budesonide Condition: Malignant Melanoma Study Design: Allocation: Randomized; Endpoint Classification: Safety Study; Intervention Model: Single Group Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment ID: NCT00135408
Clinicaltrials.gov	Ipilimumab With or Without Vaccine Therapy in Treating Patients With Previously Treated Stage IV Melanoma Condition: Melanoma (Skin) Study Design: Allocation: Randomized; Masking: Open Label; Primary Purpose: Treatment ID: NCT00357461
Clinicaltrials.gov	THE IPI - Trial in Advanced Melanoma: Melanoma Patients With Advanced Disease Condition: Malignant Melanoma Study Design: Allocation: Non-Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment ID: NCT01355120
Clinicaltrials.gov	Long-term Data Collection for Subjects in MDX-010 Studies Condition: Metastatic Melanoma ID: NCT00803374

Inclusion and exclusion criteria.

	Description	Justification
Inclusion criteria		
Population	Adults, unresectable (stage III or IV) malignant melanoma with or without brain metastases, undergoing 2nd line therapy, having been pretreated with chemo- and/or immuno-therapy	According to final scope
Interventions	Ipilimumab, DacarbazineorTemozolamide (oral dacarbazineanalog) with or withoutaldesleukin, Carboplatin-based chemotherapy (carboplatin chemotherapy, Paraplatin, Paraplatin-AQ, ParaplatinAQ, platinum therapy or platinum chemotherapy), Palliative radiation	According to final scope
Outcomes	Overall Survival (OS), Progression Free Survival (PFS), response rates, adverse effects of treatment, health related quality-of-life	According to final scope
Study design	Blinded or open-label RCTs, of parallel or crossover design, phases II-IV	To assess studies that meet the highest level in the hierarchy of evidence
Language restrictions	English only	
Exclusion criteria		
Population	Studies with mixed 1st and 2nd line patients, studies with any number of treatment-naive patients. Stage I or stage II (localised primary) melanoma. Basal cell carcinoma. Squamous cell carcinoma. Bowen's disease (intraepidermal squamous cell carcinoma.	According to final scope
Interventions	Dicarbosil®, procarbazine. Cisplatin. Oxaliplatin.	According to final scope
Outcomes	No outcomes were excluded	All outcomes were deemed important to include
Study design	Phase I, pre-clinical	To assess studies that meet the highest level in the hierarchy of evidence
Language restrictions	Non-English studies excluded on final pass	

Non-randomised evidence (e.g. open label clinical trial) were excluded from the RCT search, but were labelled at exclusion phase for subsequent interrogation.

Data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

9.3 Appendix 3: Quality assessment of RCT(s)

Study ID or acronym: (MDX010-20) *Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. (2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. New England Journal of Medicine. 363(8):711-23.*		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Adequate: Patients were randomly assigned to one of three study groups using centralised scheme with stratification according to baseline metastases stage (M0, M1a or M1b) [Publication and study protocol]	Yes
Was the concealment of treatment allocation adequate?	Adequate: Placebo for both ipilimumab and vaccine were used; The pharmacist at each study site was unblinded to study medication; other study site personnel and patients were blinded to patient assignment.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Adequate: Metastases stages among the three arms were comparable; Previous systemic therapy (including IL-2 therapy) was similar	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: All site personnel including clinicians, data management, statisticians and patients were blinded. (except pharmacists were unblinded to the study medication)	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: The drop rates among the groups were similar; Patients who didn't start treatment after randomisation were 22/403, 6/137 and 5/136 respectively; Patients who discontinued were 135/403, 43/137 and 54/136 (Supplementary Appendix)	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: Results for all the mentioned outcomes were presented in the 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 were analysed using randomised (ITT) population	Yes

Study ID or acronym: (CA184-022) Wolchok J, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L et al. (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncology 11(2):155-164.		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate: Patients were randomised in a 1:1:1 ratio by using interactive voice response system (IVRS) and were assigned unique identification number	Yes
Was the concealment of treatment allocation adequate?	Adequate: The IVRS assigned a unique identification number and the system assigned the patient to one of the three treatment groups on the basis of a randomisation schedule generated.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: Demographics and baseline characteristics were consistent across treatment groups; Patients were similar across the groups with respect to M-stage and ECOG status.	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, treating doctors, and doctors' staff were blinded to the treatment allocation; whereas pharmacists, data monitoring committee were aware of the allocations. Unblinded personnel involved in the study have minimal or no effect on study bias	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: Across the three treatment groups - 0.3mg/kg, 3.0mg/kg, and 10mg/kg - treatment discontinuations (received fewer than 4 doses) were similar; 23/73, 21/72 and 35/72, respectively. One patient from each of the three treatment groups, having been randomised, did not receive any ipilimumab dose due to not meeting a study criterion (n=2) and progressive disease (n=1)	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: Outcomes specified were reported in results section	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: Efficacy analyses were done by ITT, whereas safety analyses included only patients who received at least one dose of ipilimumab	Yes, for efficacy analyses; No for safety analyses
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym: (CA184-007) Weber J, Thompson J, Hamid O, Minor D, Amin A, Ron I et al.(2009) A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clinical Cancer Research* 15(17):5591-5598.		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Adequate: Patients were randomised 1:1 to treatment arms; Randomisation was determined using a telephone interactive voice response system (IVRS) using a permuted block procedure.	Yes
Was the concealment of treatment allocation adequate?	Adequate: The IVRS randomisation suggests the treatment allocation was concealed adequately.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: More patients received previous systemic therapy in the budesonide arm compared to the placebo arm. However, other baseline demographic and characteristics were generally similar.	No
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: Blinded oral medication was self-administered by patients; Radiologic tumour assessments in patients were done by an independent review committee.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: Treatment discontinuations in each arm were similar, i.e., discontinuation due to disease progression was 25/58 in budesonide arm and 30/57 in placebo arm; discontinuation due to AEs was 17/58 and 17/57 respectively.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: Outcomes specified were reported in results section.	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: All randomly allocated patients (n=115) were included in the efficacy as well as tolerability analyses.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for Section 5.7 (Indirect and mixed treatment comparisons)

N/A

9.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 5.7

N/A

9.6 Appendix 6: Search strategy for Section 5.8 (Non-RCT evidence)

Databases searched

Medline & Medline(R) In-Process, and Embase were searched using OVID. Any studies available in Cochrane were assumed to have been identified through the initial RCT searches as trial specific filters were not used in this search.

Date on which the search was conducted

Searches in OVID were conducted on 4th May 2011.

Date span of the search

Ovid MEDLINE(R) 1948 to current (May 4th 2011)

EMBASE (Ovid), 1980 to week 17 (May 4th 2011)

Search strategy

Table 69: EMBASE 1980 to 2011 Week 17 - performed on 4th May 2011

	Searches	Results
1	skin neoplasms.mp. or exp skin tumor/	150690
2	melanoma.mp. or exp MELANOMA/	95832
3	((skin adj1 neoplasm*) or (skin adj1 cancer*) or (skin adj1 tumo?r*) or (skin adj1 carcinoma*) or (skin adj1 adenocarcinoma*) or (skin adj1 sarcoma*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	61461
4	1 or 2 or 3	231441
5	(advanced or metasta* or recurr* or unresect* or non-resect* or disseminated* or (stage adj1 III) or (stage adj1 IIIC) or (stage adj1 IV) or (stage adj1 '3') or (stage adj1 3C) or (stage adj '4')).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	1031396
6	4 and 5	61922
7	ipilimumab.mp. or exp IPILIMUMAB/	649
8	(MDX-010 or MDX-101 or yervoy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	202
9	7 or 8	662
10	6 and 9	330
11	Clinical study/	31074
12	Case control study/	52507
13	Family study/	9086
14	Longitudinal study/	43965
15	Retrospective study/	229114
16	Prospective study/	168312
17	Randomised controlled trials/	294424
18	16 not 17	145312
19	Cohort analysis/	97038

	Searches	Results
20	(Cohort adj (study or studies)).mp.	62833
21	(Case control adj (study or studies)).tw.	51692
22	(follow up adj (study or studies)).tw.	35175
23	(observationaladj (study or studies)).tw.	34188
24	(epidemiologic$ adj (study or studies)).tw.	57294
25	(cross sectional adj (study or studies)).tw.	48301
26	or/11-15,18-25	742505
27	case-referent.mp.	600
28	(case-cohort or case-exposure).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	905
29	case-base.mp. or epidemiology/	124613
30	or/26-29	852600
31	10 and 30	6

Table 70: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present - performed on 4th May 2011

	Searches	Results
1	skin neoplasms.mp. or exp Skin Neoplasms/	83961
2	exp Melanoma/ or melanoma.mp.	78960
3	((skin adj1 neoplasm*) or (skin adj1 cancer*) or (skin adj1 tumo?r*) or (skin adj1 carcinoma*) or (skin adj1 adenocarcinoma*) or (skin adj1 sarcoma*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	86280
4	1 or 2 or 3	141828
5	(advanced or metasta* or recurr* or unresect* or non-resect* or disseminated* or (stage adj1 III) or (stage adj1 IIIC) or (stage adj1 IV) or (stage adj1 '3') or (stage adj1 3C) or (stage adj '4')).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	881300
6	4 and 5	40275
7	ipilimumab.mp.	138
8	(MDX-010 or MDX-101 or yervoy).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	18
9	7 or 8	143
10	6 and 9	86
11	Epidemiologic studies/	4973
12	exp case control studies/	499827
13	exp cohort studies/	1086075
14	Case control.tw.	56505
15	(cohortadj (study or studies)).tw.	54423
16	Cohort analy$.tw.	2516
17	(Follow up adj (study or studies)).tw.	31990

	Searches	Results
18	(observationaladj (study or studies)).tw.	27754
19	Longitudinal.tw.	105700
20	Retrospective.tw.	200132
21	Cross sectional.tw.	113938
22	Cross-sectional studies/	122457
23	or/11-22	1469152
24	(case-referent or case-cohort or case-exposure or case-base).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	1422
25	23 or 24	1469509
26	10 and 25	4

Additional searches

Conference proceedings and specific journals were hand-searched for non-RCTs as they were for RCTs. The details of these searches are given in Section 9.2.5.

The inclusion and exclusion criteria.

Following publication of the final scope, the studies selected by the non-RCT search were reviewed, applying the below selection criteria;

- Population – adults diagnosed with unresectable (stage III or IV) malignant melanoma, with or without brain metastases, undergoing 2nd line therapy, having been pretreated with chemo- and/or immuno-therapy and having progressed/relapsed after 1st line systemic therapy. Studies with mixed 1st and 2nd line patients were excluded,

- Interventions – restricted to second line systemic treatments – Ipilimumab, Dacarbazine(DTIC®, Dimethyl Triazeno Imidazole Carboxamide, DTIC, Imidazole Carboxamide, Imidazole CarboxamideDimethyltriazene, WR-139007), Temozolamide (oral dacarbazineanalog) with or withoutaldesleukin, Carboplatin-based chemotherapy (carboplatin chemotherapy, Paraplatin, Paraplatin-AQ, ParaplatinAQ, platinum therapy or platinum chemotherapy), palliative radiation,

- Comparators - agents listed under ‘interventions’, as monotherapies or in combination, placebo, or best supportive care,

- Outcomes – Overall Survival (OS), Progression Free Survival (PFS), time to progression (TTP), response rates, adverse effects of treatment,

- Study designs – non-RCTs

- Language – English only.

Study selection process

Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded. Papers included after this stage were then assessed based on the full text; further papers were excluded and allocated an “exclusion code” to document the rationale for exclusion, yielding the final data set for inclusion.

The data abstraction strategy

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

9.7 Appendix 7: Quality assessment of non-RCT(s) in Section 5.8

Not applicable, no non-RCT evidence was identified.

9.8 Appendix 8: Search strategy for Section 5.9 (Adverse events)

The clinical searches described in Section 5.1 and Section 9.2 were also designed to identify eligible studies for adverse events associated with ipilimumab.

Databases searched

N/A

Date on which the search was conducted

N/A

Date span of the search

N/A

Search strategy

N/A

Additional searches

N/A

The inclusion and exclusion criteria.

N/A

The data abstraction strategy.

N/A

9.9 Appendix 9: Quality assessment of adverse event data in Section 5.9

A quality assessment of relevant studies can be found in Section 9.3.

9.10 Appendix 10: Search strategy for Section 6.1 (Cost-effectiveness studies)

Search strategy for economic evaluations

Table 71: Embase: accessed 9th December 2010

	Searches	Results
1	Socioeconomics/	88046
2	Cost benefit analysis/	54154
3	Cost effectiveness analysis/	69311
4	Cost of illness/	11033
5	Cost control/	37246
6	Economic aspect/	84364
7	Financial management/	90217
8	Health care cost/	95259
9	Health care financing/	10213
10	Health economics/	29749
11	Hospital cost/	10453
12	(fiscal or financial or finance or funding).tw.	69263
13	Cost minimisation analysis/	1777
14	(cost adj estimate$).mp.	1317
15	(cost adj variable$).mp.	110
16	(unit adj cost$).mp.	1441
17	exp economic evaluation/	161798
18	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	155205
19	exp Models, Economic/	71292
20	markov chains/	45353
21	markov$.mp.	9677
22	Monte Carlo Method/	13449
23	monte carlo.mp.	21936
24	exp Decision Theory/	1336
25	(decision$ adj2 (tree$ or analy$ or model$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	11994
26	(economic$ or pharmacoeconomic$ or pharmaco-economic$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	385513
27	Economics/	184354
28	exp "Fees and Charges"/	29242
29	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	846957
30	exp MELANOMA/	79083
31	melanoma*.mp.	93579
32	(malignan* or metasta* or disseminat* or advanced or pre-treat* or pre treat* or stage or unresect*).mp.	1482876
33	30 or 31	93837
34	32 and 33	52900
35	29 and 34	782

Table 72: Medline and Medline In Process: accessed 9th December 2009

	Searches	Results
1	Economics/	26026
2	"costs and cost analysis"/	38881
3	Cost allocation/	1901
4	Cost-benefit analysis/	50306
5	Cost control/	18523
6	Cost savings/	6876
7	Cost of illness/	13694
8	Cost sharing/	1626
9	"deductibles and coinsurance"/	1267
10	Medical savings accounts/	437
11	Health care costs/	20737
12	Direct service costs/	932
13	Drug costs/	10217
14	Employer health costs/	1020
15	Hospital costs/	6382
16	Health expenditures/	11403
17	Capital expenditures/	1893
18	Value of life/	5176
19	exp economics, hospital/	17021
20	exp economics, medical/	13094
21	Economics, nursing/	3828
22	Economics, pharmaceutical/	2168
23	exp "fees and charges"/	25143
24	exp budgets/	10752
25	(low adj cost).mp.	16051
26	(high adj cost).mp.	6369
27	(health?care adj cost$).mp.	2655
28	(fiscal or funding or financial or finance).tw.	61294
29	(cost adj estimate$).mp.	1128
30	(cost adj variable).mp.	28
31	(unit adj cost$).mp.	1191
32	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	133373
33	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	94956
34	(economic$ or pharmacoeconomic$ or pharmaco-economic$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	167866
35	exp Models, Economic/	7618
36	economic model*.mp.	1245
37	Markov Chains/	7025
38	markov*.mp.	11653
39	Monte Carlo Method/	15123
40	monte carlo.mp.	26177

	Searches	Results
41	exp Decision Theory/	8280
42	(decision$ adj2 (tree$ or analy$ or model$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	12455
43	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 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	463206
44	exp Melanoma/	63523
45	melanoma*.mp.	79981
46	(malignan* or metasta* or disseminat* or advanced or pre-treat* or pre treat* or stage or unresect*).mp.	1292533
47	Melanoma/ec [Economics]	76
48	44 or 45	80058
48	47 or 48	1292561
50	46 and 48	44601
51	43 and 50	365

Table 73: Econlit: Accessed 9th December 2010

	Search Terms	Results
1	melanoma*.mp. [mp=heading words, abstract, title, country as subject]	9
2	(malignan* or metasta* or disseminat* or advanced or pre-treat* or pre treat).mp. [mp=heading words, abstract, title, country as subject]	7094
3	1 and 2	5

Table 74: NHS EED: Accessed 9th December 2010

	Search Terms	Results
S5	S3 and S4	56
S4	S1 or S2	56
S3	TX malignan* or TX metasta* or TX disseminat* or TX advanced or TX pre-treat* or TX pre treat*	3410
S2	TX melanoma*	56
S1	MH Melanoma	44

The data abstraction strategy.

Economic Evaluations excluded on the basis of diagnosis/screening/surveillance

1. Agnese DM, Abdessalam SF, BurakJr WE, Magro CM, Pozderac RV, Walker MJ, et al. Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. *Surgery* 2003;134 (4):542-48.
2. Basseres N, Grob JJ, Richard MA, Thirion X, Zarour H, Noe C, et al. Cost-effectiveness of surveillance of stage I melanoma. A retrospective appraisal based on a 10-year experience in a Dermatology Department in France. *Dermatology* 1995;191 (3):199-203.
3. Brobeil A, Cruse CW, Messina JL, Glass LF, Haddad FF, Berman CG, et al. Cost analysis of sentinel lymph node biopsy as an alternative to elective lymph node

dissection in patients with malignant melanoma. *SurgOncolClin N Am* 1999;8(3):435-45.

4. Collinson and Marples (2010) UK survey of second line chemotherapy use for metastatic melanoma. NCRI 2010, B23. http://www.ncri.org.uk/ncriconference/2010abstracts/abstracts/B23.htm
5. Dietlein M, Krug B, Groth W, Smolarz K, Scheidhauer K, Psaras T, et al. Positron emission tomography using 18F-fluorodeoxyglucose in advanced stages of malignant melanoma: a comparison of ultrasonographic and radiological methods of diagnosis. Nucl Med Commun 1999;20(3):255-61.
6. Freedberg KA, Geller AC, Miller DR, Lew RA, Koh HK. Screening for malignant melanoma: A cost-effectiveness analysis. *J Am AcadDermatol* 1999;41(5 Pt 1):738-45.
7. Hengge UR, Wallerand A, Stutzki A, Kockel N. Cost-effectiveness of reduced follow-up in malignant melanoma. *J* 2007;5(10):898-907.

[redacted]

9. Kalvin B, Fekeshazy A, Lengyel Z, Szakall S, Agoston P, Lengyel E, et al. Cost-effective PET scans in oncology (Brief record). OrvHetil, 2002:1255-12561.
10. Kharroubi, S, Brazier, JE, Roberts, JR, et al. Modelling SF-6D health state preference data using a nonparametric Bayesian method. Journal of Health Economics, 2007;26(3):597-612)
11. Krug B, Crott R, Roch I, Lonneux M, Beguin C, Baurain J-F, et al. Cost-effectiveness analysis of FDG PET-CT in the management of pulmonary metastases from malignant melanoma. Acta Oncol;49(2):192-200.
12. Leiter U, Marghoob AA, Lasithiotakis K, Eigentler TK, Meier F, Meisner C, et al. Costs of the detection of metastases and follow-up examinations in cutaneous melanoma. *Melanoma Res* 2009;19(1):50-7.
13. Losina E, Walensky RP, Geller A, Beddingfield FC, 3rd, Wolf LL, Gilchrest BA, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. *Arch Dermatol* 2007;143(1):21-8.
14. Maio M, Lebbe´ C, Neyns B et al Three-year survival rates for patients with advanced melanoma who received ipilimumab at10 mg/kg in phase II trials. Presented at: Perspectives in Melanoma XIV; September 17-18, 2010; Amsterdam, The Netherlands
15. Mooney MM, Mettlin C, Michalek AM, Petrelli NJ, Kraybill WG. Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis. *Cancer* 1997;80(6):1052-64.
16. Morton RL, Howard K, Thompson JF. The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma (Structured abstract). *Ann SurgOncol*, 2009:929-40.
17. Middleton et al (2010) Treatment patterns and outcomes in advanced melanoma in UK: a retrospective longitudinal survey (MELODY study). NCRI 2010, B23. LB175. http://www.ncri.org.uk/ncriconference/2010abstracts/abstracts/LB175.htm

18. ONS (2011) Office for National Statistics Interim Life Tables, England, 1980-82 to 2007-09. http://www.statistics.gov.uk/statbase/Product.asp?vlnk=14459

[redacted]

20. von Schulthess GK, Steinert HC, Dummer R, Weder W. Cost-effectiveness of whole-body PET imaging in non-small cell lung cancer and malignant melanoma. *AcadRadiol* 1998;5Suppl 2:S300-2.
21. Saenger and Wolchok (2008)The heterogeneity of the kinetics of response to ipilimumab in metastatic melanoma: patient cases. Cancer Immunity (17 January 2008) Vol. 8, p. 1
22. Thomas JM. Prognostic false-positivity and cost-effectiveness in sentinel node biopsy in melanoma. *Ann SurgOncol* 2009;16(10):2961; author reply 62-3.
23. Valk PE, Pounds TR, Tesar RD, Hopkins DM, Haseman MK. Cost-effectiveness of PET imaging in clinical oncology. *Nucl Med Biol* 1996;23(6):737-43.
24. Van der Velde-Zimmermann D, Schipper ME, de Weger RA, Hennipman A, BorelRinkes IH. Sentinel node biopsies in melanoma patients: a protocol for accurate, efficient, and cost-effective analysis by preselection for immunohistochemistry on the basis of Tyr-PCR. *Ann SurgOncol* 2000;7(1):51-4.

Economic I3 excluded studies

1. Bodera, 2006 Evaluation of survival time in patients with high-risk melanoma treated with interferon (INF), based on clinical reports, using regression analysis and the hidden Markov model. International Review of Allergology and Clinical Immunology 2006 Volume 12 (4) 147-151.
   No cost data were used in this study, therefore not an economic evaluation

2. Brown, 1999 Benefit valuation in economic evaluation of cancer therapies: A systematic review of the published literature. Pharmacoeconomics 1999. Volume 16 (1) 17-31.
   Systematic review and therefore not original data

3. Crott, 2004 Cost effectiveness and cost utility of adjuvant interferon alpha in cutaneous melanoma: a review. Pharmacoeconomics 2004. Volume 22, issue 9, 569-80.
   Systematic review and therefore not original data

4. Hillner, 1997 Economic analyses of benefit from interferon-alpha 2B in high-risk melanoma: trade-offs between completeness, simplicity and clarity. European Journal of Cancer 1997. Volume 33, issue 9, 1345-6.
   Review/editorial and therefore provides no primary data

5. Hofmann, 2002 Primary staging and follow-up in melanoma patients--monocenter evaluation of methods, costs and patient survival. British Journal of Cancer 2002. Volume 87, issue 2, 151-7.
   Only Stage II melanoma data included

6. Lafuma, 2001 Economic analysis of adjuvant therapy with interferon alpha-2a in stage II malignant melanoma. European Journal of Cancer 2001. Volume 37, issue 3, 369-75.
   Only Stage II melanoma data included

9.11 Appendix 11: Quality assessment of cost-effectiveness studies

Study title: Dixon S, Walters SJ, Turner L, Hancock BW. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. *Br J Cancer* 2006;94(4):492-8.		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The model was to assess the cos-effectiveness of two products within the confines of a clinical trial, therefore while the format was appropriate for the aim, it is not generalizable to the wider world
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	

Study title: Dixon S, Walters SJ, Turner L, Hancock BW. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. *Br J Cancer* 2006;94(4):492-8.		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	No utility scores used were listed in the paper
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	n/a	
16. Were quantities of resources reported separately from their unit cost?	No	No resource costs were listed
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	While the sources were given for this data including PSSRU, details were not given
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	The analysis was said to be performed using the NICE Guide to the methods of technology appraisal (therefore one would assume 3.5%), however this is not explicitly states
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	

Study title: Dixon S, Walters SJ, Turner L, Hancock BW. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. *Br J Cancer* 2006;94(4):492-8.		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	The limitation of the lack of extrapolation was not fully justified – judging the model by the Guide to the methods of technology appraisal, an insufficient time horizon was used

9.12 Appendix 12: Search strategy for Section 6.4 (Measurement and valuation of health effects)

Table 75: Embase: accessed 14th August 2009

	Searches	Results
1	exp MELANOMA/	78728
2	melanoma*.mp.	93158
3	(malignan* or metasta* or disseminat* or advanced or pre-treat* or pre treat*).mp.	1112830
4	1 or 2	93415
5	3 and 4	51402
6	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp.	14764
7	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp.	2053
8	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	2787
9	(GLQ* or QLQ* or QWB*).mp.	2248
10	(Health utilities index or HUI).mp.	1604
11	(time trade off or TTO).mp.	879
12	(standard gamble or SG).mp.	5387
13	quality of life.mp. or *"quality of life"/	191745
14	health status.mp. or *health status/	75159
15	health status indicators.mp.	257
16	activities of daily living.mp. or *daily life activity/	18409
17	*health survey/ or health survey*.mp.	125307
18	quality adjusted life years.mp. or *quality adjusted life year/	2908
19	psychometrics.mp. or *psychometry/	6376
20	(QOL or HRQOL or HRQL or QALY*).mp.	27156
21	(health* year* equivalent* or HYE*).mp.	810
22	(Quality of wellbeing index or QWB).mp.	152
23	(medical outcomes survey or MOS).mp.	4868
24	(willingness to pay or WTP).mp.	1932
25	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	398084
26	5 and 25	844

Table 76: Medline: accessed 19th November 2010

	Searches	Results
1	exp Melanoma/	63445
2	melanoma*.mp.	79656
3	(malignan* or metasta* or disseminat* or advanced or pre-treat* or pre treat*).mp.	961872
4	1 or 2	79733
5	3 and 4	43328
6	(sf36 or sf 36).mp.	9563
7	(short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty	4448

	Searches	Results
	six).mp.	
8	(sf12 or sf 12).mp.	1350
9	(short form 12 or shortform 12 or sf twelve or short form twelve).mp.	509
10	(euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).mp.	2182
11	(GLQ* or QLQ* or QWB* or qlq-c30 or fact-c or facit or qli-cp).mp.	1929
12	(Health utilities index or HUI or health utilit$ index or health utilit$ indices).mp.	827
13	(time trade off or TTO).mp.	756
14	(standard gamble or SG).mp.	4701
15	(quality of life or (quality adj3 life) or qol).mp.	140430
16	value of life/	5174
17	health status indicators.mp.	15905
18	health status.mp.	80006
19	Quality-Adjusted Life Years/	4766
20	"Activities of Daily Living"/	41987
21	Health Surveys/ or health survey*.mp.	48644
22	Quality-Adjusted Life Years/	4766
23	quality adjusted life year*.mp.	6554
24	(qaly$ or qald$ or qale$ or qtime$).mp.	3383
25	(disability adjusted life or daly).mp.	953
26	(QOL or HRQOL or HRQL or QALY).mp.	20553
27	(health* year* equivalent* or HYE*).mp.	578
28	(index of wellbeing or Quality of wellbeing index or QWB).mp.	141
29	(utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease)).mp.	4447
30	(medical outcomes survey or MOS).mp.	4131
31	(willingness to pay or WTP).mp.	1578
32	*Psychometrics/ or psychometric*.mp.	51679
32	or/6-32	289130
33	5 and 33	392

Table 77: Econlit

	Search Terms	Results
1	melanoma*.mp. [mp=heading words, abstract, title, country as subject]	9
2	(malignan* or metasta* or disseminat* or advanced or pre-treat* or pre treat).mp. [mp=heading words, abstract, title, country as subject]	7094
3	1 and 2	5

Table 78: NHS EED

	Search Terms	Results
S5	S3 and S4	56
S4	S1 or S2	56
S3	TX malignan* or TX metasta* or TX disseminat* or TX advanced or TX pre-treat* or TX pre treat*	3410
S2	TX melanoma*	56

S1	MH Melanoma	44

9.13 Appendix 13: Search strategy for Section 6.5 (Resource identification, measurement and valuation)

N/A

9.14 Appendix 14: Kaplan-Meier curve fits

Single Curve Fits

Ipilimumab - Overall Survival, Ipi + GP100

	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	0.926	0.002	**5.713**	1.322	-5.935
Beta	512.276	0.000	**1.304**	0.003	-0.001
AIC	1653.343	1655.136	**1607.488**	1609.746	1625.652

Ipilimumab – Progression Free Survival, Ipi + GP100

	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	1.005	0.007	4.557	**2.355**	-4.691
Beta	148.359		0.846	**0.011**	-0.002
AIC	1160.499	1160.521	993.604	**936.411**	1106.148

Ipilimumab – Overall Survival, Ipi Only

	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	0.896	0.002	**5.781**	1.291	-5.919
Beta	554.806		**1.324**	0.003	-0.001
AIC	424.931	424.841	**409.140**	410.676	413.746

Ipilimumab – Progression Free Survival, Ipi Only

	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	0.870	0.005	4.787	**1.981**	-4.804

Beta	201.195		0.977	**0.010**	-0.003
AIC	441.423	444.552	379.306	**363.061**	399.065

Ipilimumab – Overall Survival, Ipi Only + Ipi + GP100

	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	0.926	0.002	**5.713**	1.322	-5.935
Beta	512.276		**1.304**	0.003	-0.001
AIC	1653.343	1655.136	**1607.488**	1609.746	1625.652

Ipilimumab – Progression Free Survival, Ipi Only + Ipi + GP100

	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	0.955	0.006	4.615	**2.242**	-4.713
Beta	161.009		0.885	**0.011**	-0.002
AIC	1614.067	1614.378	1378.979	**1303.058**	1507.868

GP100 – Overall Survival

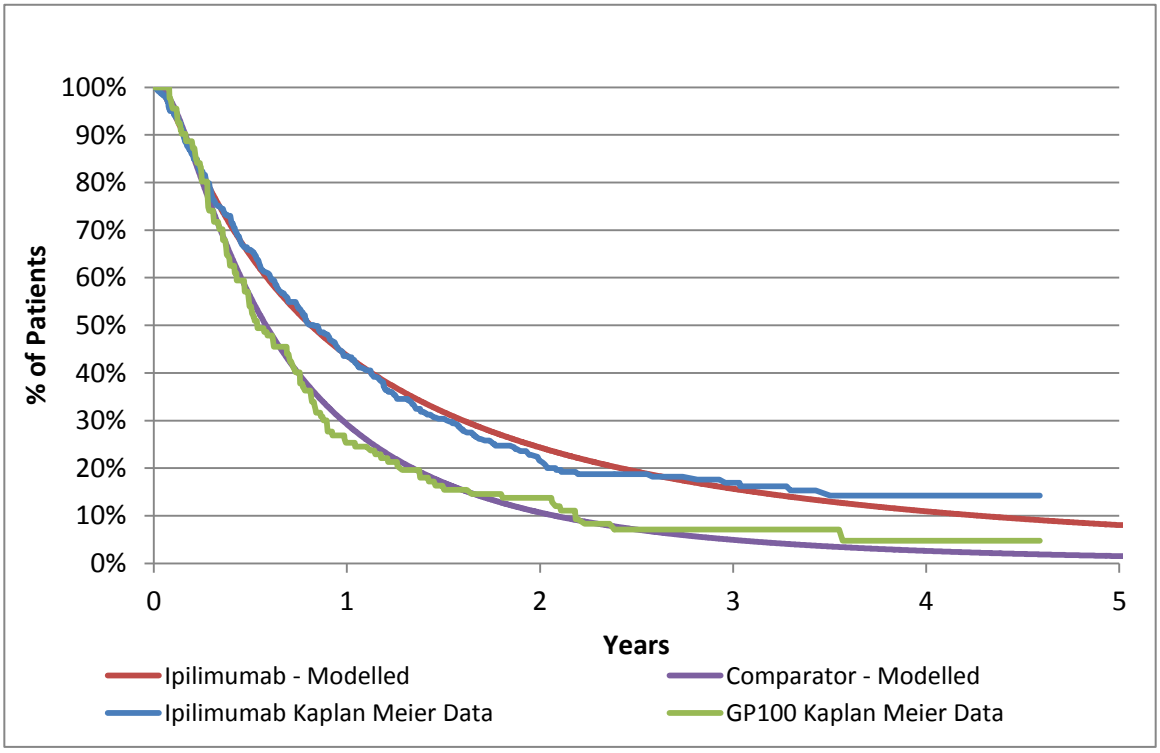
	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	1.071	0.003	**5.353**	1.742	-5.669
Beta	338.793		**0.996**	0.005	-0.001
AIC	389.879	388.826	**368.579**	369.336	388.716

GP100 – Progression Free Survival

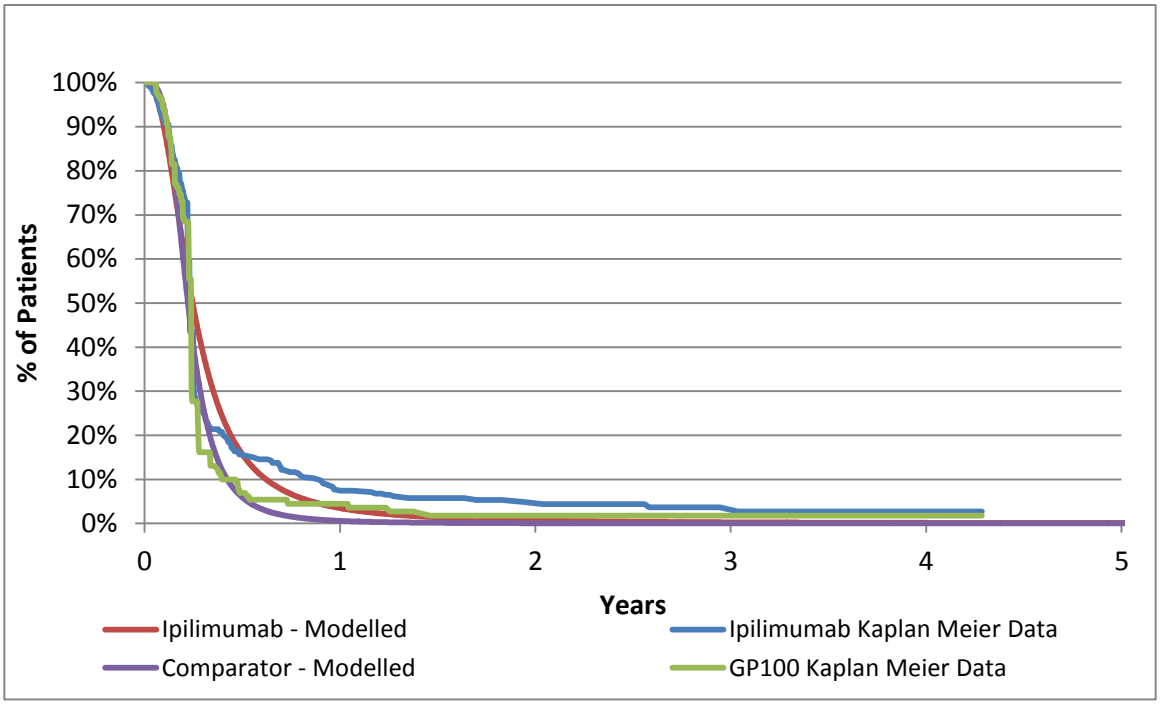
	Weibull	**Exponential**	**Lognormal**	**Log-logistic**	**Gompertz**
Alpha	1.184	0.009	4.419	**3.388**	-4.539
Beta	116.697		0.622	**0.012**	-0.001
AIC	333.145	339.084	254.269	**224.234**	334.699

Single Curve Fits - Graphs

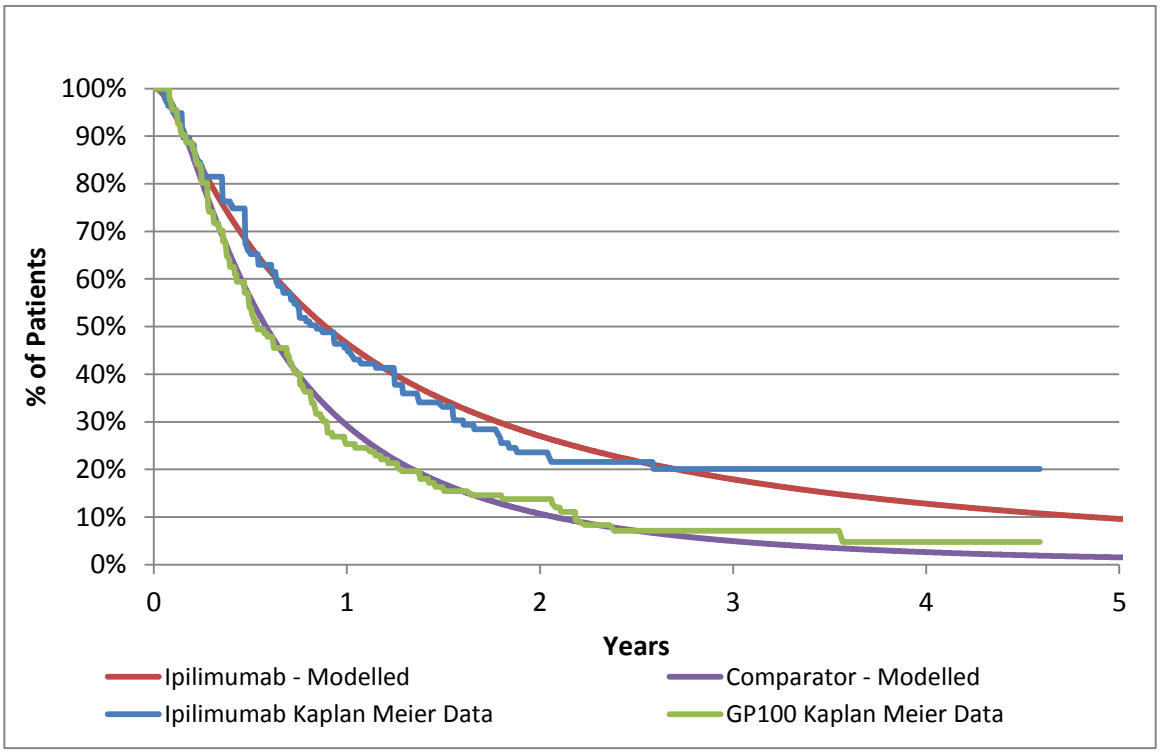
Ipi + GP100 – Overall Survival



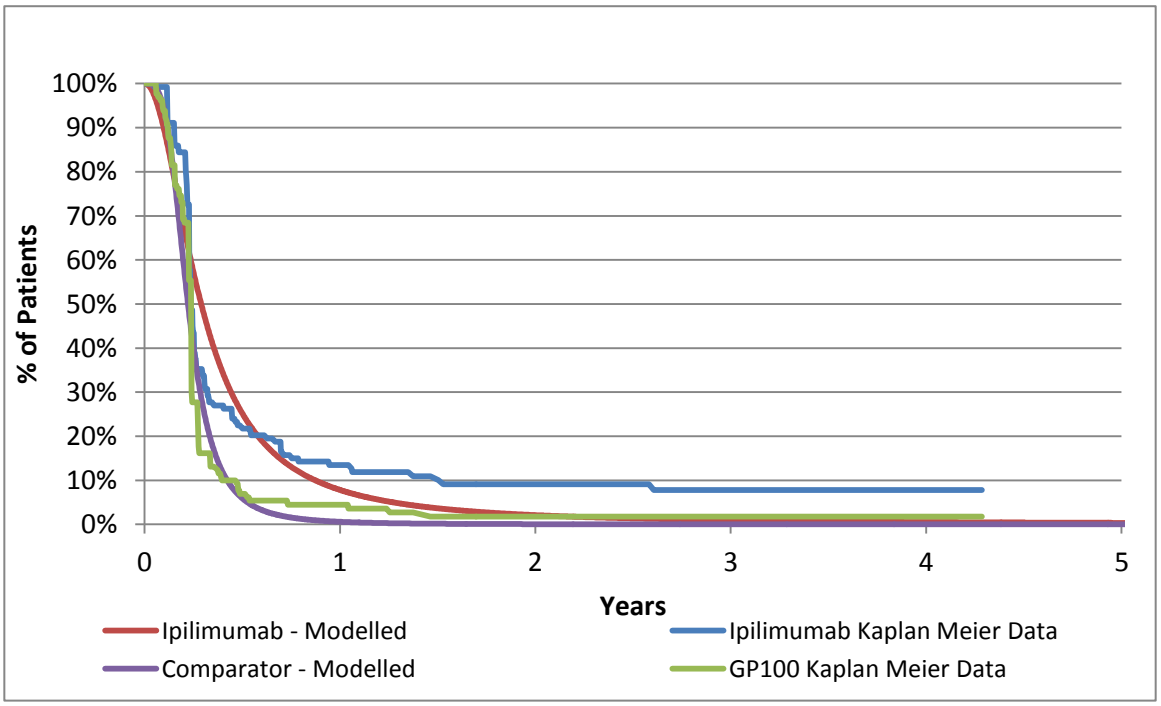
Ipi + GP100 – Progression Free Survival



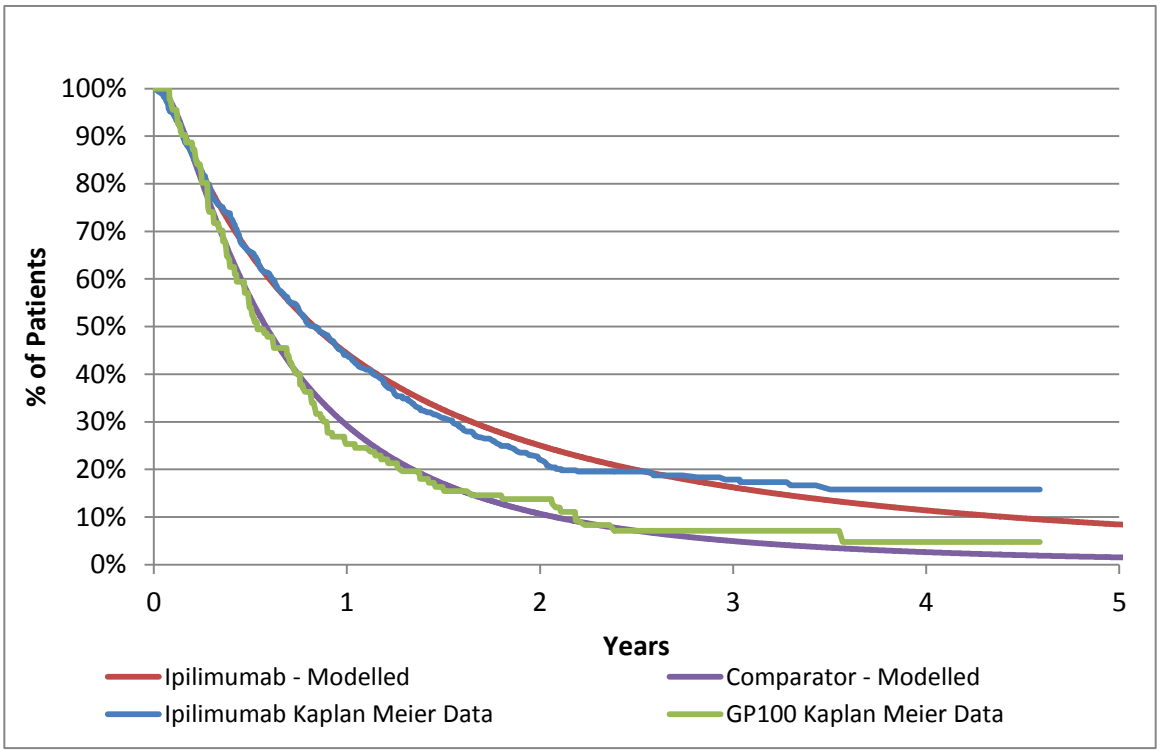
Ipi Only – Overall Survival



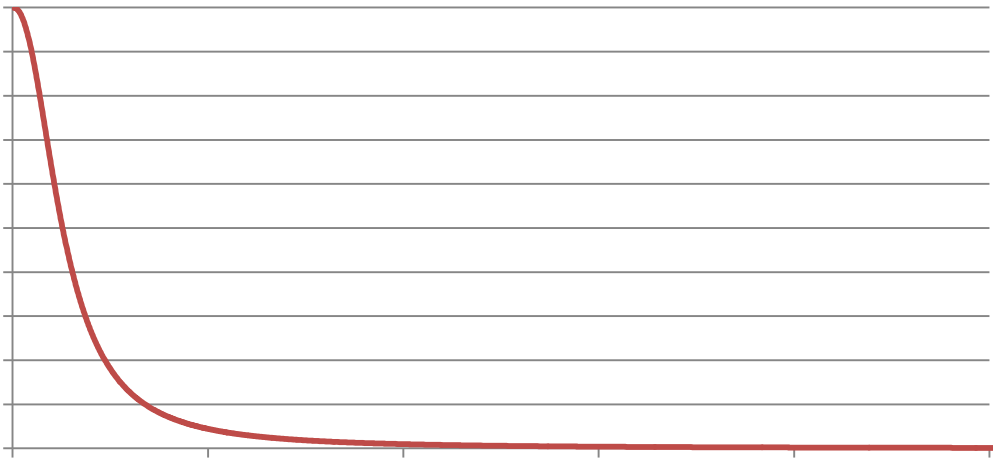
Ipi Only – Progression Free Survival



Ipi Only + Ipi + GP100 – Overall Survival



Ipi Only + Ipi + GP100 – Progression Free Survival



Two Part Curve Fits

Ipilimumab - Overall Survival, Ipi + GP100

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	0.782	0.001	**6.476**	0.942	-6.201
Beta	1045.231		**1.830**	0.002	-0.002
AIC	227.267	228.874	**221.745**	224.220	221.980

Ipilimumab – Progression Free Survival, Ipi + GP100

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	1.174	**0.001**	6.618	1.408	-7.002
Beta	1035.249		1.224	0.001	0.000
AIC	30.125	**28.309**	29.240	29.679	30.296

Ipilimumab – Overall Survival, Ipi Only

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	0.548	0.001	6.911	0.648	**-5.676**
Beta	1854.753		2.635	0.001	**-0.007**
AIC	99.242	105.199	96.829	98.027	**93.315**

Ipilimumab – Progression Free Survival, Ipi Only

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	0.413	0.001	**8.916**	0.445	-6.349
Beta	10630.433		**4.029**	0.000	-0.005
AIC	29.108	30.754	**28.725**	29.032	30.662

Ipilimumab – Overall Survival, Ipi Only + Ipi + GP100

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	0.705	0.001	6.595	0.842	**-6.081**
Beta	1207.340		2.052	0.001	**-0.003**
AIC	324.394	332.316	316.937	320.305	**314.751**

Ipilimumab – Progression Free Survival, Ipi Only + Ipi + GP100

	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	0.726	**0.001**	7.464	0.796	-6.859
Beta	2073.268		2.401	0.001	-0.001
AIC	58.269	**57.423**	58.328	58.310	58.709

GP100 – Overall Survival

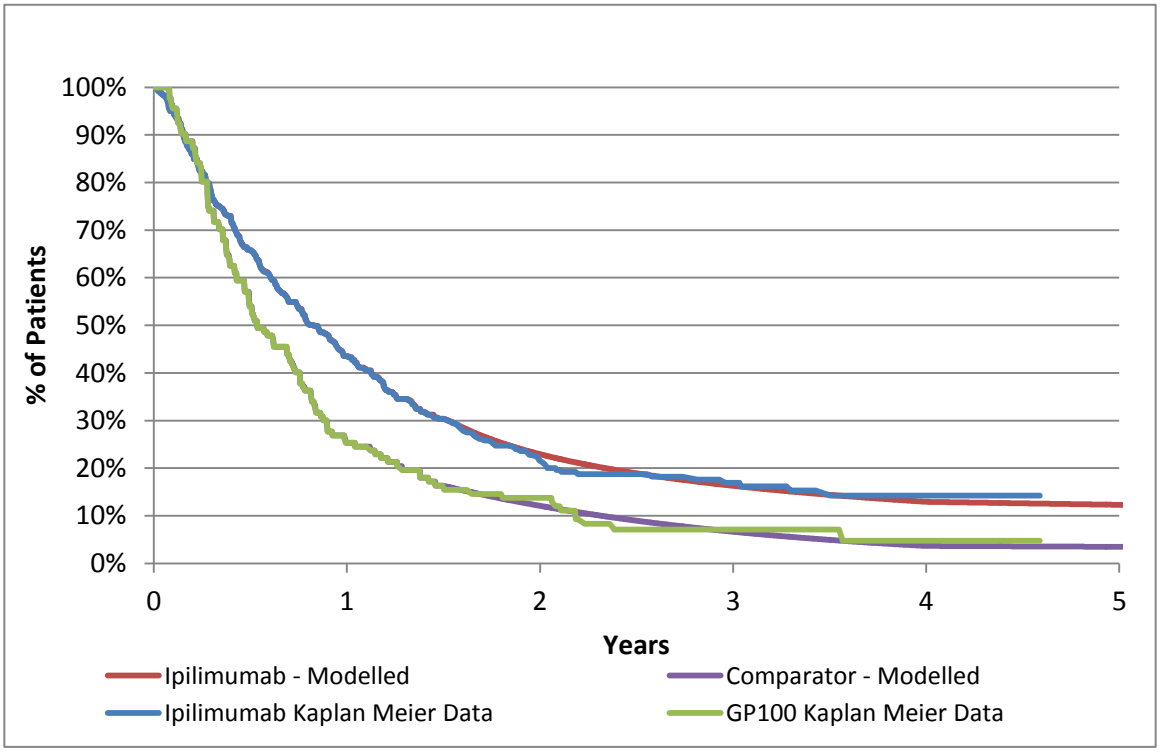
	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	1.032	**0.002**	6.036	1.300	-6.374
Beta	604.836		1.481	0.002	0.000
AIC	54.271	**52.285**	55.281	54.184	54.274

GP100 – Progression Free Survival

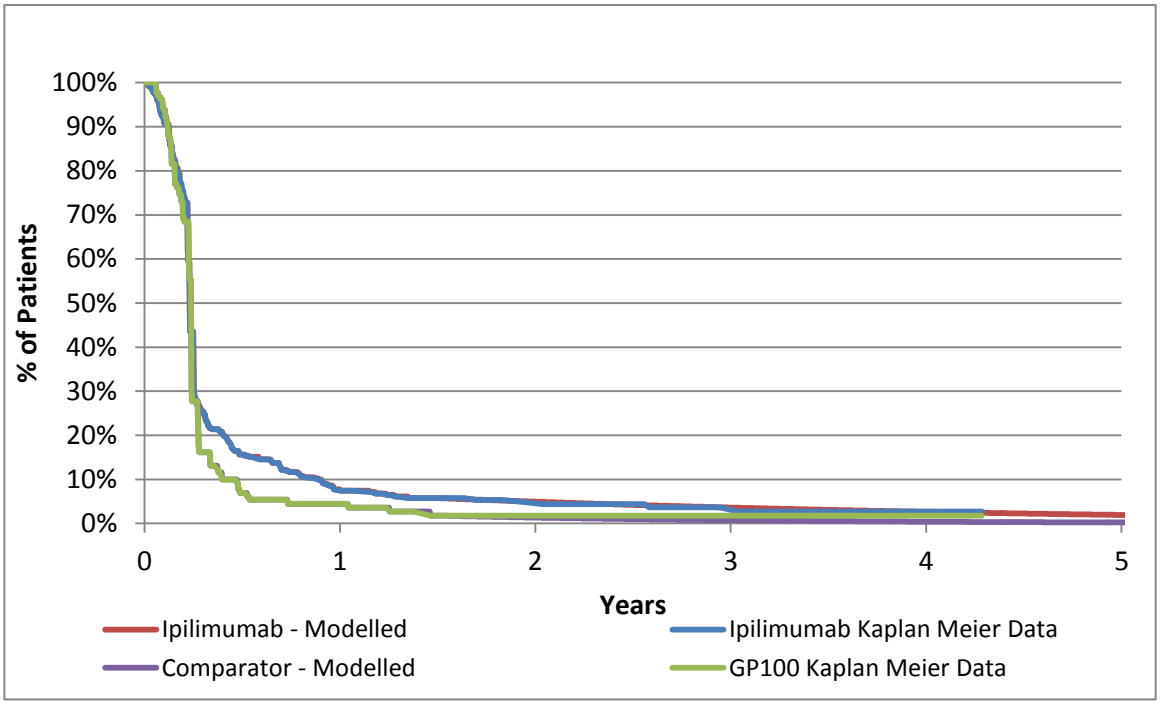
	Weibull	Exponential	Lognormal	Log-logistic	Gompertz
Alpha	1.032	**0.002**	6.036	1.300	-6.374
Beta	604.836	**0.000**	1.481	0.002	0.000
AIC	54.271	**52.285**	55.281	54.184	54.274

Two Part Curve Fit – Graphs

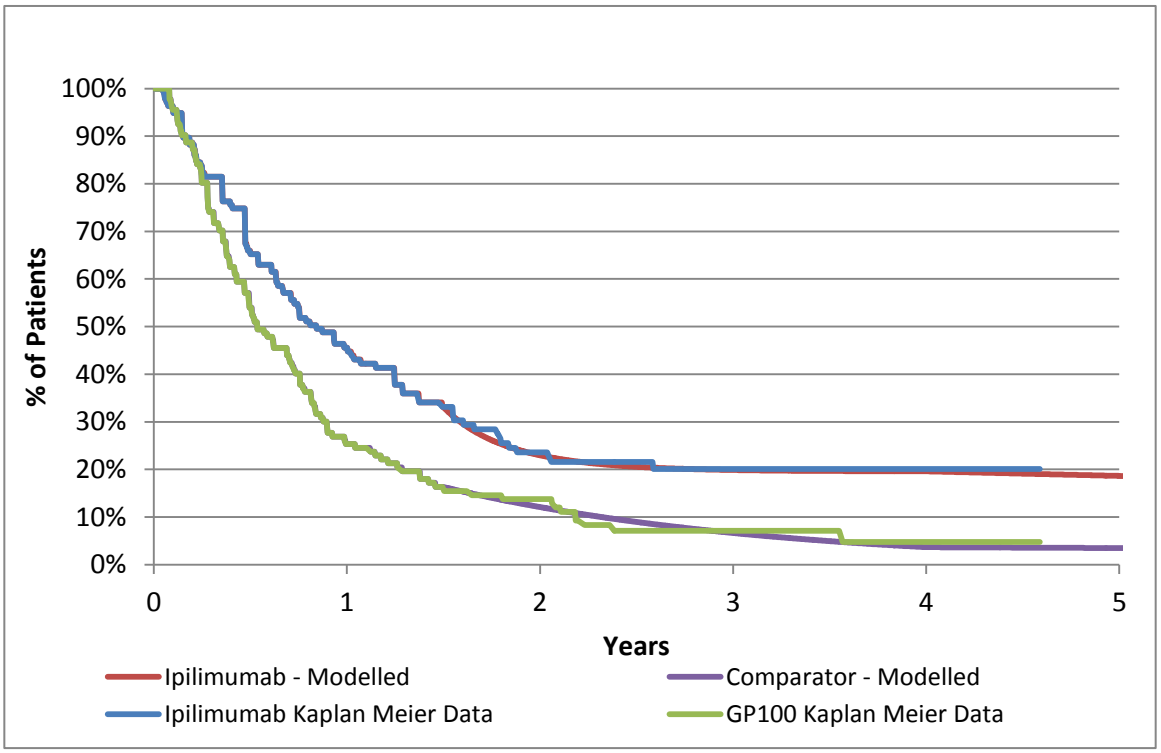
Ipi + GP100 – Overall Survival



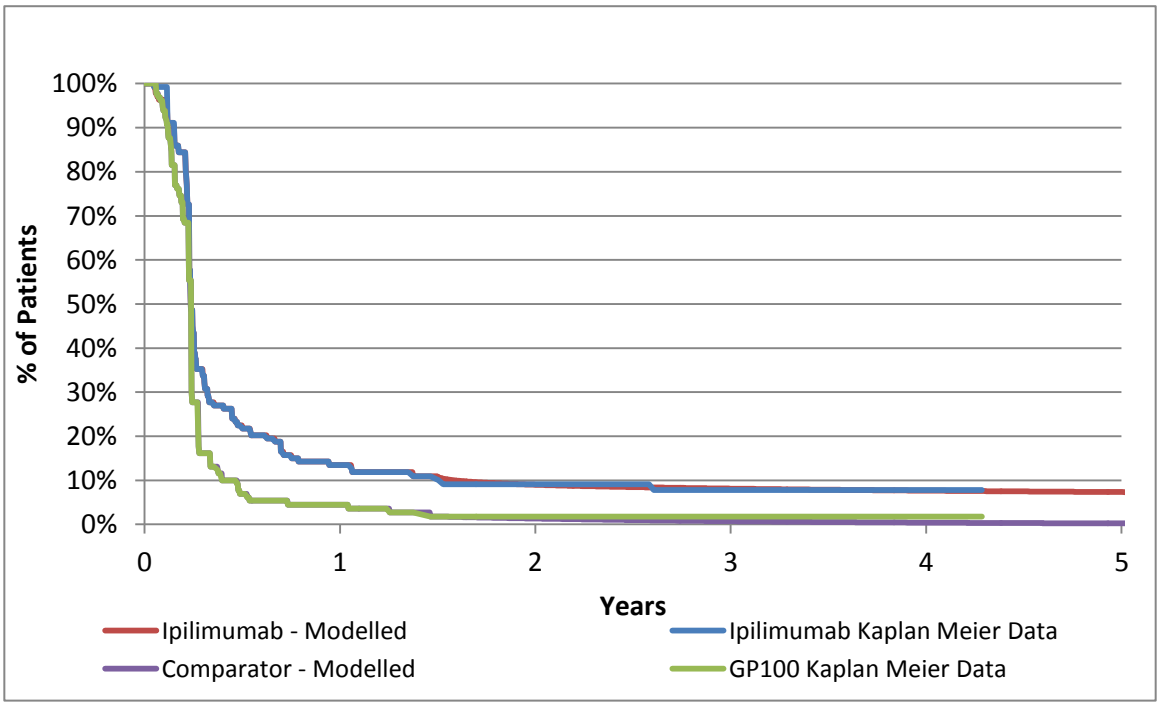
Ipi + GP100 – Progression Free Survival



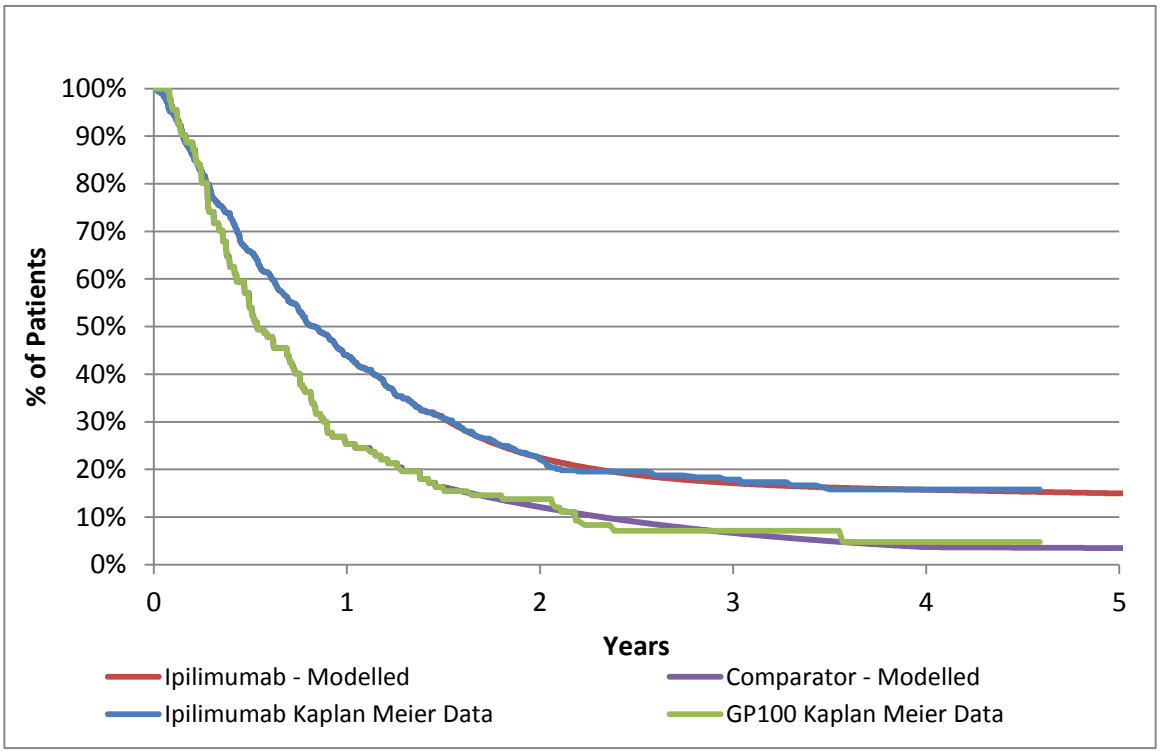
Ipi Only – Overall Survival



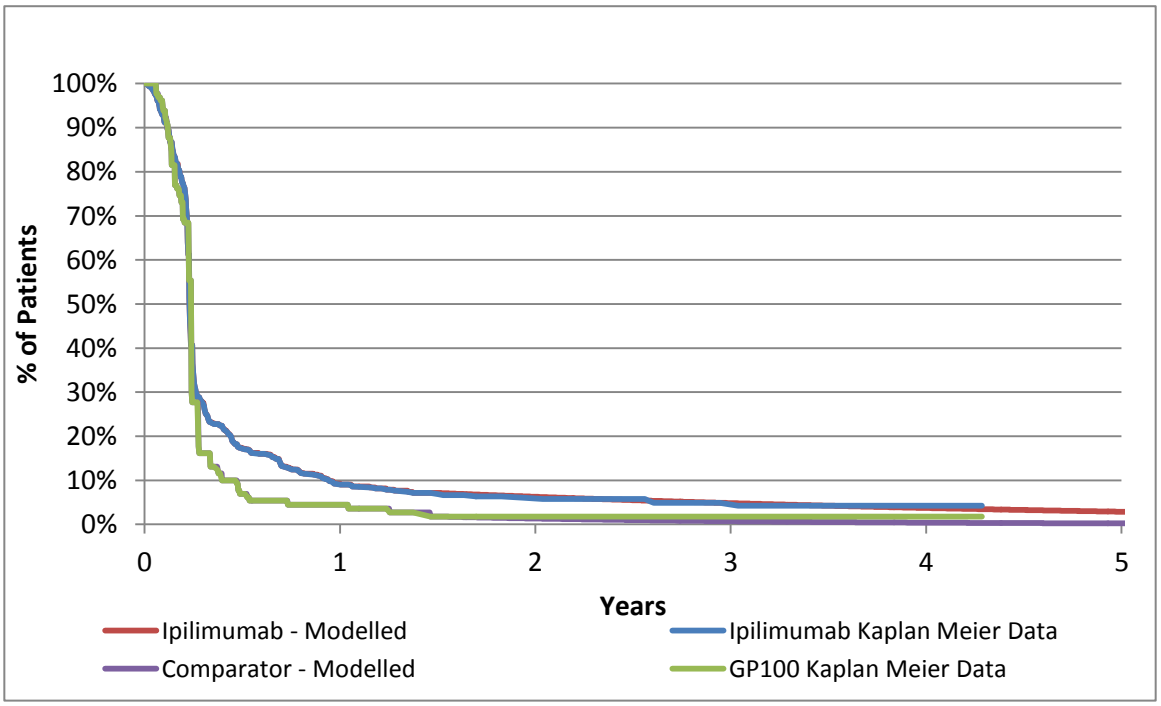
Ipi Only – Progression Free Survival



Ipi Only + Ipi + GP100 – Overall Survival



Ipi Only + Ipi + GP100 – Progression Free Survival



9.15 Appendix 15: Model assumptions relating to comparator data

Comparator Dosing

Drug	Dose	Dose Units	Target Dose	Intensity if Reduced	Total Dose	Source of Dosing & Intensity Information
Dacarbazine	850.0	*mg/m²*	1640.5	96%	1580.5	Dosing: SPC Intensity: Bedikian 2006. The dosage that is used in the model is 850 mg/m2, while the dose in the Bedikian source is 1,000.
Paclitaxel	175.0	*mg/m²*	337.8	90%	303.2	SPC Intensity: Walker et al, Phase II trial of weekly paclitaxel in patients with advanced melanoma, Melanoma Res. 2005 Oct;15(5):453-9.
Paclitaxel when used with Carboplatin	175.0	*mg/m²*	337.8	90%	303.2	
Carboplatin for use with Paclitaxel	AUC = 5		221.9	98%	216.5	AUC taken from consultation with clinicians (lower than that used in the Prism study (AUC = 6) Serum creatine clearance of 329.5 assumed – average of range from freekinetics calculator Using AUC calculator formula http://www.freekinetics.com/auccalc1.htm
Carboplatin	AUC = 5		221.9	98%	216.5	
Cisplatin	75.0	*mg/m²*	144.8	100%	144.8	Clinician consultation
Cisplatin for use with Interferon alfa-2b	15.0	*mg/m²*	29.0	100%	29.0	Assumed as 5 day dosing regimen from SPC
Interferon alfa-2b for use with Cisplatin	3.0	*MU*	3.0	100%	3.0	Low dose from European countries in Oxford Outcomes Research
Interferon alfa-2b	6.0	*MU*	6.0	100%	6.0	Clinician consultation
Vindesine	3.0	*mg/m²*	5.8	100%	5.8	Melanoma Res. 2003 Jun;13(3):299-302.
Treosulfan	3	*g/m²*	3.0	100%	3.0	Atzpodien, Terfloth, Fluck, & Reitz, 2007 and Ugurel et al., 2006
Temozolomide	1000.0	*mg/m²*	1930.0	100%	1930.0	5 x 200mg/m2 per month, SPC monotherapy phase
Imatinib	11200	*mg*	11200	100%	11200.0	Wyman et al and Ugurel et al, 400mg twice daily, 2 weekly physician visit

Comparator Dosing – Days Between Administrations and Administration Period Assumed

Drug	Days Between Administrations	Length of Administration Period (Days)	Length of Break Between Administrations (Days)	Equivalent Doses per Week
Dacarbazine	21	Indefinite		0.3
Paclitaxel	7	42	14	0.8
Paclitaxel + Carboplatin	7	42	14	0.8
Carboplatin	21	Indefinite		0.3
Cisplatin	21	Indefinite		0.3
Cisplatin + Interferon alfa-2b	2	Indefinite		3.5
Interferon alfa-2b	2	Indefinite		3.5
Vindesine	14	Indefinite		0.5
Treosulfan	7	8	32	0.1
Temozolomide	28	Indefinite		0.3
Imatinib	14	Indefinite		0.5

Other Variables Required for Dosing

Body Surface Area = 1.93m^2 : MDX-020 trial and Rituximab for the 1st line treatment of Chronic Lymphocytic Leukaemia Manufacturer Submission, 2008

Body Weight = 78.8kg: As assumed for ipilimumab

Comparator Administration Costs

Treatment	Type of Administration Required	Inpatient or Outpatient?	1st Cycle Cost	Subsequent Cost
Dacarbazine	Complex Chemotherapy	Inpatient	£271.00	£284.00
Paclitaxel	Complex Chemotherapy	Inpatient	£271.00	£284.00
Paclitaxel + Carboplatin	Complex Chemotherapy	Inpatient	£271.00	£284.00
Carboplatin	Complex Chemotherapy	Inpatient	£271.00	£284.00
Cisplatin	Complex Chemotherapy	Inpatient	£271.00	£284.00
Cisplatin + Interferon alfa-2b	Complex Chemotherapy	Inpatient	£271.00	£284.00
Interferon alfa-2b	Complex Chemotherapy	Inpatient	£271.00	£284.00
Vindesine	Complex Chemotherapy	Inpatient	£271.00	£284.00
Treosulfan	Complex Chemotherapy	Inpatient	£271.00	£284.00
Temozolomide	Oral Chemotherapy	Outpatient	£171.00	£171.00
Imatinib	Oral Chemotherapy	Outpatient	£171.00	£171.00

Comparator Drug Costs – Dacarbazine

Treatment	Source	Vial Price	Vial Size (mg)	Price per mg	Vials Needed for Patient
100mg vial	BNF 61	£5.05	100	£0.05	1.00
200mg vial	BNF 61	£7.16	200	£0.04	0.00
500mg vial	BNF 61	£16.50	500	£0.03	1.00
600mg vial	BNF 61	£22.50	600	£0.04	0.00
1000mg vial	BNF 61	£31.80	1000	£0.03	1.00

Comparator Drug Costs – Paclitaxel

Treatment	Source	Vial Price	Vial Size (mg) - 6 mg/mL	Price per mL	Vials Needed for Patient – Paclitaxel Alone	Vials Needed for Patient - Paclitaxel + Carboplatin
5mL vial	BNF 61	£66.85	30	£2.23	1.00	1.00
16.7mL vial	BNF 61	£200.35	102	£1.96	0.00	0.00
25mL vial	BNF 61	£300.52	150	£2.00	0.00	0.00
50mL vial	BNF 61	£601.03	300	£2.00	1.00	1.00

Comparator Drug Costs – Carboplatin

Treatment	Source	Vial Price	Vial Size (mL)	Price per mL	Vials Needed for Patient – Carboplatin Alone	Vials Needed for Patient - Paclitaxel + Carboplatin
5mL vial	BNF 61	£22.04	5	£4.41	2.00	2.00
15mL vial	BNF 61	£56.29	14	£4.02	2.00	2.00
45mL vial	BNF 61	£168.85	45	£3.75	0.00	0.00
60mL vial	BNF 61	£260.00	60	£4.33	3.00	3.00

Comparator Drug Costs – Cisplatin

Treatment	Source	Vial Price	Vial Size (mL)	Price per mL	Vials Needed for Patient – Cisplatin Alone	Vials Needed for Patient – Cisplatin + Interferon
10mL vial	BNF 61	£5.85	10	£0.59	5.00	3.00
50mL vial	BNF 61	£24.50	50	£0.49	0.00	0.00
100mL vial	BNF 61	£50.22	100	£0.50	1.00	0.00

Comparator Drug Costs – Interferon alpha 2b – Intron A

Treatment	Source	Vial Price	Vial Size (MU)	Price per MU	Vials Needed for Patient – Interferon Alone	Vials Needed for Patient – Cisplatin + Interferon
1mL vial - 10 MU	BNF 61	£42.35	10	£4.24	1.00	1.00
2.5mL vial - 25MU	BNF 61	£105.95	25	£4.24	0.00	0.00

Vindesine

Treatment	Source	Vial Price	Vial Size (mg)	Price per mg	Vials Needed for Patient
5mg vial	BNF 61	£78.30	5	£15.66	1.00

Treosulfan – IV

Treatment	Source	Vial Price	Pack Size (g)	Price per mg	Packs Needed for Patient
1g pack for reconstitution	BNF 61	£39.44	1	£39.44	1.00
5g pack for reconstitution	BNF 61	£152.41	5	£30.48	1.00

Imatinib

Treatment	Source	Pack	Mgs	Price per mg	Packs Needed for Patient
30 tab pack, 400mg per tab	BNF 61	£1,604.08	12000	£0.13	1.00

Temozolomide

Treatment - 5 cap pack	Source	Pack Price	Pack Size (mg)	Price per mg	Packs Needed for Patient
5mg cap	BNF 61	£13.58	25	£0.54	4.00
20mg cap	BNF 61	£54.30	100	£0.54	1.00
100mg cap	BNF 61	£271.52	500	£0.54	1.00
140mg cap	BNF 61	£380.18	700	£0.54	0.00
180mg cap	BNF 61	£488.74	900	£0.54	0.00
250mg cap	BNF 61	£678.80	1250	£0.54	1.00

Comparator Adverse Events Profiles

% of Patients Experiencing AE	Dacarbazine[1]	Paclitaxel[2]	Paclitaxel + Carboplatin[3]	Carboplatin[4]	Cisplatin[5]	Cisplatin & Interferon[6]	Interferon[7]	Vindesine[8]	Treosulfan[9]	Temozolomide[10]	Imatinib[11]
Fever											
Infection											
Myalgia/Pain			5%	5%						3%	
Sepsis											
Skin Reaction											
Fatigue	4%		10%	10%	3.0%	3.0%	3.0%	3.0%	3.0%	10%	
Hypotension		4%									3%
Diarrhea (not including colitis)	4%	11%	3%	3%	18.9%	18.9%	18.9%	18.9%	18.9%		
Nausea/Vomiting	4%									16%	
Stomatitis											
Colitis											
Dyspnea					4.5%	4.5%	4.5%	4.5%	4.5%		
Respiratory Distress/Pulmonary Edema		7%									3%
Anemia					8.3%	8.3%	8.3%	8.3%	8.3%		
Thrombocytopenia											
Neutropenia			7%	7%							
Oliguria											6%
Anuria											5%
Endocrine disorders											
Glomerulonephritis											

1. Bedikian et al (2006),
2. Walker et al (2005)
3. Hauschild et al (2009),
4. Hauschild et al (2009)
5. GP 100 adverse events profile assumed,
6. GP 100 adverse events profile assumed
7. GP 100 adverse events profile assumed,
8. GP 100 adverse events profile assumed
9. GP 100 adverse events profile assumed,
10. Kaufmann et al (2005)
11. Wyman et al (2005)

9.16 Appendix 16: [redacted]

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