NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Ipilimumab for previously treated unresectable malignant melanoma

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- the protocols, statistical analysis plans and clinical study reports for the MDX010-20 (Hodi 2010) and CA 184-022 (Wolchok 2010) trials
- additional information on treatment discontinuation rates in the trials
- updated overall survival analyses by treatment group
- further details relating to the patients in the clinical trials including gender balance, body surface area compared with patient weight, and the number of patients enrolled in UK centres
- product-limit survival tables for progression-free survival, overall survival and post-progression survival
- a comparison of population characteristics for patients in the Hodi 2010 pivotal trial
- further information regarding protocol violations, previous systemic therapy received by patients and adverse-event rates in the key trials
- further information regarding the methods employed for assessing efficacy endpoints.

Licensed indication

Ipilimumab (Yervoy, Bristol-Myers Squibb) has a UK marketing authorisation for the 'treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy'.

Key issues for consideration

Clinical effectiveness

- The manufacturer considered that the melanoma gp100 peptide vaccine, which was compared with ipilimumab in the key clinical trial (MDX010-20), is clinically equivalent to best supportive care. Is this assumption clinically plausible?
- Clinical data suggest that ipilimumab provides survival benefit to a small subgroup of people, but it is not yet possible through patient characteristics or prognostic factors to predict who these people will be before treatment. Does the Committee consider there are any particular subgroups of people with advanced metastatic melanoma who are likely to respond better to treatment with ipilimumab?
- There were low numbers of patients who received the full four courses of treatment with ipilimumab (which is mandated in the marketing authorisation regardless of disease progression), mainly because of disease progression in the pivotal clinical trials. What is the Committee's view on the effect this may have on the clinical results?
- The manufacturer considers that ipilimumab represents a true innovation. Does the Committee agree that this technology provides a 'step-change' in the current management of people with advanced metastatic melanoma? If so, how should this innovation be valued?

Cost effectiveness

- Does the model reflect the treatment of unresectable advanced metastatic melanoma in line with clinical practice?
- The clinical data suggest that ipilimumab yields an overall survival benefit over gp100. However, approaches to estimating survival in people with advanced metastatic melanoma are complex and the ERG has suggested that the manufacturer may have overestimated the survival benefit. What is

the Committee's view on the appropriateness of the manufacturer's assumptions and modelling approaches for overall survival?

- Does the Committee consider that the disutility of treatment-related adverse events has been adequately captured in the economic model?
- Does the economic model fully represent the uncertainty in the evidence?

End of life

- Should ipilimumab be considered in the context of the end-of-life criteria?

Related NICE guidance

- Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma. NICE technology appraisal guidance. Publication date to be confirmed.
- Skin cancer prevention: prevention using public information, sun protection resources and changes to the environment. NICE public health guidance 32 (2011). Available from: www.nice.org.uk/guidance/PH32
- Metastatic malignant disease of unknown primary origin. NICE clinical guidance 104 (2010). Available from: www.nice.org.uk/guidance/CG104
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Available from: www.nice.org.uk/guidance/CG27

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

	Decision problem	Manufacturer's approach
Population	Adults with previously treated unresectable stage III or IV malignant melanoma	As per scope
Intervention	Ipilimumab (3 mg/kg every 3 weeks for a total of four doses by intravenous infusion, with re-induction treatment if necessary)	As per scope
Comparators	• Best supportive care • Carboplatin-based chemotherapy • Dacarbazine	Best supportive care. Carboplatin-based chemotherapy and dacarbazine for sensitivity analysis
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope
Economic evaluation	Cost effectiveness expressed in incremental cost per quality-adjusted life year (QALY) gained	As per scope. The time horizon is 30 years

1.2 Evidence Review Group comments

1.2.1 Population

The population considered by the manufacturer was 'people with previously treated unresectable stage III or IV malignant melanoma'. This population is consistent with the UK marketing authorisation for ipilimumab and is in line with the NICE scope.

The ERG noted that although the pivotal clinical evidence submitted is derived from a trial that exclusively recruited human leukocyte antigen (HLA)-A2*0201-positive patients, the manufacturer made a convincing case that the clinical effectiveness of ipilimumab is unaffected by HLA status.

1.2.2 Intervention

The intervention, ipilimumab, is in accordance with the scope and the UK marketing authorisation. The licensed dose of ipilimumab is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses. The summary of product characteristics states that 'patients should receive the entire induction regimen (four doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions'. In addition, the summary of product characteristics states that 'dose reduction is not recommended. Doses that are omitted due to an adverse reaction must not be replaced'.

1.2.3 Comparators

The comparators in the scope were best supportive care, carboplatin-based chemotherapy, and dacarbazine. Carboplatin-based chemotherapy and dacarbazine are typically used in clinical practice for people who are fit enough to receive treatment, while best supportive care is used for those who are not.

The ERG noted that the pivotal trial in the manufacturer's submission did not include any of the comparators in the scope and instead compared ipilimumab with ipilimumab and gp100 peptide vaccine (gp100) and with gp100 alone.

The manufacturer considered that the gp100was equivalent to best supportive care. The ERG noted that the assessment report from the European Medicines Agency (EMA) for ipilimumab describes the gp100as an experimental anti-cancer agent whose effect on overall survival of patients with melanoma is unknown. Clinical advisers to the ERG indicated that they did not consider that gp100was the ideal comparator, but that its use in the trial was reasonable. The manufacturer considers that the use of best supportive care as the comparator in the base-case economic evaluation is a conservative approach because most of the active therapies available

(carboplatin-based chemotherapy and dacarbazine) are more costly than best supportive care.

1.2.4 Outcomes

The ERG noted that the outcomes included in the manufacturer's submission are in accordance with the NICE scope. However, the ERG considered that the nature of the disease and the action of the intervention are such that standard outcomes may not adequately reflect the effectiveness of immunotherapy treatments such as ipilimumab. This is highlighted by the fact that the SPC for ipilimumab differs from those for typical chemotherapy regimens in that it recommends continuation of treatment even if there is evidence of new lesions or the progression of existing lesions.

1.2.5 Economic evaluation

The manufacturer submitted a de novo economic model comparing ipilimumab with best supportive care (base case) in people with previously treated unresectable malignant melanoma. The ERG considered the economic approach defined in the manufacturer's submission conforms to the prescriptions specified in the appraisal scope. A lifetime horizon of 30 years was chosen by the manufacturer. This is the only deviation from the final scope; however, the ERG considered that this time horizon was appropriate given the average age of onset of the disease and its poor prognosis.

1.3 Statements from professional/patient groups and nominated experts

NICE received statements from the British Association of Dermatologists, Royal College of Physicians, Royal College of Nursing, the Skin Care Campaign, one patient expert and a clinical specialist from an NHS Foundation Trust.

The clinical specialists stated that there are more than 2000 new cases of metastatic malignant melanoma diagnosed in the UK every year.

Unresectable advanced melanoma is usually treated first-line with dacarbazine in clinical practice. Radiotherapy, immunotherapy and combination chemotherapy may be considered as alternative options or as subsequent lines of treatment.

The clinical specialist and patient expert highlighted that there have been no advances in the treatment of advanced melanoma in the last 30 years. Median survival for people with advanced melanoma is less than 1 year (usually 6 to 9 months) and the majority of people do not benefit from standard chemotherapy, with median progression-free survival of 6 weeks with standard chemotherapy. In view of this poor outcome, clinical consensus is that standard care for people with advanced malignant melanoma is enrolment in a clinical trial.

The incidence of melanoma increases with age, but it is disproportionately high in younger age groups. In 2008, 110 people under the age of 40 years died from malignant melanoma. The average loss of life is 20 years for a patient with advanced melanoma, but for the younger patients this is significantly greater.

A significant proportion of people with advanced melanoma will develop brain metastases that are very disabling, and treatment is largely ineffective. The prognosis for people with brain metastases is typically less than 3 months.

The clinical specialists suggested that ipilimumab is a palliative treatment for people with unresectable metastatic melanoma, but noted that it has been shown to prolong life in some patients in clinical trials. The patient experts considered that if ipilimumab was not made available to NHS patients, then they would be denied a therapy that might prolong survival and enable patients to continue their usual activities and maintain quality of life.

The clinical specialists noted that because of the mechanism of action of ipilimumab (that is, immune stimulation), assessment of response in the early stages of treatment is unreliable as tumour deposits may swell because of

infiltration by inflammatory cells. Therefore patients need to receive the full four cycles of treatment with ipilimumab because there are no early indicators of either treatment response or failure.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The key evidence for the clinical effectiveness of ipilimumab is derived from three studies. The primary evidence is derived from one phase III trial (MDX010-20; Hodi 2010), which is supported by results from the CA 184-022 dose ranging trial (Wolchok 2010), and safety and tolerability data from the CA 184-007 trial (Weber 2009). None of the trials compared ipilimumab with any of the comparators in the decision problem.

2.1.1 MDX010-20 (Hodi 2010)

The MDX010-20 trial was an international, multi-centre, double-blind, three-armed, phase III randomised controlled trial (RCT) that included 676 patients with advanced or metastatic unresectable stage III or IV melanoma who were previously treated with interleukin-2 (IL-2), dacarbazine and/or temozolomide. Participants with brain metastases were excluded from the trial. Approximately 38% of participants were from Europe, with 8% from the UK. At study entry, nearly all participants (98.2%) had unresectable stage IV disease. The study inclusion criteria also required participants to be HLA-A*0201 positive because of use of the gp100. Participants were stratified according to baseline metastasis stage and by whether or not they had previously received IL-2 therapy. The participants were generally well balanced for key baseline characteristics. They were randomised in a 3:1:1 ratio to one of three treatment options: ipilimumab plus gp100 (n = 403), ipilimumab plus placebo (n = 137), or gp100 plus placebo (n = 136).

The primary outcome measure was changed during the trial from best objective response rate (BORR) to overall survival for people treated with ipilimumab plus gp100 compared with gp100 alone, based on the advice of health authorities. Secondary outcomes included overall survival in people treated with ipilimumab plus gp100 compared with ipilimumab alone, BORR, disease control rate, duration of response, progression-free survival, time to progression (TTP) and health-related quality of life. A summary of the results is shown in table 1.

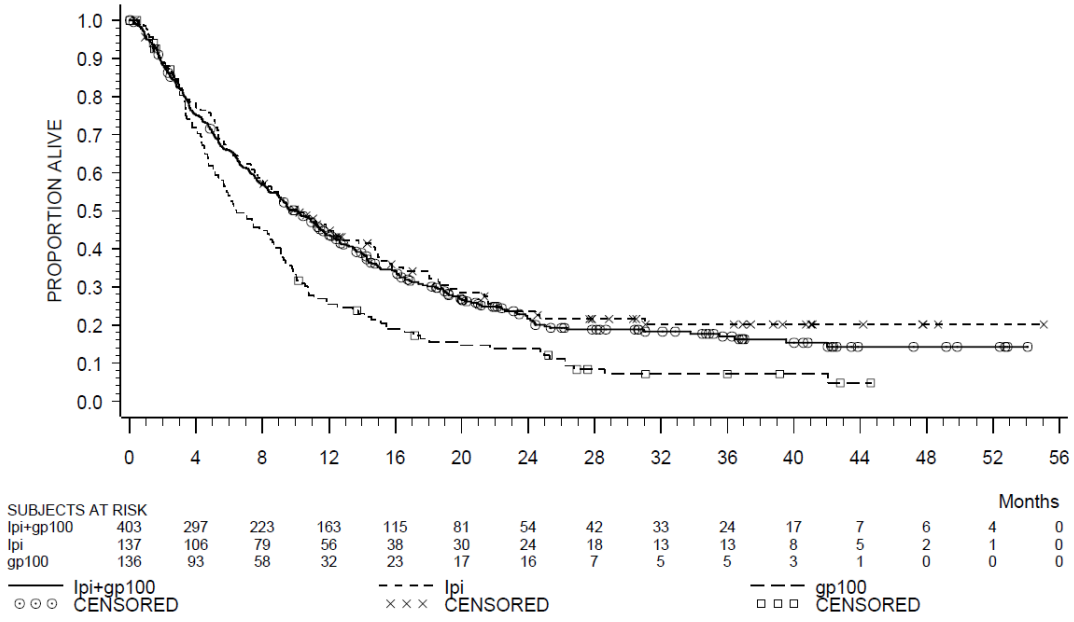
Table 1 Overall survival by treatment in ITT population (MDX010-20 study)

	Primary comparison	**Ipilimumab + gp100 (n = 403)**	**gp100 (n = 136)**
Overall survival	Hazard ratio (95% CI)	0.68 (0.55, 0.85)	
p value = 0.0004	Median OS, months (95% CI)	9.95 (8.48, 11.50)	6.44 (5.49, 8.71)
	Secondary comparisons	**Ipilimumab (n = 137)**	**gp100 (n = 136)**
Overall survival	Hazard ratio (95% CI)	0.66 (0.51, 0.87)	
p value = 0.0026	Median OS, months (95% CI)	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)
		Ipilimumab + gp100 (n = 403)	**Ipilimumab (n = 137)**
Overall survival	Hazard ratio (95% CI)	1.04 (0.83, 1.30)	
p value = 0.7575	Median OS, months (95% CI)	9.95 (8.48, 11.50)	10.12 (8.02, 13.80)
CI, confidence interval; OS, overall survival **Source: Manufacturer's submission page 64**			

Overall, ipilimumab plus gp100 significantly improved survival by 32% compared with gp100 alone (hazard ratio [HR] = 0.68; 95% confidence interval [CI] 0.55 to 0.85) and increased median survival by approximately 3.5 months. In the comparison of ipilimumab monotherapy compared with

gp100 alone, ipilimumab increased median survival by approximately 3.7 months (HR = 0.66; 95% CI 0.51 to 0.87). There was no statistically significant difference in median overall survival between people treated with ipilimumab plus gp100 compared with those treated with ipilimumab alone (HR = 1.04; 95% CI 0.83 to 1.30), which the manufacturer considered was evidence that gp100 did not influence the overall survival outcome with ipilimumab treatment.

The Kaplan-Meier survival curves were similar for the three treatment groups for the first 4 months of treatment, after which a separation occurred, demonstrating an overall survival advantage for ipilimumab, as shown in **figure 1**. However, overall there is a high risk of death in the first 18 months of the trial, after which death rates level off with a small but steady decrease. Reasons for the lack of response in a large proportion of patients are not explained in the manufacturer's submission.



GROUP	# DEATHS / # RANDOMISED	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)

Figure 1 Overall survival by treatment in the ITT population (MDX010-20 study)

Source: Manufacturer's submission page 65

After 1 year, participants treated with ipilimumab plus gp100 had a survival rate of 43.6% (95% CI 38.6 to 48.5) compared with 45.6% (95% CI 37.0 to 54.1) for those who received ipilimumab alone, or 25.3% (95% CI 18.1 to 32.9) for those who received gp100 alone. The 2-year survival rate was 21.6% (95% CI 17.2 to 26.1) for participants who received ipilimumab plus gp100, 23.5% (95% CI 16.0 to 31.5) for those who received ipilimumab alone, and 13.7% (95% CI 8.0 to 20.0) for those who received gp100 alone.

The survival benefit was observed across all relevant subgroups for advanced melanoma including age, gender, race, HLA-A2*0201 subtype, stage of metastasis, prior use of IL-2, response to prior systemic therapy and Eastern Cooperative Oncology Group (ECOG) performance status.

All response-related endpoints (including BORR and progression-free survival) showed positive results for participants who received treatment with an ipilimumab-containing regimen compared with participants who received gp100 alone, as shown in table 2.

Table 2 Summary of response-related outcomes in MDX010-20 study

		Ipilimumab + gp100 (n = 403)	**gp100 (n = 136)**
BORR (CR and PR)	N (%)	23 (5.7)	2 (1.5)
p value = 0.0433	95% CI for proportion	3.7 to 8.4	0.2 to 5.2
CR	N (%)	1 (0.2)	0
PR	N (%)	22 (5.5)	2 (1.5)
Median PFS (months)	Months (95% CI)	2.76 (2.73 to 2.79)	2.76 (2.73 to 2.83)
p value = 0.0464	HR (95% CI)	0.81 (0.66 to 1.00)	
		Ipilimumab (n = 137)	**gp100 (n = 136)**
BORR (CR and PR)	N (%)	15 (10.9)	2 (1.5)
p value = 0.0012	95% CI for proportion	6.3 to 17.4	0.2 to 5.2
CR	N (%)	2 (1.5)	0
PR	N (%)	13 (9.5)	2 (1.5)
Median PFS (months)	Months (95% CI)	2.86 (2.76 to 3.02)	2.76 (2.73 to 2.83)
p value = 0.0007	HR (95% CI)	0.64 (0.50 to 0.83)	
		Ipilimumab + gp100 (n = 403)	**Ipilimumab (n = 137)**
BORR (CR and PR)	N (%)	23 (5.7)	15 (10.9)
p value = 0.0402	95% CI for proportion	3.7 to 8.4	6.3 to 17.4
CR	N (%)	1 (0.2)	2 (1.5)
PR	N (%)	22 (5.5)	13 (9.5)
Median PFS (months)	Months (95% CI)	2.76 (2.73 to 2.79)	2.86 (2.76 to 3.02)
p value = 0.0371	HR (95% CI)	1.25 (1.01 to 1.53)	

BORR, best overall response rate; CI, confidence interval; CR, complete response; HR, hazard ratio; PFS, progression-free survival; PR, partial response

Sources: CHMP assessment report for ipilimumab page 45 and manufacturer's submission page 66

In response to a request for clarification the manufacturer provided an updated survival analysis that included only individuals who received all four induction doses of their study treatment. The results of this analysis are considerably more favourable than those in the original analysis, with median survival times of [redacted] for participants who received ipilimumab plus gp100, [redacted] for those who received ipilimumab alone, and [redacted] for those who received gp100 alone (results provided as academic in confidence).

It should be noted that under the assumption that the CTLA-4 blockade action of ipilimumab is independent of HLA status, the manufacturer concludes that the results of the study can also be generalised to HLA-A*201 negative patients.

2.1.2 CA 184-022 (Wolchok 2010) and CA 184-007 (Weber 2009)

The CA 184-022 trial was a double-blind, multicentre, dose-ranging phase II RCT that included 217 participants with previously treated, treatment-refractory or treatment-intolerant, stage III (unresectable) or stage IV melanoma who were randomised on a 1:1:1 ratio to receive either ipilimumab 0.3 mg/kg, 3 mg/kg or 10 mg/kg every 3 weeks for four cycles followed by maintenance therapy every 3 months. The outcomes included estimated BORR, progression-free survival at 24 weeks, median overall survival and duration of response. The CA 184-007 trial was a double-blind, multicentre, phase II RCT. A total of 115 participants with unresectable stage III or IV melanoma that were treatment-naive or who had been previously treated were randomised on a 1:1 ratio to receive open-label ipilimumab (10 mg/kg at weeks 1, 4, 7 and 10) with either concomitant oral budesonide or placebo. Outcomes included adverse events (specifically diarrhoea), BORR, duration of response and overall survival.

A summary of the main outcomes from these trials is shown in table 3.

Table 3 Summary of outcomes from CA 184-022 and CA 184-007 studies

Outcomes	CA 184-022		CA 184-007	
Overall survival: median months (95% CI)	10 mg/kg (n = 72)	11.4 (6.9; 16.1)	Ipi + budesonide (n = 58)	17.7 (6.8; NR)
	3 mg/kg (n = 72)	8.7 (6.9; 12.1)		19.3 (12.0; NR)
	0.3 mg/kg (n = 73)	8.6 (7.7; 12.7)	Ipi + placebo (n = 57)	
BORR (CR/PR) % (95% CI)	10 mg/kg (n = 72)	11% (5; 21)	Ipi + budesonide (n = 58)	12% (5; 23)
	3 mg/kg (n = 72)	4% (<1; 12)	Ipi + placebo (n = 57)	16% (8; 28)
	0.3 mg/kg (n = 73)	0% (0; 5)		
Survival at 1 year % (95% CI)	10 mg/kg (n = 72)	49% (37; 60)	Ipi + budesonide (n = 58)	56% (43; 69)
	3 mg/kg (n = 72)	40% (28; 51)	Ipi + placebo (n = 57)	62% (49; 75)
	0.3 mg/kg (n = 73)	40% (28; 51)		
Survival at 2 years % (95% CI)	10 mg/kg (n = 72)	30% (19; 41)	Ipi + budesonide (n = 58)	45% (27; 54)
	3 mg/kg (n = 72)	24% (14; 35)	Ipi + placebo (n = 57)	42% (28; 55)
	0.3 mg/kg (n = 73)	18% (10; 28)		

BORR, best overall response rate; CI, confidence interval; CR, complete response; Ipi, ipilimumab; NR, not reached; PR, partial response; SD, standard deviation

Source: ERG report, page 33

2.1.3 Adverse events

The rate of adverse events was high across all treatment groups in the included studies, as shown in table 4.

Table 4 Adverse events reported in included studies

Adverse events	MDX010-20		CA 184-022		CA 184-007	
Any AE	Ipi + gp100 (n=380)	98%	10 mg/kg (n=71)	100%	Ipi + budesonide (n=58)	NR
	Ipi + placebo (n=131)	98%	3 mg/kg (n=71)	97%	Ipi + placebo (n=57)	
	gp100 + placebo (n=132)	97%	0.3 mg/kg (n=72)	94%		
Any AE (grade 3 or 4)	Ipi + gp100 (n=380)	51%	10 mg/kg (n=71)	41%	Ipi + budesonide (n=58)	90%
	Ipi + placebo (n=131)	56%	3 mg/kg (n=71)	30%	Ipi + placebo (n=57)	95%
	gp100 + placebo (n=132)	52%	0.3 mg/kg (n=72)	29%		
Any immune-related AE (all grades)	Ipi + gp100 (n=380)	58%	10 mg/kg (n=71)	70%	Ipi + budesonide (n=58)	81%
	Ipi + placebo (n=131)	62%	3 mg/kg (n=71)	65%	Ipi + placebo (n=57)	84%
	gp100 + placebo (n=132)	32%	0.3 mg/kg (n=72)	26%		
Immune-related AE (grades 3 or 4)	Ipi + gp100 (n=380)	10%	10 mg/kg (n=71)	25%	Ipi + budesonide (n=58)	41%
	Ipi + placebo (n=131)	15%	3 mg/kg (n=71)	7%	Ipi + placebo (n=57)	38%
	gp100 + placebo (n=132)	3%	0.3 mg/kg (n=72)	0%		
AE leading to discontinuation	Ipi + gp100 (n=380)	7%				
	Ipi + placebo (n=131)	10%				
	gp100 + placebo (n=132)	3%				
Treatment-related deaths	Ipi + gp100 (n=380)	2.1%				
	Ipi + placebo (n=131)	3.1%				
	gp100 + placebo (n=132)	1.5%				
AE with outcome of death	Ipi + gp100 (n=380)	6%	10 mg/kg (n=71)	unclear	Ipi + budesonide (n=58)	NR
	Ipi + placebo (n=131)	10%	3 mg/kg (n=71)		Ipi + placebo (n=57)	
	gp100 + placebo (n=132)	6%	0.3 mg/kg (n=72)			

AE, adverse event; Ipi, ipilimumab; NR, not reported

Source: ERG report, table 6, page 35

A summary of the immune-related adverse events in the MDX010-20 trial are shown in table 5.

Table 5 Summary of immune-related adverse events in MDX010-20 trial

	Ipi+gp100	Ipi	gp100	Total
	(n = 380)	**(n = 131)**	**(n = 132)**	**(n = 643)**
Subject with any AE (n %)	374 (98.4)	128 (97.7)	128 (97.0)	630 (98.0)
irAE				
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; Ipi, ipilimumab; irAE, immune-related AE

Source: Manufacturer's submission, table 16, page 77

Ipilimumab is most commonly associated with adverse events resulting from increased or excessive immune activity (table 5). The most common adverse events (in at least 10% of participants) reported in the MDX010-20 study were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. Most adverse events were of mild to moderate severity.

Progressive disease was the most frequent reason for death in the MDX010-20 and CA 184-022 studies. There were 14 (2.2%) adverse events with an outcome of death in the MDX010-20 trial that related to the study treatments; 8 deaths in the ipilimumab plus gp100 group, 4 in the ipilimumab alone group and 2 in the gp100 alone group. Seven of the deaths were

associated with immune-related adverse events (including colitis, bowel perforation and organ failure); 5 in the ipilimumab plus gp100 group and 2 in the ipilimumab alone group.

Overall, the manufacturer considered that ipilimumab alone or in combination with gp100 was tolerated in people with advanced metastatic melanoma with adverse events being generally medically manageable and usually reversible with topical and/or systemic immunosuppressants.

2.1.4 Health-related quality of life

Health-related quality of life (HRQoL) data were taken from the MDX010-20 study using the EORTC QLQ-C30 and the short form 36 (SF-36v2) questionnaires. The EORTC QLQ-C30 values were mapped to EQ-5D scores from the 971 trial observations using a published algorithm (Rowen et al., 2011). SF-36 observations (n = 963) were mapped using the SF-6D algorithm. The manufacturer also conducted a systematic review to identify studies that included HRQoL data for people with metastatic melanoma. One study was identified that included 63 participants from the UK and 77 participants from Australia (Beusterien et al., 2009). A summary of the utility values from the three sources identified by the manufacturer are shown in table 6.

Table 6 Summary of HRQoL values

Health state	Utility value from EORTC QLQ-C30	Utility value from SF-36	Utility value from Beusterien et al. (UK mean)
Progression-free disease	0.80 (95% CI [0.53; 0.97])	0.64	0.77
Progressive disease	0.76 (95% CI [0.46; 0.97])	0.62	0.59
Difference	0.04	0.02	0.18

CI, confidence interval

Source: ERG report page 45

2.2 Evidence Review Group comments

The ERG commented that the manufacturer's search for studies was appropriate except that a search of their own internal databases was not

reported. The ERG noted that the MDX010-20 study provided the primary clinical evidence in the manufacturer's submission and that the CA 184-007 study was included to provide safety data. However, the ERG was unclear why the CA 184-022 had been included in the manufacturer's submission.

The ERG commented that the MDX010-20 study was well designed and was satisfied that the participants are representative of patients in UK clinical practice.

The ERG expressed concern about the robustness of the results. This was because of the numerous protocol amendments that occurred during the study, and the fact that the manufacturer and pharmacist were unblinded and therefore aware of treatment assignment. However, given that the modified primary outcome was overall survival, none of these issues were considered serious enough by the ERG to throw doubt on the conduct of the study or its results.

The ERG noted that the effects on overall survival of additional treatments that patients received after participating in the MDX010-20 study are not measurable. However, the ERG heard from the clinical advisers that, given the lack of available effective third-line therapies, these treatments are unlikely to have made a difference to overall survival estimates across the treatment arms of the study.

The ERG noted that none of the included studies compared ipilimumab with any of the comparators listed in the decision problem (that is best supportive care, carboplatin-based chemotherapy and dacarbazine).

In addition, although the manufacturer argued that gp100 is clinically equivalent to best supportive care, the ERG noted that the patient outcomes in the gp100 arm of the MDX010-20 study are less favourable than might be expected in untreated patients.

The statistical methods that were used to analyse the outcomes in the MDX010-20 study were considered appropriate by the ERG. However, the ERG noted that p values cannot be interpreted for the secondary outcomes.

The ERG commented that the clinical data provided by the manufacturer suggest that ipilimumab yields an overall survival benefit over gp100. However, the ERG noted that immunotherapy appears to yield different patient responses to treatment and, in the case of advanced melanoma, patients may move from progressive disease into stable disease or partial response. Existing criteria for measuring cancer tumour progression (such as the modified WHO or 'Response evaluation criteria in solid tumors' (RECIST) criteria) do not appear to be sufficiently adequate to assess the treatment response to ipilimumab. In addition, to date no patient characteristics or biomarkers have been identified that can prospectively target treatments to the minority of patients most likely to benefit from treatment with ipilimumab. The ERG noted that the EMA considered a number of ancillary analyses that were carried out by the manufacturer in an attempt to identify possible subgroups of people who might benefit (or did not receive any benefit) from the treatment. However, the subgroups were small and the ERG determined that no conclusions could be drawn from this post hoc analysis.

The ERG commented that the most clinically effective dose of ipilimumab is still unknown and noted that the manufacturer has been directed by the EMA and FDA to conduct further research to compare the currently licensed 3 mg/kg dose with a 10 mg/kg dose.

The ERG's clinical advisers, who have experience in using ipilimumab, agreed with the manufacturer that the adverse events seen in the clinical trials for ipilimumab are manageable and that, as experience with ipilimumab grows, adverse events will be more quickly identified and treated more proactively than in the past.

2.3 Statements from professional/patient groups and nominated experts

The clinical specialists noted that ipilimumab is associated with a variety of side effects, including fatigue, diarrhoea, rashes, pruritus, endocrine deficiencies and colitis. Deaths because of treatment side effects have also been recorded. In light of these adverse events, the clinical specialists considered that people with a poor performance status may not be able to tolerate ipilimumab. In addition, ipilimumab may not be suitable for people who are pre-morbidly immune-compromised because there is a risk of immunosuppression with treatment.

The clinical specialists noted that ipilimumab is associated with significant risk of toxicity. However, there is an expectation that toxicity is reduced with increased treatment experience. Patients should be managed by a clinical specialist in specialist centres.

The patient experts considered that some of the side effects of ipilimumab are substantially less severe than those experienced with current palliative chemotherapy. Overall, the more common side effects such as diarrhoea, fatigue, and skin rash were considered to be manageable. Additional side effects reported by people who have received treatment with ipilimumab include whitening of patches of skin, food intolerances and colitis.

The clinical specialists did not consider that there will be a need for any extra tests when using ipilimumab over and above those routinely required for systemic therapy.

The clinical specialists and patient experts noted that the clinical trials to date have suggested that only a minority of people are likely to have their disease respond to treatment with ipilimumab. However, for those who do, ipilimumab may prolong a patient's life and enable them to return to work, perform normal daily activities and make a positive contribution to society.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer undertook a de novo economic evaluation of ipilimumab as a treatment for patients with previously treated unresectable (stage III or IV) malignant melanoma. The manufacturer developed a partitioned survival model in which people treated with ipilimumab were compared with those who received best supportive care. The modelling approach, which is similar to a Markov 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, rather than employing traditional Markov model transition probabilities. The four mutually exclusive states in the model are: baseline disease, non-progressive disease, progressive disease and death, as shown in **figure 2**.

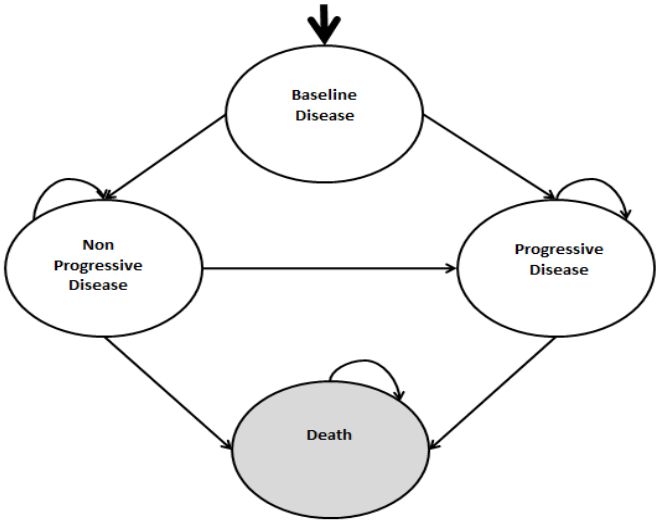


Figure 2 Model health states

Source: ERG report page 41

The proportion of patients in each state was calculated using progression-free

survival and overall survival data for participants in the MDX010-20 study. The manufacturer noted that because data on progression-free survival and overall survival for people receiving best supportive care were not available directly from the study, data from the gp100 arm of the MDX010-20 study were assumed to be an appropriate proxy for underlying disease progression in people receiving best supportive care. The model uses daily cycles for the first 5 years during the trial period, and weekly thereafter for a lifetime (30 year) horizon. The full list of variables applied in the economic model can be found in section 6.3 of the manufacturer's submission.

3.1.1 Clinical evidence

Results of the MDX010-20 study were used to populate the economic model. The manufacturer combined the two ipilimumab arms from the study (ipilimumab and ipilimumab plus gp100) to extrapolate the best available estimate of the survival of ipilimumab-treated patients. For the base-case analysis, the comparator treatment was best supportive care. Alternative treatments were considered as comparators in sensitivity analyses. Adverse-event rates for ipilimumab and best supportive care were estimated using results from the MDX010-20 trial. The rates for people receiving best supportive care were assumed to be the same as for those who received gp100 in the MDX010-20 study. In sensitivity analyses where other treatments were included as comparators, adverse event rates were obtained from the literature.

The manufacturer presented two approaches to parametric curve fitting for the survival modelling undertaken. The first strategy involved a single curve fit approach that showed that none of the curves fit the Kaplan-Meier data from MDX010-20 study. The second strategy involved using a two-part curve fit where the Kaplan-Meier estimates for overall survival and progression-free survival were used for the first 18 months and 'best-fit' parametric curves were used thereafter. The manufacturer concluded that the 'best-fit' curves were: exponential for progression-free survival in ipilimumab, Gompertz for overall

survival in ipilimumab and exponential for overall survival in best supportive care. Progression-free survival in the best supportive care arm was represented by the overall survival arm.

Table 7 summarises the clinical parameters used to populate the manufacturer's economic model.

Table 7 Summary of variables applied in manufacturer's model

Parameter	Value used	Distribution	Source
Patient/treatment characteristics			
Average patient body weight	81.7 kg	Normal SD = 18.1	UK patients in MDX010-20; compassionate use programme
Patient starting age	56 years	Normal SD = 13.4	MDX010-20
% Male	59%		MDX010-20
Ipilimumab dose (mg/kg)	3		MDX010-20
Average number of 200mg vials	0.99		Weights from UK patients in MDX010-20 and compassionate use programme
Average number of 50 mg vials	1.24		
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)
Ipilimumab OS parameter alpha: second curve	−6.081	Multivariate normal covariance matrix	MDX010-20 (Section 6.3)
Ipilimumab OS parameter beta: second curve	−0.0032		MDX010-20 (Section 6.3)
BSC PFS parameter alpha: second curve	−6.4148	Normal SE = 0.302	MDX010-20 (Section 6.3)
BSC OS parameter alpha: second curve	−6.4148	Normal SE = 0.302	MDX010-20 (Section 6.3)
Unit costs			
Ipilimumab administration first attendance	£271	Normal SD = 124*	NHS Reference costs 09/10
Ipilimumab administration other attendances	£284	Normal SD = 61*	NHS Reference costs 09/10
Ipilimumab unit cost	£3750		BMS, 50 mg 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	

BSC, best supportive care; OS, overall survival; PFS, progression-free survival; SD, standard deviation; SE, standard error

*** Standard deviations calculated using upper and lower quartile values**

Source: ERG report, page 42

3.1.2 Costs

The manufacturer presented detailed disease management micro-costing information in their submission (pages 136–138, table 37) and discussed six different cost categories:

- on initiation of treatment (one-off)
- on treatment pre-progression (monthly)
- best supportive care cost (monthly)
- on progression cost (one-off)
- palliative care off treatment (monthly)
- terminal care (one-off).

Additionally, the manufacturer provided information on unit costs associated with ipilimumab and also provided a list of health states and associated costs as used in the economic model (see table 8).

Table 8 List of health states and associated costs in the economic model

Health states	Items	Value
Progression-free disease	Drug costs	Ipilimumab = £19,565 per dose; BSC = £0
	One-off treatment initiation cost	Ipilimumab = £365; BSC = £0
	Drug administration	Ipilimumab = £271 (first administration), £284 per administration thereafter BSC = £0
	Routine treatment per month	Ipilimumab = £162; BSC = £378
Progressive disease	One-off cost on progression	£648
	Routine treatment post-progression per month (prior to palliative care)	£378
	Palliative care per month (4 months before death)	£838
Death	One-off terminal care cost	£5401
BSC, best supportive care **Source: manufacturer's submission page 139 (table 39)**		

The cost of adverse events were taken from research conducted by Oxford Outcomes with five clinicians and was provided as academic-in-confidence in the submission (see page 140 of the manufacturer's submission).

3.1.3 Results

The manufacturer's base-case results show undiscounted mean life years of overall survival of 19.5 months for best supportive care (based on gp100 data) and 53.3 months for ipilimumab treatment (based on the combined ipilimumab trial arms), indicating an incremental gain in overall survival of 33.8 months.

Table 9 below summarises the results of the manufacturer's base-case incremental analysis.

Table 9 Base-case results

Technology	Total			Incremental			ICER (incremental cost per QALY)
	Costs	Life years gained	QALYs	Costs	Life years gained	QALYs	
BSC	£12,837	1.33	1.01				
Ipilimumab	£96,188	3.19	2.38	£83,351	1.86	1.37	£60,737

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

The manufacturer noted that despite ipilimumab having a large net QALY benefit, the cost of the treatment takes it above the range that would normally be considered a cost-effective use of NHS resources. However, the manufacturer suggests that ipilimumab should be considered in the context of its innovative nature, and in line with supplementary advice for end-of-life technologies.

The manufacturer carried out deterministic and probabilistic sensitivity analyses to model the impact on the base-case incremental cost-effectiveness ratio (ICER) of changes to different variables in the model. Results from the deterministic sensitivity analysis showed that the ICER was most affected by the utility assumed for progressive disease. An increase in this utility value

reduced the ICER and conversely a reduction in utility increased the ICER. Other variables that significantly affect the ICER were:

- the curve type selected – because many of the potential curve fits do not fit the clinical data well, in particular:
  - the curve fit parameters assumed for overall survival for ipilimumab – because the majority of the benefits associated with ipilimumab come from increased survival over best supportive care
  - the curve fit parameters assumed for overall survival for best supportive care – because the majority of the benefits associated with ipilimumab come from increased survival over best supportive care
- the cost of ipilimumab – because this forms a high proportion of the total costs on the ipilimumab arm
- the patient's starting age – because 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
- the utility assumed for progressive disease – because this affects the QALY gain seen for ipilimumab over best supportive care, where the vast majority of patients will have died.

The manufacturer also explored the effect on the ICER of assumptions about the amount of each induction dose of ipilimumab needed per patient, the possibility of vial sharing, and decreasing the utility assumed for the progressive disease state. Results from these analyses showed that the dose of ipilimumab given per patient per induction has a large impact on the ICER with the minimum dose given in the trial and compassionate use programme (3 x 50 mg) resulting in an ICER of £38,387 per QALY gained and the maximum dose (2 x 200 mg) given resulting in an ICER of £88,788 per QALY gained. In addition, the results showed that vial sharing has the potential to reduce the base-case ICER to £55,824 per QALY gained.

Using a lower utility for progressive disease increased the base-case ICER, as shown in table 10. The manufacturer considered that the assumption in the

model for the utility of progressive disease contains more downside than upside risk, but noted that the utility used meets the NICE reference case and has been validated by clinicians.

Table 10 Impact of changing 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
0.771 (base case)	£60,737
0.775	£59,979
0.8	£58,411
ICER, incremental cost-effectiveness ratio **Source: manufacturer's submission page 148**	

The results of the manufacturer's probabilistic sensitivity analysis showed that there is a 14% chance of ipilimumab being cost effective compared with best supportive care at £50,000 per QALY gained.

The manufacturer also conducted a series of scenario analyses as described in table 11.

Table 11 Summary of manufacturer's scenario analyses

Scenario description	Summary of results
(1) No discounting	ICER **reduces** to £42,871
(2) Alternative comparators to BSC	ICER **reduces** in all situations
(3) Alternative utility estimates	Use of SF-36/SF-6D utility values from MDX010-20 trial and Beusterien et al paper **increases** the size of the ICER; using drug specific utility values **reduces** the size of the ICER; adjusting utilities for age only slightly affects the ICER
(4) Maximum dosing assumptions	ICER **increases** when: patients receive all four doses (£70,163 per QALY gained); 50% more patients receive induction; ICER **decreases** when 50% fewer patients receive induction
(5) Alternative curve fits	ICER **reduces** when: one curve fit/BSC arm/best AIC/without background mortality; one curve fit/BSC arm/Weibull/without background mortality; two part curve fit/best AIC/without background mortality; two part curve fit/best AIC/with background mortality; two part curve fit/IPI only/best AIC/with background mortality only after 5 years; two part curve fit/IPI only/Weibull/with background mortality only after 5 years ICER **increases** when: one curve fit/both arms/best AIC/without background mortality; one curve fit/both arms/Weibull/without background mortality; two part curve fit/Weibull/without background mortality; two part curve fit/both arms/Weibull/with background mortality only after 5 years
(6) Use of alternative data for ipilimumab	Use of ipilimumab only data **reduces** the size of the ICER; use of ipilimumab plus gp100 data **increases** the size of the ICER
(7) Use of alternative time horizons	As expected reducing the time horizon **increases** the size of the ICER; when a lifetime horizon is used, the ICER decreases
(8) Use of alternative weight data	Using UK patient weights from MDX010-20 trial slightly **increases** the size of the ICER; using weights from the compassionate use programme very slightly **decreases** the size of the ICER
AIC, Akaike Information Criterion; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Ipi, ipilimumab; QALY, quality-adjusted life year **Source: Manufacturer's submission tables 51 to 58; ERG report page 51**	

3.2 Evidence Review Group comments

The ERG considered that the manufacturer's model was well constructed. The ERG noted that the main weakness of the manufacturer's model is the

estimation of mean overall survival. The ERG acknowledged that the natural history and prognosis for metastatic melanoma is not well understood and the manufacturer claims a substantial improvement in mean survival on the basis of results from a single RCT. The ERG cite a study published in 1999 involving a re-analysis of eight trials of IL-2 for people with metastatic melanoma, in which 80% of patients died within 2 years, but a majority of those surviving the 2-year follow-up period survived for a further 9 years. The ERG noted that this response pattern is also replicated in the MDX010-20 study, and commented that the best explanation for this observation is that the population of people with advanced metastatic melanoma is severely heterogeneous in its prospects of survival for distinct subgroups. In light of this, it is possible that the data available for analysis is at its weakest where enhanced survival is likely to generate the most added life years from the treatment. The ERG therefore noted that while the MDX010-20 trial used by the manufacturer may have been adequately powered to demonstrate a survival advantage for ipilimumab, it may have been underpowered to provide a reliable quantification of that benefit, requiring substantially more patients surviving follow-up after 2 years. The ERG suggested that in order to establish a long-term pattern of survival, a trial would need to extend the follow-up period by several years.

The ERG noted that the model developers failed to achieve a coherent and credible interpretation of the MDX010-20 trial data on which to predict future outcomes and to allow reliable estimates of patient benefit to be made. In particular, they noted that the fitted overall survival functions beyond 18 months follow-up generate mortality risks lower than those in the general (healthy) population at a comparable age, and as a consequence the model predicted significant numbers of patients surviving to unreasonably advanced ages (beyond 100 years). To counter this anomaly, the model developers replaced the calculated model mortality risks with those experienced by the general population beyond 5 years follow-up. The ERG noted that this approach implies that any patient surviving beyond 5 years of second-line

systemic treatment is effectively cured; however, no evidence has been submitted by the manufacturer to support this claim.

3.2.1 ERG exploratory analyses

The ERG proposed a number of minor corrections/modifications to the manufacturer's economic model, which had a limited effect on the base-case ICER, but slightly improved the case for ipilimumab. For example, correcting drug acquisition costs to reflect the different weight distributions of males and females leads to a 1% decrease in the size of the ICER and addressing an error identified in the adverse-event costs led to a reduction in the ICER by £1073 per QALY gained. For more information on the minor corrections, see pages 55–61 of the ERG report.

In an exploratory analysis, the ERG considered two approaches to estimating overall survival benefit from the trial data:

- by direct modelling of overall survival trial outcome data
- by separate modelling of progression-free survival and post-progression survival, combining estimates to yield an estimate of overall survival.

Both approaches yielded smaller overall survival estimates than obtained in the manufacturer's model, with life extension of between 5 and 17 months. However, when these results were compared with the trial Kaplan-Meier results by treatment, the fit obtained with both models was found to be unacceptable. As a result, the ERG adopted a pragmatic approach to explore survival differences by calculating the area under the Kaplan-Meier curve to a common late time-point beyond which both the ipilimumab and best supportive care arms could be seen to be following long-term trend lines, and then projecting further life expectancy based on calibrating an appropriate parametric function. The results from this method suggest mean life-years of 11.2 months for gp100 and 27.5 months for the combined ipilimumab arms, which equates to a mean gain in overall survival of 16.3 months. These results were noted to be less than half the value calculated in the base case

of the manufacturer's model (that is, a mean gain in overall survival of 33.8 months). Using the revised projections, the ERG noted that the base-case ICER substantially increased to over £96,000 per QALY gained as shown in table 12.

Table 12 Revised base-case cost-effectiveness analysis, incorporating the ERG's exploratory analyses

		Manufacturer's base-case analysis	ERG revised base-case analysis (all minor changes included)	ERG revised base-case analysis + exploratory survival modelling
BSC	Cost per patient	£12,837	£12,933	£11,027
	QALYs per patient	1.0077	1.0098	0.7043
Ipilimumab	Cost per patient	£96,188	£94,347	£88,618
	QALYs per patient	2.38	2.414	1.5066
Incremental	Cost per patient	£83,351	£81,415	£77,591
	QALYs per patient	1.3723	1.4043	0.8022
ICER	Cost per QALY gained	£60,737	£57,977	£96,717

BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Source: ERG report, pages 69–80

The ERG stated that its exploratory analyses on overall survival cannot be considered definitive, as the volume and duration of patient data available from the MDX010-20 trial proved to be inadequate to achieve survival projections that can be used as a basis for decision making. However, the ERG considered that the manufacturer's model is likely to have substantially overestimated the extent of survival benefit that is likely to occur from treatment with ipilimumab.

3.3 End-of-life criteria

The manufacturer considers that ipilimumab may be eligible for appraisal as an 'end-of-life' treatment as follows.

Patient life expectancy less than 24 months

The manufacturer considers that the prognosis of untreated patients with previously treated malignant melanoma is very poor. The manufacturer stated that for patients with stage III disease (with regional lymph node involvement), 5-year survival rates range from 40% to 50%, while stage IV disease (that is, the melanoma has spread to distant sites) has an extremely poor prognosis (5-year survival rate is approximately 5 to 15%; median survival is 6 to 9 months).

Life extension of at least 3 months

The manufacturer reports (see page 110 of the manufacturer's submission) that compared with best supportive care, ipilimumab increases both median overall survival (10.0 months [303 days] compared with 6.4 months [196 days]) and estimated mean overall survival (23.1 months [703 days] compared with 12.5 months [381 days]). The manufacturer commented that such a level of survival benefit is in excess of what is considered significant in terms of the end-of-life criteria.

In the manufacturer's base-case analysis, the undiscounted mean life years of overall survival were 19.5 months for best supportive care (based on gp100 data) and 53.3 months for ipilimumab treatment (based on the combined ipilimumab trial arms), indicating an incremental gain in overall survival of 33.8 months. The ERG questioned the robustness of the manufacturer's estimate in their economic model of life extension. The ERG considered that the true value of the mean extension in overall survival is considerably less than the manufacturer's base case (33.8 months). The ERG's exploratory analysis resulted in a mean extension in overall survival of 16.3 months, which it considered to be more credible, but the ERG noted that this could not be considered robust because both patient numbers and follow-up time were

inadequate to reliably project the experience of the small number of patients with extended survival. The ERG agreed that evidence from the trial strongly indicates that there is a genuine life extension, and that it is highly likely that the mean life extension exceeds 3 months, but noted that the true size of the benefit remains unclear.

Licensed for a small population

The manufacturer suggests that

’[redacted]

[redacted]Ipilimumab does not currently have UK marketing authorisation for any other indications.

4 Equalities issues

No equality issues were identified during the scoping process or in the submissions received.

5 Authors

Richard Diaz (Technical Lead) and Fiona Rinaldi (Technical Adviser), with input from the Lead Team (Peter Heywood [clinical effectiveness], Ann Richardson [lay member] and Eldon Spackman [cost effectiveness]).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Liverpool Reviews & Implementation Group:

- Dickson R, Boland A, Bagust A et al. Ipilimumab for previously treated unresectable malignant melanoma: a single technology appraisal, August 2011

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Bristol-Myers Squibb

II Professional/specialist, patient/carer and other groups:

- British Association of Dermatologists
- Dr Paul Lorigan, clinical specialist
- Richard Jackson, patient expert
- Royal College of Physicians
- Royal College of Nursing
- Skin Care Campaign

C Additional references used:

Rowan D, Brazier J, Young T et al. (2011) Deriving a preference-based measure for cancer using the EORTC QLQ-C30. Value in Health (in press).