NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Updated analysis with revised patient access scheme for ipilimumab for previously treated unresectable malignant melanoma

Submitted by

Bristol-Myers Squibb

for Single Technology Appraisal (STA)

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Contents

1. Executive summary

More information is now available on the survival of patients treated with 3 mg/kg ipilimumab (the licensed dose) from the following trials:

- CA184-007 (randomised, double-blind, placebo controlled, Phase 2 study in previously treated, Stage III (unresectable)/IV melanoma patients – combination therapy),
- CA184-008 (open-label, single-arm, multi-centre Phase 2 study in previously treated, Stage III (unresectable)/IV melanoma who had progressed – monotherapy);
- CA184-022 (randomised, double-blind, multi-arm, multi-centre, Phase 2 study in Stage III (unresectable/IV melanoma – fixed dose investigation of multiple doses.

These trials have provided Overall Survival (OS) data on a total of 487 additional patients, 72 of these patients received ipilimumab at a dose of 3mg/kg. Of the 487 additional patients, 82 have a 60 month follow up and 10 of these patients with a 60 month follow up were on 3mg/kg ipilimumab.

In order to refine the estimated survival gain, and reduce any uncertainty surrounding the estimation of long term survival, the base case for this current analysis has been taken from the communication from NICE (11/04/2012) which was based on the MDX010-20 trial data alone. In addition, a revised Patient Access Scheme has been approved by the Department of Health (August 2012).

The following new analyses were conducted with data for all available trials (including at dosages of 0.3mg/kg and 10mg/kg) as well as separately for trials using the licensed dose (3mg/kg):

- Survival analysis using standard parametric curve fitting
- Survival analysis using the 3 part curve fit approach, utilising natural history data (the final approach from the most recent BMS submission to NICE (23/01/2012))
    - Investigation of the effect of the cut-off point chosen to implement the 3 part curve fit
- Survival analysis using the 'pragmatic approach' presented by the Evidence Review Group (ERG)
- Evaluation of the effect of the source of natural history data on survival estimation
- Assessment of goodness of fit, and external validity of the different approaches

The addition of new clinical data has reduced the uncertainty around long term survival of previously treated unresectable malignant melanoma patients on ipilimumab which we believe provides enough evidence to support a positive recommendation.

2. Introduction

This addendum aims to address any concerns raised by NICE about the degree of uncertainty concerning the long term survival benefits of ipilimumab treatment in previously treated unresectable malignant melanoma patients, by providing recent longer term clinical data.

Further to the previously submitted Phase III data upon which the original analyses were conducted these new data consist mainly of 4 to 5 year follow up of the relevant Phase II ipilimumab clinical trials across a wide spectrum of previously treated unresectable malignant melanoma patients.

3. Trial data available

Table 1 provides an overview of more recent trial data which were identified to NICE in the letter sent 17 April 2012. Further details of all the studies are provided in Section 6.

Table 1 Summary of Ipilimumab Data

Study Name	Randomised	Number of Patients	Treatment Line	Ipilimumab Dose & regimen	Latest Longer term Overall Survival Data in Public Domain	Longer term OS data available outside public domain
CA184-025 Phase II studies continuation	Yes	Study 022: 217	Previously treated	0.3 mg/kg (n=73). 24 patients crossed over to 10m/kg. 3 mg/kg (n=72). 30 patients crossed over to 10m/kg. 10 mg/kg (n=72)	• Median OS • 4-year OS rate • # of pts at risk at 4-years: 74	5-year OS follow-up
	No	Study 008: 155	Previously treated	10 mg/kg		
	Yes	Study 007: 115	Previously untreated and treated	10 mg/kg Ipilimumab +/- budesonide		
CA184-024 Phase III	Yes	Ipilimumab + DTIC: 250 DTIC + Placebo: 252	Previously untreated	10 mg/kg Ipilimumab + dacarbazine (DTIC) vs DTIC + placebo	• Median OS • 3-year OS rate • # of ipilimumab + DTIC pts at risk at 3 years: 41 pts	4-year OS follow-up
CA184-045	No	803	Previously treated	10 mg/kg	• Safety data for total population and 2 and 3 yr OS rates • 15% of pts still at risk after 3 years	

Study Name	Randomised	Number of Patients	Treatment Line	Ipilimumab Dose & regimen	Latest Longer term Overall Survival Data in Public Domain	Longer term OS data available outside public domain
	No	2000	Previously treated	3 mg/kg	[redacted]	
CA184-089 Early Access Programme (Italy)	No	74 patients	Previously treated	10mg/kg	None	3- yr OS follow-up
	No	848 patients	Previously treated	3mg/kg	None	Efficacy and safety data for 563 patients, no OS data

AE = adverse effects; BORR = best overall response rate; OS = overall survival; pts = patients; DTIC = dacarbazine; mets = metastases

Analyses have been conducted for four trials: the CA184-007, CA184-008 and CA184-022 trials (which are individual parent studies included within the CA184-025 trial and contain patients who initially received 0.3mg/kg, 3mg/kg and 10mg/kg ipilimumab), as well as additional analyses including the previously submitted MDX010-20 3mg/kg data.

All analyses have been conducted by merging the relevant datasets for the analysis, and in order to retain the original trial information, no adjustments have been made for inter-trial differences in patient characteristics.

Analyses have not been conducted for the following studies:

- CA184-024: Phase III study in treatment-naive metastatic melanoma patients at a 10mg/kg dose with 4 years overall survival (OS) follow up. **Error! Reference source not found.** in Section 6 presents the OS Kaplan–Meier data from this study. As this was a first line study, an analysis was not conducted; however the pattern for longer term survival is supportive of the other available data presented.
- CA184-045:
    - 3mg/kg population: data are not yet available. In October 2012, only 2 year OS data will be available which is unlikely to add extra information on long term survival. The pattern for longer term survival is supportive of the other available data presented.
    - 10mg/kg population: Survival data are only available up to 3 years; therefore, the inclusion of this study would do little to address uncertainty around long term survival. [redacted] in Section 6 presents available Kaplan–Meier data from this study.
- CA184-089: As OS has not been reported within the 3mg/kg cohort, and only a maximum of 3 years' survival data are available in the 10mg/kg cohort, this study was not relevant to addressing any uncertainty surrounding long term survival. Once again, the pattern for longer term survival is supportive of the other available data presented.

The resulting database includes over 50 patients at 62 months however; few patients remain beyond this time point due to censoring. Figure 1 below shows a breakdown by dataset.

Figure 1 Number of Patients at Risk

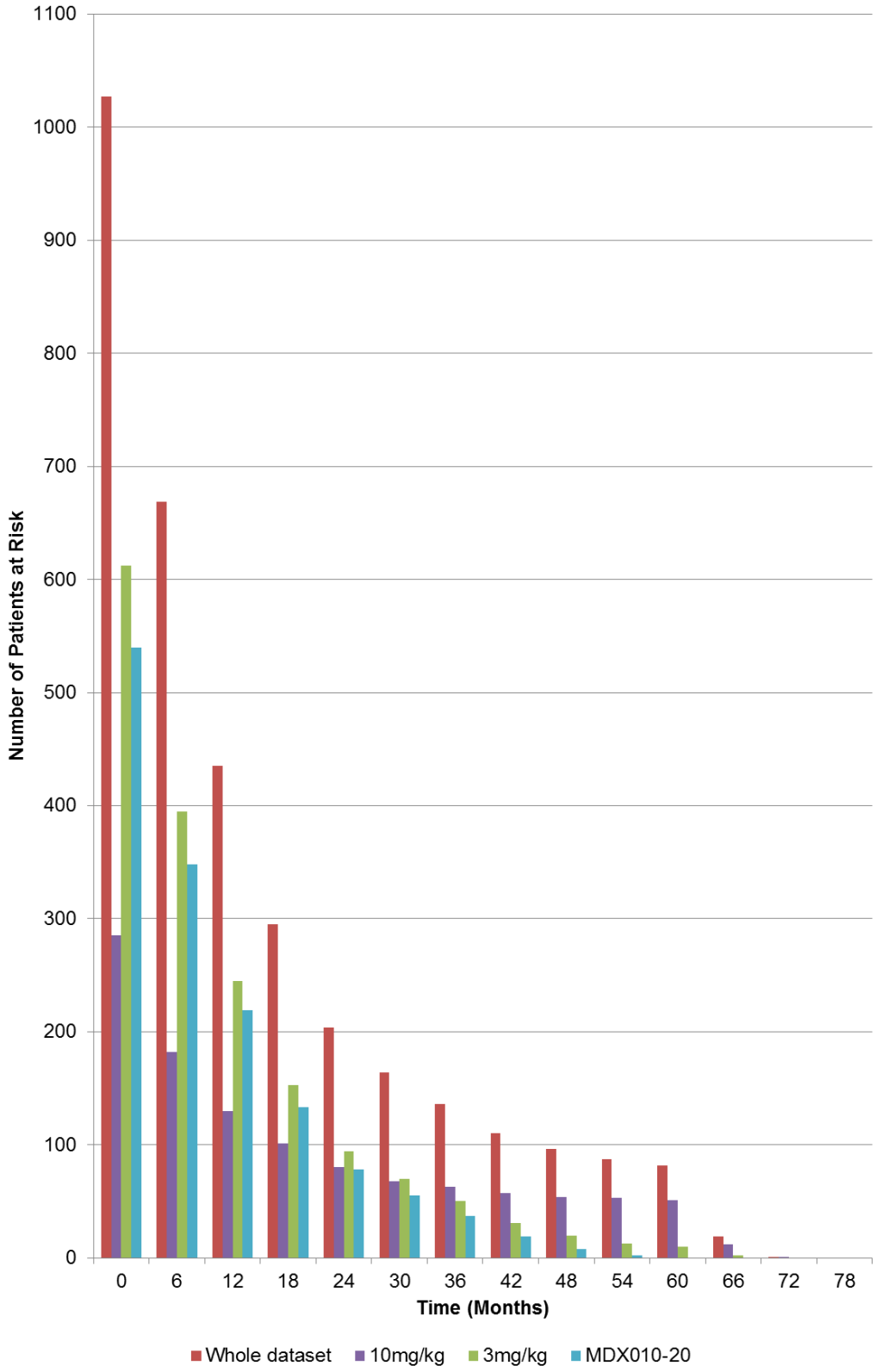
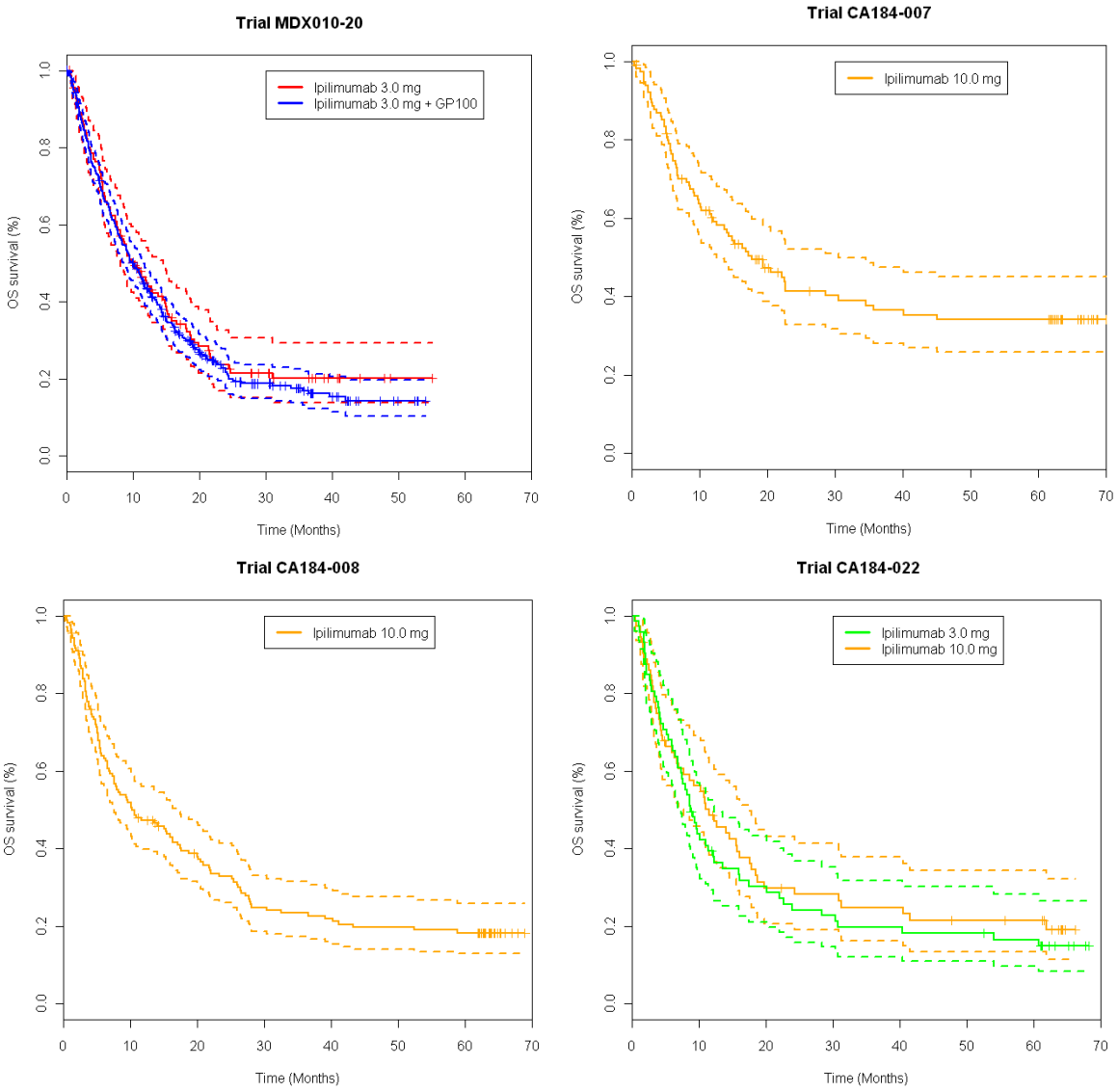


Figure 2 shows The OS for ipilimumab patients within each individual trial included in this analysis for the relevant trial arms.

Figure 2 Overall Survival, by Trials Used Within This Analysis*



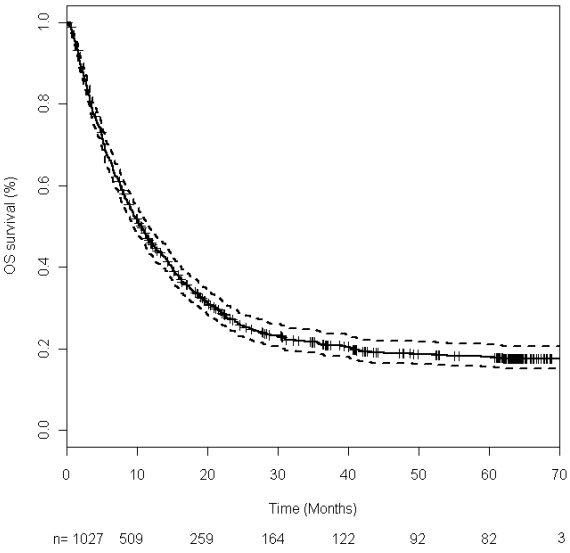
*95% confidence intervals denoted by dashed lines

Figure 3 shows the OS for ipilimumab patients within the following combined datasets:

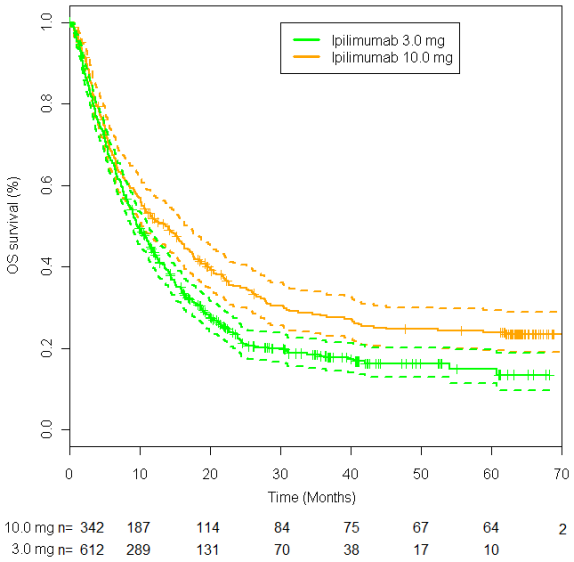
- All trial data – data from all 4 trials including patients at all doses (0.3mg/kg, 3mg/kg and 10mg/kg)
- All 3mg/kg trial data compared to 10mg/kg trial data from all 4 trials
    - data from the MDX010-20 and CA184-022 trials at the 3mg/kg dose, compared to
    - data from the CA184-007, CA184-008 and CA184-022 trials at the 10mg/kg dose

Figure 3 Overall Survival, Combined Datasets*

All Trial Data



All 3mg Data vs All 10mg Data

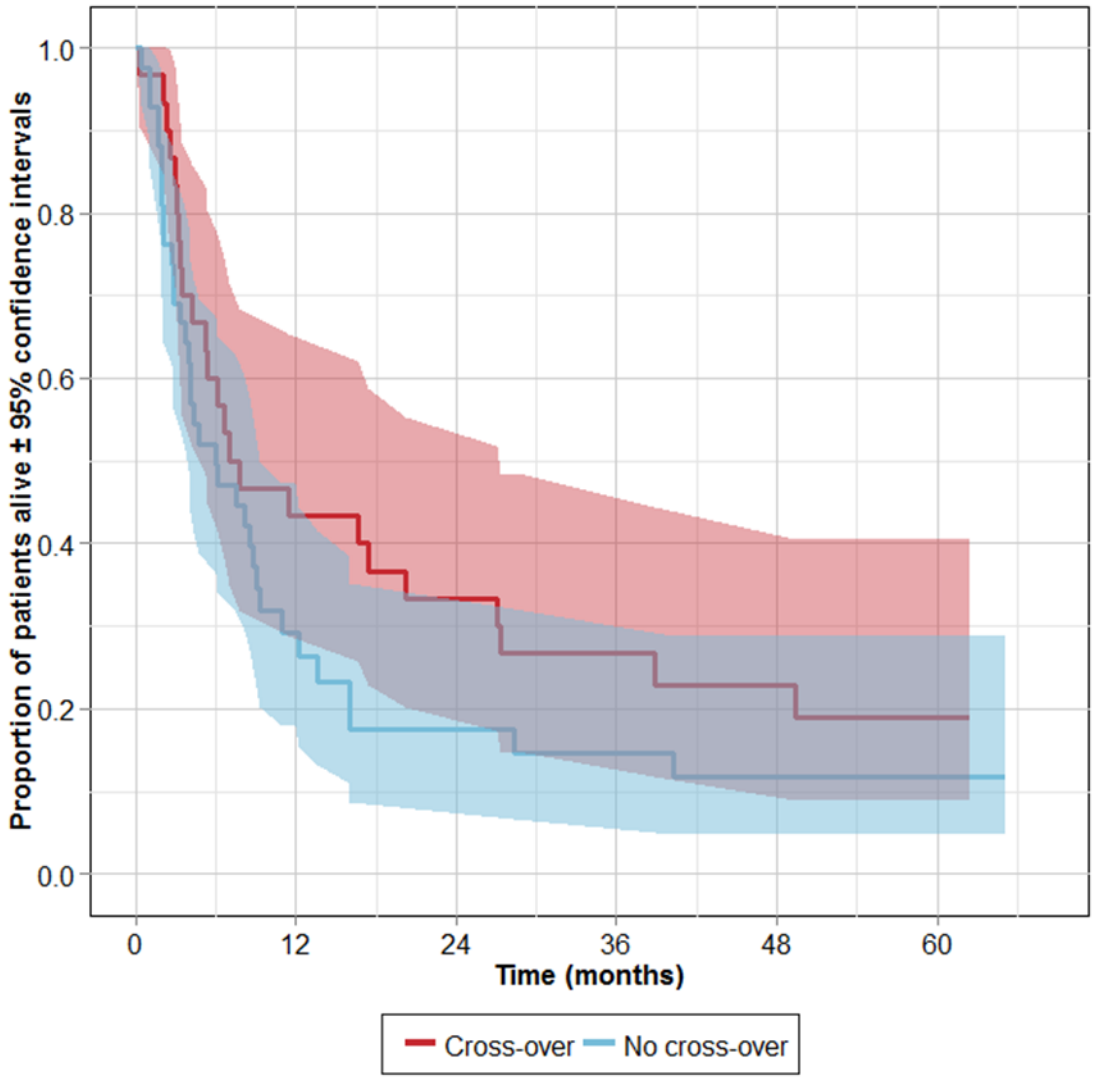


*95% confidence intervals denoted by dashed lines

As Study-022 includes patients crossing over from 0.3mg/kg and 3mg/kg to 10mg/kg upon disease progression, analyses were conducted to determine whether crossover had a significant effect upon survival. As can be seen in Figure 4 below, the crossover was not a substantial factor. Although crossover patients fared slightly better in the long term, there is a large overlap of the confidence intervals for the crossover and non-crossover groups. Performing the Chi squared test to determine if there is a significant difference between crossover and non-crossover patients initially assigned to 3mg/kg gives a non-significant p-value of 0.184.

As crossover has not had a significant effect on overall survival in the model base case, all patients initially assigned to 3mg/kg are included within the 3mg/kg analysis. A sensitivity analysis to test the impact of excluding crossover patients is presented in Section 4f. Excluding crossover patients is shown to marginally reduce the ICER.

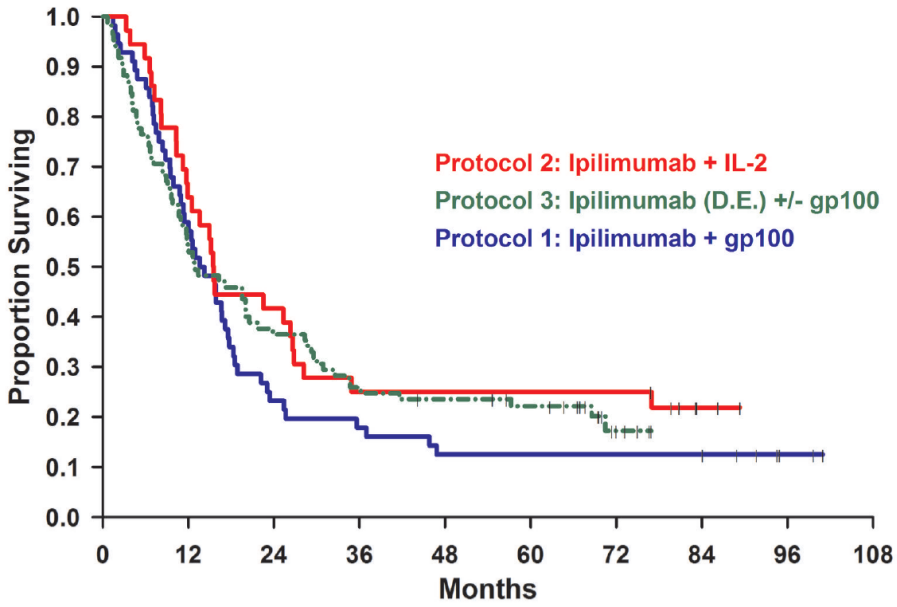
Figure 4 Overall Survival, Crossover vs. Non Crossover Patients within Study 022*



*95% confidence intervals denoted by shaded areas

In addition to the datasets presented within this analysis, an additional publication by Prieto et al (2012) is now available, which provides long-term follow-up data for 177 patients, including follow-up of greater than 99 months, across a range of ipilimumab doses (Figure 5).

Figure 5 Overall Survival, Prieto et al[1]



DE: dose escalation

The authors conclude that ipilimumab can induce durable and even potentially curative tumour regression in a proportion of patients with metastatic melanoma.[1] BMS does not have access to these data to combine with the internal survival dataset; however they do provide external validation of the durability of survival of ipilimumab.

The 025 phase II clinical trial data presented are in addition to those data already presented in the original submission to NICE in June 2011. These clearly demonstrate the consistency of ipilimumab's effect on long term survival.

Across the studies discussed above, all the OS curves plateau, and remain flat over an extended period of time, irrespective of the dose of ipilimumab used and patient population. These curves are indicative of longer term survival in a proportion of ipilimumab patients, which is an inherent characteristic of ipilimumab's clinical efficacy and innovative mode-of-action.

It is especially important to put these longer term data into clinical perspective. Metastatic melanoma normally has a median survival of 6-9 months – in this addendum we present ipilimumab survival data of a much longer duration than this time period in a meaningful proportion of patients.

Comparing these 5 year survival data to the equivalent early part of the survival curves in the American Joint Committee on Cancer (AJCC) data (
Figure 6, Balch et al 2001[2]) only reinforces the consistency of these survival curves.

This suggests that even at 4-5 years there is a difference in response, with the ipilimumab curves shifting to the right, and the tail plateauing relative to the slow decline seen by Balch et al.[2]

Overall, this demonstrates the durability of the clinical benefit of ipilimumab in some patients.

Figure 6 Natural History of Disease – Metastatic Melanoma By Disease Stage, Balch (2001)

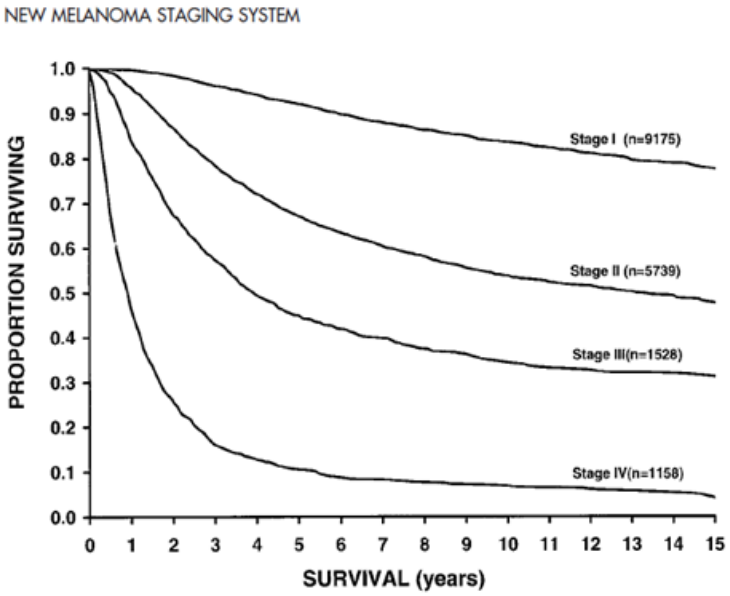


Fig 1. Fifteen-year survival curves comparing localized melanoma (stages II and I), regional metastases (stage III), and distant metastases (stage IV). The numbers in parentheses are patients from the AJCC melanoma staging database used to calculate the survival rates. The differences between the curves are significant ($P < .0001$).

4. Modelling the new survival data

a. Background

Over the course of the ipilimumab appraisal, several iterations of modelling have been considered. In the initial manufacturer submission (June 2011), BMS used a cost-effectiveness model which produced an ICER of £60,737. This incorporated longer term survival of patients (described in Section 6.3 of the submission as the 'two-part curve fit') by using general population background survival for patients after 5 years. This model implicitly assumed patients were cured of their melanoma if they survived to 5 years. This was raised as an issue by the ERG.

Following the first Appraisal Committee meeting, 15-year mortality data was identified from the literature (Balch, 2001)[2] and used in modelling. This allowed longer term melanoma mortality of more than 5 years as well as all cause background mortality to be included in the model. Additionally, the assumption that 50% of the open vials could be shared was endorsed by clinicians and incorporated into the model. The resulting model produced an ICER of £62,632. This revised model was discussed at the second NICE Appraisal Committee meeting, (November 2011). However, the assumption around vial sharing was not accepted; removing this raised the ICER to £65,303.

At this stage a Patient Access Scheme (PAS) was submitted by BMS - a confidential discount of [redacted]- reducing the cost of a 50mg vial of ipilimumab from £3,750 to [redacted]. The PAS resulted in a reduced ICER of £49,844. This PAS was discussed at the NICE meeting in February 2012.

[redacted]

[redacted]

These newly available trial data reduce the uncertainty in long term survival estimates by incorporating OS data from ipilimumab Phase II studies with long term data from the pivotal Phase III MDX-010-20 trial:

- In the original MDX010-20 dataset there were 37 ipilimumab patients at risk at 36 months.
- With the new trial data the number of patients at risk at 36 months was 50 in the 3mg/kg dataset (MDX010-20 and CA184-022), and 136 in the total dataset of the 0.3mg/kg, 3mg/kg and 10mg/kg doses from the 4 trials (MDX010-20, CA184-007, CA184-008 and CA184-022).
- Incorporating the new dataset increases the patient numbers by 487 of whom 72 received ipilimumab 3mg/kg.
- At 60 months follow-up there were 82/487 patients of whom 10 patients received ipilimumab 3mg/kg.

In addition to the clinical trial data, a revised patient access scheme has been approved by the Department of Health (a confidential discount of [redacted] which reduces the cost of a 50mg vial from £3,750 without the PAS (and [redacted] with the previous PAS) to [redacted]

Different approaches to modelling on these survival data are presented below: parametric curve fit; part curve fit; effect of the cut-off point; effect of registry data; ERG approach; comparison of all methods.

All results within this submission are presented in three ways; No PAS (without any PAS), Previous PAS (January 2012, confidential discount of [redacted]) and New PAS (August 2012, confidential discount of [redacted]).

b. Parametric curve fitting

Standard parametric curves were fitted to the trial data using a single parametric curve approach.

Parameters for each potential curve fit, AIC and BIC, are shown in Table 2 and Figure 7 which show the best-fitting curves compared to the Kaplan–Meier data for overall survival using a single-curve fit. The fitted curves (red) are shown compared to the Kaplan Meier data (black) with the 95% confidence interval based upon the Kaplan Meier data (dashed black) also presented.

In both datasets the Gompertz provided the best fit.

To validate this approach, the ipilimumab modelled survival using the best-fitting curve (Gompertz) has been compared to two sets of long-term registry data for Stage IV melanoma (Balch 2001[2] and Balch 2009[3]) and gp100 survival from the MDX010-20 trial (see Figure 8).

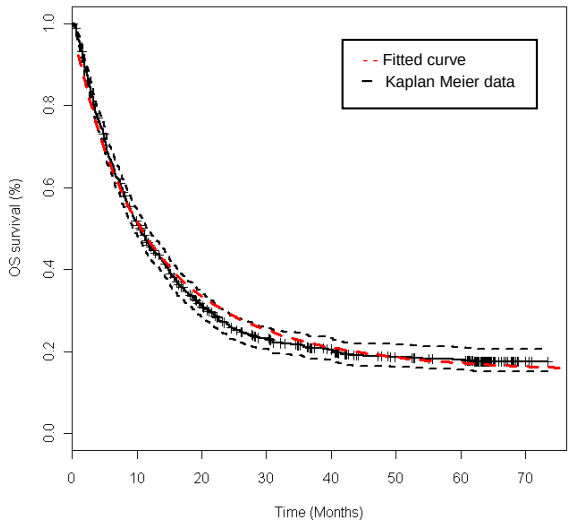
Table 2 Goodness of Fit – OS, Single-curve Fit

		Constant	ln(p / sigma / gamma)	AIC	BIC
All Trial Data	**Weibull**	-2.425	-0.228	6203.66	6213.52
	Exponential	-3.077		6272.07	6277
	Log Normal	2.437	0.36	6054.78	6064.65
	Log Logistic	2.398	-0.18	6061.39	6071.25
	Gompertz	-2.509	-0.043	**6052.49**	**6062.35**
3mg/kg	**Weibull**	-2.544	-0.115	3599.82	3594.72
	Exponential	-2.867		3591.32	3622.12
	Log Normal	2.307	0.276	3534.11	3534.83
	Log Logistic	2.295	-0.268	3546.54	3545.49
	Gompertz	-2.495	-0.034	**3523.65**	**3531.28**

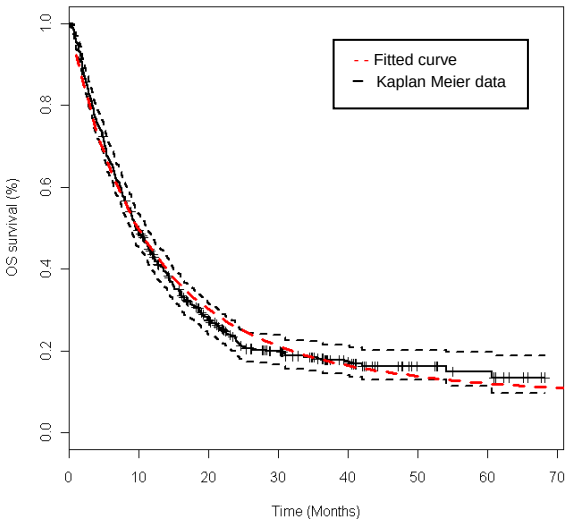
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Figure 7 Overall Survival, Single-curve Approach

All trial data



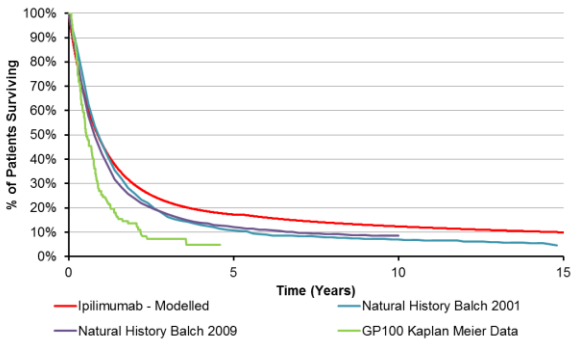
3mg/kg trial data



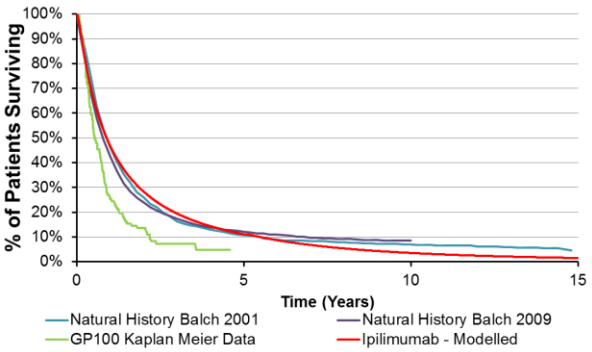
*95% confidence intervals denoted by dashed lines

Figure 8 Overall Survival, External Validity, Single-curve Fit

All Trial Data



3mg/kg Trial Data



For all trial data, the ipilimumab modelled survival is higher than the registry data and has a similar structure with the mortality rate reducing after 5 years. This is expected for an efficacious treatment, when none has been available previously. The gp100 survival is lower than registry data, as this represents a less effective 2nd line treatment, whereas the registry may also include some first line patients.

For the 3mg/kg ipilimumab trial data, the single-curve approach is slightly above that observed in the registries in the short term while in the long-term ipilimumab survival falls below registry data. However, it would be expected that in the longer term, survival for patients receiving an active treatment, with proven survival benefit would be above registry data, taking into consideration that some of the treatments received by registry patients may not have had any demonstrable clinical benefit.

Using the single-curve fit, with melanoma and background mortality after 5 years and the new PAS scheme, the ICER for all trial data is **£35,169** and for the 3mg/kg trial data is **£49,940**.

Whilst a single curve fit seems to be suitable for all trial data, BMS considers it unsuitable for the 3mg/kg data as a single curve fit does not provide external validity when compared to available registry data.

Additional results are shown in Table 3.

Table 3 Model Results Using Single-curve Fit

PAS	Analysis	Treatment	Total			Incremental			ICER	% Chance Cost Effective at WTP £50,000
			Costs	LY	QALYs	Costs	LY	QALYs		
No PAS	All trial data – melanoma & background mortality after 5 years	BSC	[redacted]	0.92	0.71	[redacted]	2.32	1.68	£50,011	51
		Ipilimumab	[redacted]	3.24	2.39					
	All trial data	BSC	[redacted]	0.92	0.71	[redacted]	3.26	2.30	£38,159	100
		Ipilimumab	[redacted]	4.18	3.01					
	3mg/kg trial data – melanoma & background mortality after 5 years	BSC	[redacted]	0.92	0.71	[redacted]	1.53	1.11	£72,328	1
		Ipilimumab	[redacted]	2.45	1.82					
	3mg/kg trial data	BSC	[redacted]	0.92	0.71	[redacted]	2.08	1.48	£55,853	25
		Ipilimumab	[redacted]	3.00	2.19					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New (August 2012) PAS	All trial data – melanoma & background mortality after 5 years	BSC	[redacted]	0.92	0.71	[redacted]	2.32	1.68	£35,169	100
		Ipilimumab	[redacted]	3.24	2.39					
	All trial data	BSC	[redacted]	0.92	0.71	[redacted]	3.26	2.30	£27,340	100
		Ipilimumab	[redacted]	4.18	3.01					
	3mg/kg trial data – melanoma & background mortality after 5 years	BSC	[redacted]	0.92	0.71	[redacted]	1.53	1.11	£49,940	53
		Ipilimumab	[redacted]	2.45	1.82					
	3mg/kg trial data	BSC	[redacted]	0.92	0.71	[redacted]	2.08	1.48	£39,049	91
		Ipilimumab	[redacted]	3.00	2.19					

BSC = best supportive care; ICER = incremental cost effectiveness ratio; LY = life years; PAS = patient access scheme; QALYs = quality adjusted life years; WTP = willingness to pay.

c. 3 part curve fit approach used in the final manufacturer submission

The most recent (January 2012) manufacturer submission used a 3-part curve fit:

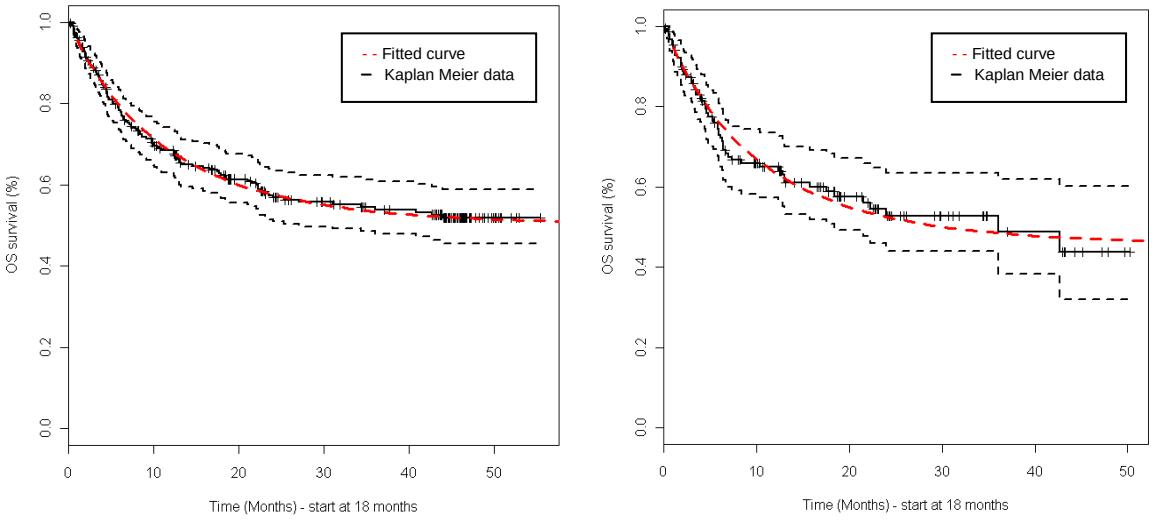
- Kaplan–Meier data up to 18 months where hazards were shown to change
- Fitted parametric curve from 18 to 60 months based upon survivors beyond 18 months
- Natural history data for melanoma mortality and background mortality data beyond 60 months

A full description of the 3 part curve fit approach used in the most recent manufacturer submission can be found in Section 6.3 of the January 2012 HTA submission. Survival analysis has been conducted in line with this methodology.

The best-fitting curves for overall survival starting from 18 months, based on the AIC and BIC and compared to the Kaplan–Meier data, are shown in Figure 9. These curves are used to inform survival from 18 months to 5 years (the end of the available trial data). No further benefit was assumed after 5 years where both arms were considered to have continuing survival in line with the registry data for Stage IV melanoma. It can be seen that the best-fitting curves (Gompertz in both cases) provide a good representation of the available trial data with the fitted curve staying well within the 95% confidence interval of the Kaplan–Meier data for the selected period. Parameters for each potential curve fit, AIC and BIC, are shown in Table 4.

Figure 9 Overall Survival, 3 part curve fit Approach – Fit Starting at 18 Months

All trial data *3mg/kg trial data*



*95% confidence intervals denoted by dashed lines

Table 4 Goodness of Fit – Overall Survival, 3 part curve fit approach

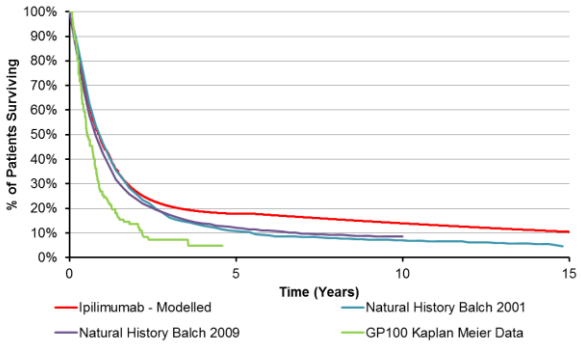
		Constant	ln(p / sigma / gamma)	AIC	BIC
All Trial Data	**Weibull**	-2.767	-0.441	1137 .44	1144.81
	Exponential	-3.957		1171.92	1175.6
	Log Normal	3.74	0.803	1120.27	1127.64
	Log Logistic	3.68	0.262	1127.9	1135.27
	Gompertz	-3.063	-0.068	**1112.06**	**1119.43**
3mg/kg	**Weibull**	-2.649	-0.374	538.57	544.63
	Exponential	-3.568		550.18	553.21
	Log Normal	3.341	0.752	531.57	537.62
	Log Logistic	3.272	0.193	534.24	540.3
	Gompertz	-2.872	-0.072	**530.97**	**537.02**

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

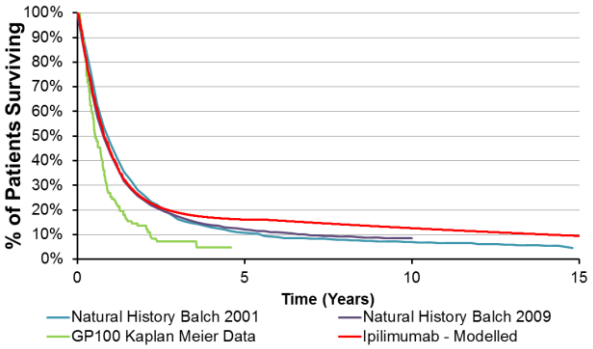
Figure 10 provides a comparison between ipilimumab modelled survival, available registry data for Stage IV melanoma (Balch 2001 & 2009) and gp100 survival from the MDX010-20 trial. For both sets of trial data, ipilimumab survival is higher than the registry data.

Figure 10 Overall Survival, External Validity, 3 part curve fit approach

All Trial Data



3mg/kg Trial Data



Using the 3 part curve fit approach with the new PAS (August 2012), the ICER for all trial data is **£38,707** and for the new 3mg/kg trial data is **£46,739**.

Using all 3mg/kg data (in contrast to using just MDX010-20 data), increases the ICER by approximately £2,000

The ICER decreases by approximately £10,000 using all trial data (0.3mg/kg, 3mg/kg and 10mg/kg).

Full model results are shown in Table 5.

Table 5 Model Results Using 3 Part Curve Fit Approach with Melanoma & Background Mortality after 5 years

PAS	Analysis	Treatment	Total			Incremental			ICER	% Chance Cost Effective at WTP £50,000
			Costs	LY	QALYs	Costs	LY	QALYs		
No PAS	All Trial Data	BSC	[redacted]	1.07	0.82	[redacted]	2.05	1.49	£55,339	8
		Ipilimumab	[redacted]	3.12	2.31					
	3mg/kg Trial Data	BSC	[redacted]	1.07	0.82	[redacted]	1.64	1.20	£67,463	0
		Ipilimumab	[redacted]	2.71	2.02					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]					
New (Aug 2012) PAS	All Trial Data	BSC	[redacted]	1.07	0.82	[redacted]	2.05	1.49	£38,707	99
		Ipilimumab	[redacted]	3.12	2.31					
	3mg/kg Trial Data	BSC	[redacted]	1.07	0.82	[redacted]	1.64	1.20	£46,739	81
		Ipilimumab	[redacted]	2.71	2.02					

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life years; PAS = patient access scheme; QALYs = quality-adjusted life years; WTP = willingness to pay.

d. Effect of the cut-off point used in the 3 part curve fit approach

The point at which the hazards change for the 3 part curve fit approach was determined using a Nelson–Aalen plot based upon the MDX010-20 data. The Nelson–Aalen estimator is a non-parametric measure of the cumulative hazard rate that is used when there is censored data (i.e. the empirical data is incomplete). The analysis looks at how a population evolves over time and the shape of the plot is indicative of the hazard rate.

At the 2nd appraisal committee meeting (16 November 2011) there was some uncertainty regarding the month at which the hazards changed based upon the original Nelson-Aalen plot for MDX010-20. Therefore, the NICE committee requested that the effect of the cut-off point be tested.

Updated Nelson–Aalen plots have been produced and are presented in Figure 11 for three data sets:

- All trial data
- All 3mg/kg trial data
- MDX010-20 trial data (as in the Jan 2012 submission)

In each of these it is clearly shown that the hazard rate changes over time. An 18-month point was used as a cut-off point in the model base case for the most recent manufacturer's submission (January 2012) and also within these revised analyses. This is the cut-off point where the hazard appears to change in all 3 datasets, and the use of this cut-off enables a sufficiently large number of patients to produce stable estimates.

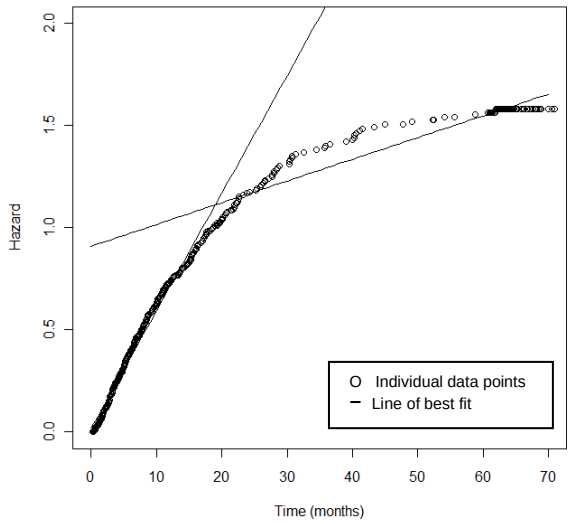
The effect of changing the cut-off point within the reasonable variation defined by the Nelson–Aalen plot (16–20 months) has been investigated within this analysis. Table 6 shows scenario cost-effectiveness analyses using cut-off points of 16 and 20 months (compared to 18 months used in the base case) for both the ipilimumab and best supportive care (BSC) arms, for each of the three datasets.

While 406 deaths occurred in the entire study period on both ipilimumab arms, it should be noted that the 20-month cut-off point for MDX010-20 could not be evaluated as there were only 35 deaths in the study between 20 months and the end of the available study data (56 months). This small number of deaths was not considered adequate to reliably fit a curve to this part of the data using only this trial.

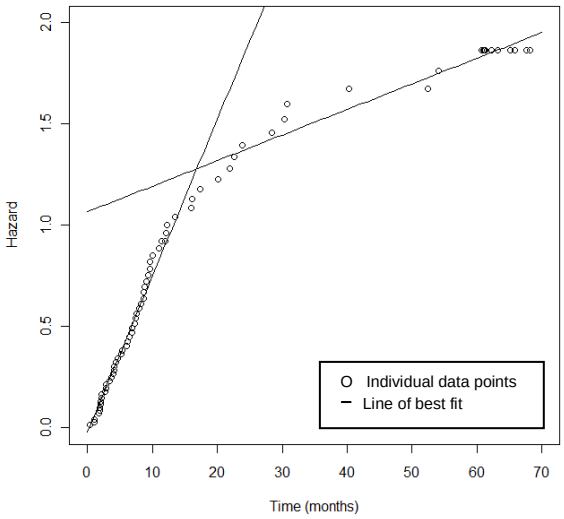
The results of this analysis show that the cut-off point has minimal effect on the curves fitted for OS or the modelled ICER. In all cases the ICER increases or decreases by approximately £1,000, suggesting that the cut-off point used does not influence the ICER in any meaningful sense.

Figure 11 Hazard Rate over Time for Ipilimumab Overall Survival (Nelson–Aalen Plots), fitted lines for <18 months & >18 months

Ipilimumab: All Trial Data



Ipilimumab 3mg/kg



Ipilimumab MDX010-20

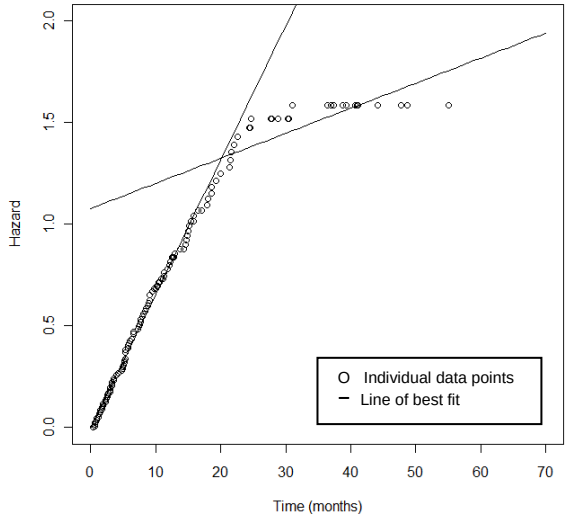


Table 6 Model Results with Different Model Cut-off Points, 3 part curve fit Approach with Melanoma & Background Mortality After 5 Years

PAS	Analysis	Treatment	Total			Incremental			ICER	ICER 18 month cut-off	% Chance Cost Effective at WTP £50,000
			Costs	LY	QALYs	Costs	LY	QALYs			
No PAS	MDX010-20 Gompertz : 16 months cut off	BSC	[redacted]	1.10	0.84	[redacted]	1.67	1.22	**£66,503**	£65,303	0
		Ipilimumab	[redacted]	2.77	2.06						
	All trial data Gompertz : 16 months cut off	BSC	[redacted]	1.10	0.84	[redacted]	2.01	1.47	**£56,200**	£55,339	7
		Ipilimumab	[redacted]	3.12	2.31						
	All trial data Gompertz : 20 months cut off	BSC	[redacted]	1.06	0.81	[redacted]	2.05	1.50	**£55,258**	£55,339	8
		Ipilimumab	[redacted]	3.12	2.31						
	3mg/kg Gompertz: 16 months cut off	BSC	[redacted]	1.10	0.84	[redacted]	1.60	1.17	**£68,988**	£67,463	0
		Ipilimumab	[redacted]	2.71	2.01						
	3mg/kg Gompertz: 20 months cut off	BSC	[redacted]	1.06	0.81	[redacted]	1.65	1.20	**£67,254**	£67,463	0
		Ipilimumab	[redacted]	2.71	2.02						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
New (Aug 2012) PAS	MDX010-20 Gompertz : 16 months cut off	BSC	[redacted]	1.10	0.84	[redacted]	1.67	1.22	**£46,105**	£42,211	72
		Ipilimumab	[redacted]	2.77	2.06						
	All trial data Gompertz : 16 months cut off	BSC	[redacted]	1.10	0.84	[redacted]	2.01	1.47	**£39,278**	£38,707	98
		Ipilimumab	[redacted]	3.12	2.31						
	All trial data Gompertz : 20 months cut off	BSC	[redacted]	1.06	0.81	[redacted]	2.05	1.50	**£38,653**	£38,707	100
		Ipilimumab	[redacted]	3.12	2.31						
	3mg/kg Gompertz: 16 months cut off	BSC	[redacted]	1.10	0.84	[redacted]	1.60	1.17	**£47,750**	£46,739	63
		Ipilimumab	[redacted]	2.71	2.01						
	3mg/kg Gompertz: 20 months cut off	BSC	[redacted]	1.06	0.81	[redacted]	1.65	1.20	**£46,600**	£46,739	70
		Ipilimumab	[redacted]	2.71	2.02						

e. Effect of the Source of Registry Data

The Balch 2001 registry data was used in the original manufacturer's submission to NICE, however these data were mentioned as a source of uncertainty during the 2nd appraisal committee meeting (16 November 2011). Therefore the Balch 2009 data have also been used in this submission.

The Balch 2001 registry[2] provides 15-year survival rates for 1,158 patients with Stage IV melanoma. Balch 2009[3] provides 10-year survival rates for 7,635 patients with Stage IV melanoma. Although the patient numbers have increased substantially, the time horizon has been shortened. The survival rates reported in the Balch 2009 paper are similar to those in Balch 2001 at all time-points up to the 10 year limit of the Balch 2009 data.

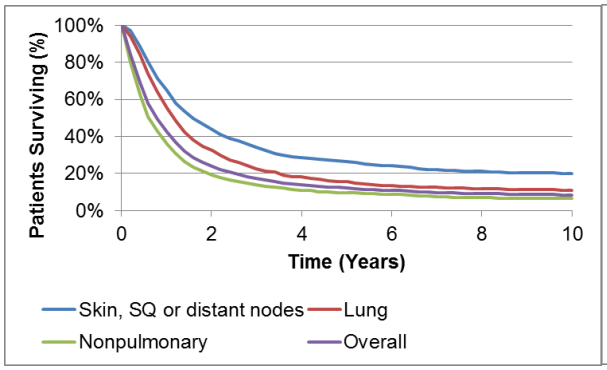
As registry data have been used for long-term extrapolation (beyond the 5-year trial data), the 2001 data was used in the original analysis because it contributes an additional 10 years' data to the analysis. In contrast, the 2009 data only provides an additional 5 years.

Data from the Balch papers were digitised to allow use within the economic model. The digitisation of the Balch data is shown in Figure 12. To simulate survival for the ipilimumab patient population, the percentage of patients with each subset of advanced melanoma has been used to weight the survival by type. Within the MDX010-20 trial, 9% of Stage IV patients had metastases of the skin, subcutaneous tissues or distant nodes; 18% had lung metastases; and 72% had 'other' metastases. As only 1.5% of patients within MDX010-20 had Stage III unresectable melanoma these patients have not been added to the calculations as the numbers are too small to affect the results.

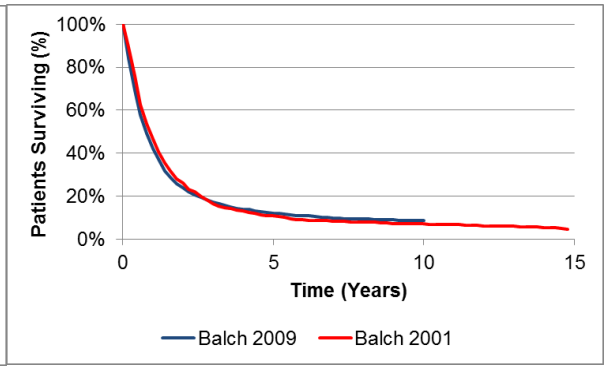
The overall data from Balch 2009 has been used to form a linear equation for longer term survival, using the hazards method, the same method used for the 2001 data within the most recent manufacturer submission.

Figure 12 Digitised Registry Data – Mortality from Stage IV Melanoma

Balch 2009



Balch 2009 vs Balch 2001



SQ = subcutaneous.

Table 7 shows the model results using Balch 2009 rather than Balch 2001.

Table 7 Model Results Using Alternative Sources of Registry Data

PAS	Analysis	Treatment	Total			Incremental			ICER	% Chance Cost Effective at WTP £50,000	ICER 2001 Data
			Costs	LY	QALYs	Costs	LY	QALYs			
No PAS	Balch 2009;	BSC	[redacted]	1.07	0.82	[redacted]	1.68	1.23	**£65,909**	1	£65,303
	MDX010-20*	Ipilimumab	[redacted]	2.75	2.05						
	Balch 2009;	BSC	[redacted]	1.07	0.82	[redacted]	2.03	1.48	**£55,811**	18	£55,339
	All Trial Data**	Ipilimumab	[redacted]	3.09	2.30						
	Balch 2009;	BSC	[redacted]	1.07	0.82	[redacted]	1.63	1.19	**£68,043**	0	£67,463
	3mg/kg data*	Ipilimumab	[redacted]	2.69	2.00						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]						
New (Aug 2012) PAS	Balch 2009;	BSC	[redacted]	1.07	0.82	[redacted]	1.68	1.23	**£45,703**	82	£42,211
	MDX010-20*	Ipilimumab	[redacted]	2.75	2.05						
	Balch 2009;	BSC	[redacted]	1.07	0.82	[redacted]	2.03	1.48	**£39,019**	100	£38,707
	All Trial Data**	Ipilimumab	[redacted]	3.09	2.30						
	Balch 2009;	BSC	[redacted]	1.07	0.82	[redacted]	1.63	1.19	**£47,123**	64	£46,739
	3mg/kg data*	Ipilimumab	[redacted]	2.69	2.00						

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life years; PAS = patient access scheme; QALYs = quality-adjusted life years; WTP = willingness to pay.

*3 part curve fit approach with melanoma & background mortality after 5 years
** Single curve fit with melanoma & background mortality after 5 years

For all three datasets there is little change in the predicted ICER between the two sources of registry data.

f. Alternative Method for Handling Crossover

The potential for crossover applied to patients who survived CA184-022 and enrolled in CA184-025 and experienced disease progression. The crossover of patients was shown to not significantly impact overall survival (Section 3) and it was felt that completely excluding these patients from the analysis might bias the base case results.

Nevertheless, to test the sensitivity of the base case ICER produced by the broken curve approach to the exclusion of the cross-over patients, an exploratory analysis was conducted. The analysis showed that excluding these patients marginally reduced the base case ICER produced when all patients were included in the analysis

Parameters for each potential curve fit, AIC and BIC, are shown in Table 8 and the best-fitting curve for overall survival starting from 18 months, based on the AIC and BIC, compared to the Kaplan–Meier data, is shown in Figure 13.

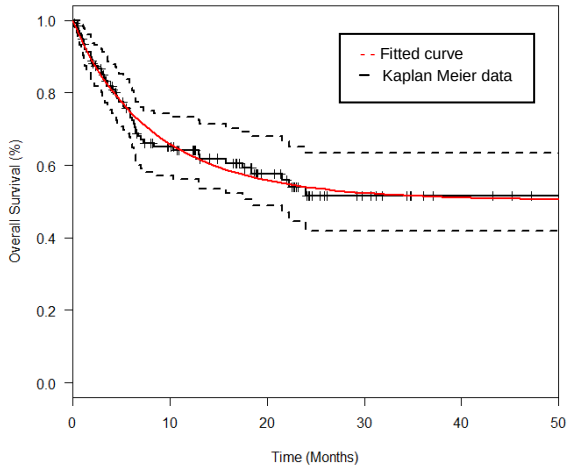
As in the case for both the MDX010-20 data and the 3mg/kg data including all patients, the Gompertz curve provides a good representation of the available trial data with the fitted curve staying well within the 95% confidence interval of the Kaplan–Meier data for the selected period.

Table 8 Goodness of Fit – Excluding Crossover Patients

	Constant	Ln (p / sigma / gamma)	AIC	BIC
Weibull	-2.610	-0.385	330.70	336.57
Exponential	-3.513		341.01	343.95
Log Normal	3.341	0.774	324.39	330.26
Log Logistic	3.260	0.210	326.79	332.65
Gompertz	**-2.743**	**-0.094**	**321.04**	**326.91**

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion Ln = natural logarithm

Figure 13 Overall Survival, Excluding Crossover Patients – Fit Starting at 18 Months



*95% confidence intervals denoted by dashed lines

As can be seen in Table 9 excluding the crossover patients marginally reduced the ICER compared to the base case where all patients are included (from £46,739 to £44,426, incorporating the new PAS)

Table 9 Model Results With and Without Crossover Patients

PAS	Treatment	Total			Incremental			ICER excl. crossover patients	Base Case ICER incl. crossover patients
		Costs	LY	QALYs	Costs	LY	QALYs		
No PAS	BSC	[redacted]	1.07	0.82	[redacted]	1.74	1.27	£63,968	£67,463
	Ipi	[redacted]	2.818	2.09					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]					
New PAS (Aug 2012)	BSC	[redacted]	1.07	0.82	[redacted]	1.74	1.27	£44,426	£46,739
	Ipi	[redacted]	2.81	2.09					

Ipi= ipilimumab

g. ERG approach

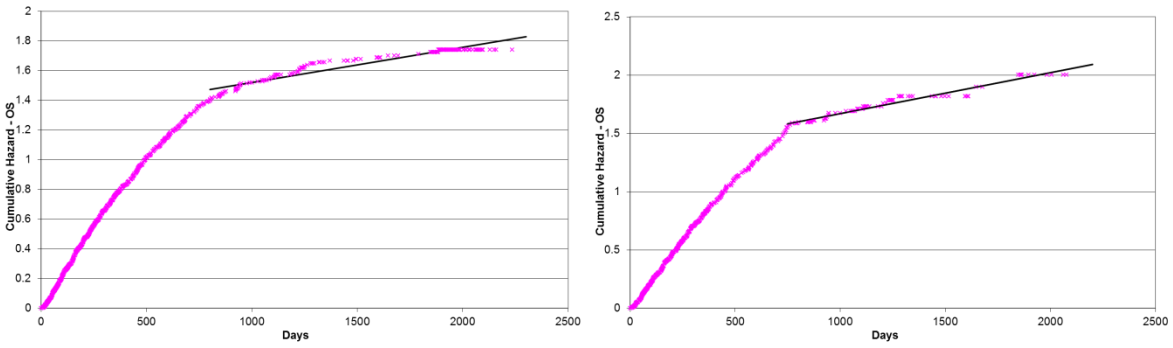
In response to our original submission, the ERG recommended an alternate methodology to the curve fit. Whilst this may have been appropriate for the original data, it is our opinion that this approach is not suitable for the extension data as it overestimates mortality in long term survivors in both ipilimumab and control populations. The approach taken by the ERG is described within the ERG report (Section 6.1.2)[4]. Following this method we have plotted the cumulative hazard for survival against time (see Figure 14) and then:

- Calculated the area under the Kaplan-Meier curve (AUC) to a common late time point beyond which both the intervention and the comparator arms could be seen to be following long-term trendlines. For overall survival, the time point at which AUC was deemed to be augmented by a long-term time trend was 770 days after randomisation, and for progression free survival this occurred at 365 days.
- Projected further life expectancy based on calibrating an appropriate parametric function. A simple linear trend was used for longer term projection, equivalent to a simple exponential survival function.

Using all trial data, the hazards now appear to change at 800 days rather than 770, as estimated by the ERG who used the MDX010-20 data only. For the all trial data analysis we have fitted a linear function to this trend for 800 days onwards, for both ipilimumab and gp100, and used Kaplan–Meier data for both arms prior to this point. In the 3mg/kg data, the hazards appear to change at 740 days. This is 30 days earlier than in the ERG report. For the 3mg/kg analysis we have fitted a linear function to this trend for 740 days onwards, for both ipilimumab and gp100, and used Kaplan–Meier data for both arms prior to this point.

Figure 14 Plot of Overall Survival Against Cumulative Hazard

All Trial Data *3mg/kg Trial Data*

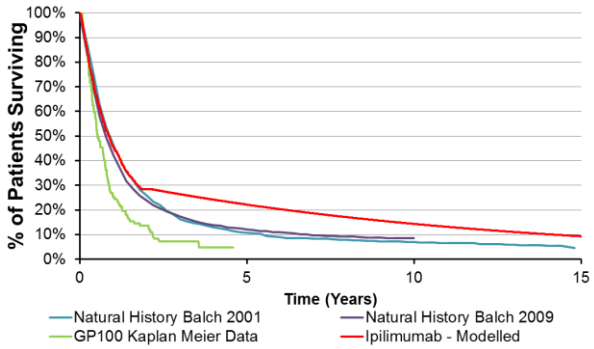


To validate the approach, the ipilimumab modelled survival has been compared to the registry and trial data. Long-term survival in both registry data and trial data does not follow a constant hazard pattern (Figure 15). Whilst fitting a linear function to the cumulative hazard could be considered appropriate with the original data, the new data shows this is likely to over-estimate survival in the short term and under-estimate it in the long term. This is key as the shape of the long term survival curve is particularly important in determining the cost per QALY of the treatment.

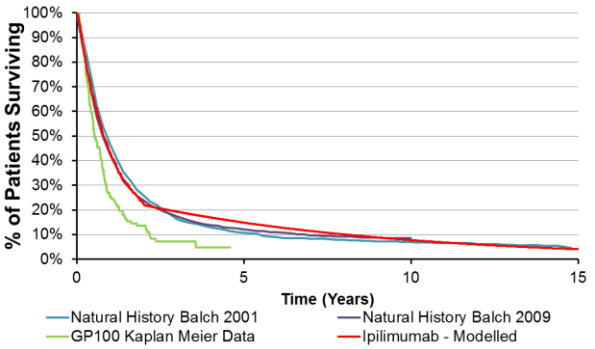
In summary the three part curve fit provides a better long term fit to the long term data. The ERG approach overestimates mortality in long term survivors in both ipilimumab and control populations.

Figure 15 Overall Survival, External Validity, ERG Approach

All Trial Data



3mg/kg Trial Data



When using all the trial data with the new PAS (August 2012) the ICER is **£35,147**; however, this rises to **£55,807** using only the 3mg/kg trial data.

The key component in the ICER for treatment with ipilimumab is the estimation of long-term survival; this is determined by the shape of the tail of the survival curve. Over the very long-term the ERG survival curve for the 3mg/kg data falls below registry data (Figure 15). This is not clinically plausible. The data presented within this document shows that when using the manufacturer approach the long term survival tends towards, but does not fall under, the available registry data and is therefore likely to produce a much more clinically relevant ICER.

In addition the difference between ICERs for the two datasets is much larger using the ERG method than that observed within the other potential methods. This suggests that the method is highly variable depending upon the amount of data available and can be considered as a sign of poor fit of the method to the data.

Table 10 shows the model results using the ERG methodology.

Table 10 Model Results Using ERG Method

PAS	Analysis	Treatment	Total			Incremental			ICER	% Chance Cost Effective at WTP £50,000
			Costs	LY	QALYs	Costs	LY	QALYs		
No PAS	All Trial Data	BSC	[redacted]	0.95	0.73	[redacted]	2.29	1.68	£49,983	46
		Ipilimumab	[redacted]	3.24	2.41					
	3mg/kg Trial Data	BSC	[redacted]	0.93	0.72	[redacted]	1.32	0.98	£81,198	0
		Ipilimumab	[redacted]	2.24	1.69					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New (Aug 2012) PAS	All Trial Data	BSC	[redacted]	0.95	0.73	[redacted]	2.29	1.68	£35,147	100
		Ipilimumab	[redacted]	3.24	2.41					
	3mg/kg Trial Data	BSC	[redacted]	0.93	0.72	[redacted]	1.32	0.98	£55,807	0
		Ipilimumab	[redacted]	2.24	1.69					

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life years; QALYs = quality-adjusted life years; WTP = willingness to pay.

h. Comparison of ICERs for all methods

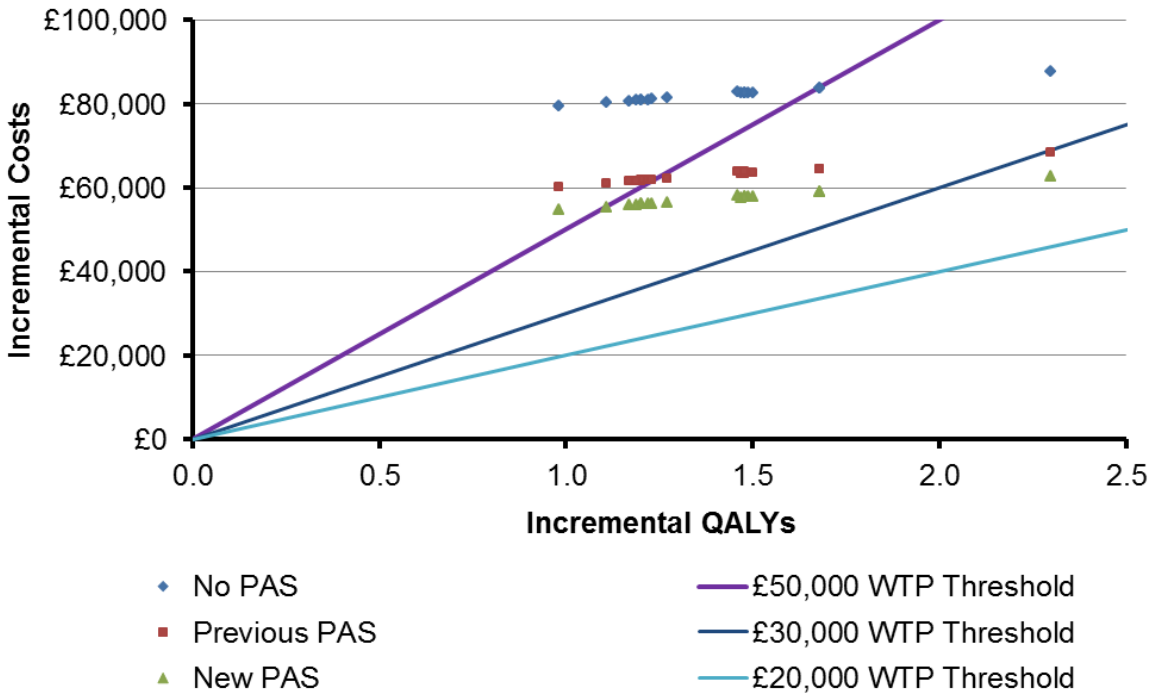
When plotting the scenarios presented in this document the ICER varies, but remains under £50,000/QALY in 16 out of 17 scenarios.

Using the previous PAS (January 2012), scenarios are equally likely to lie either side of the £50,000 threshold.

Using the new PAS (August 2012) the only scenario above the £50,000 threshold is the one produced on the basis of the ERG approach.

Figure 16 shows a plot of all the survival scenarios conducted within this analysis compared to the £50,000 willingness to pay threshold.

Figure 16 Comparison of All Survival Scenarios

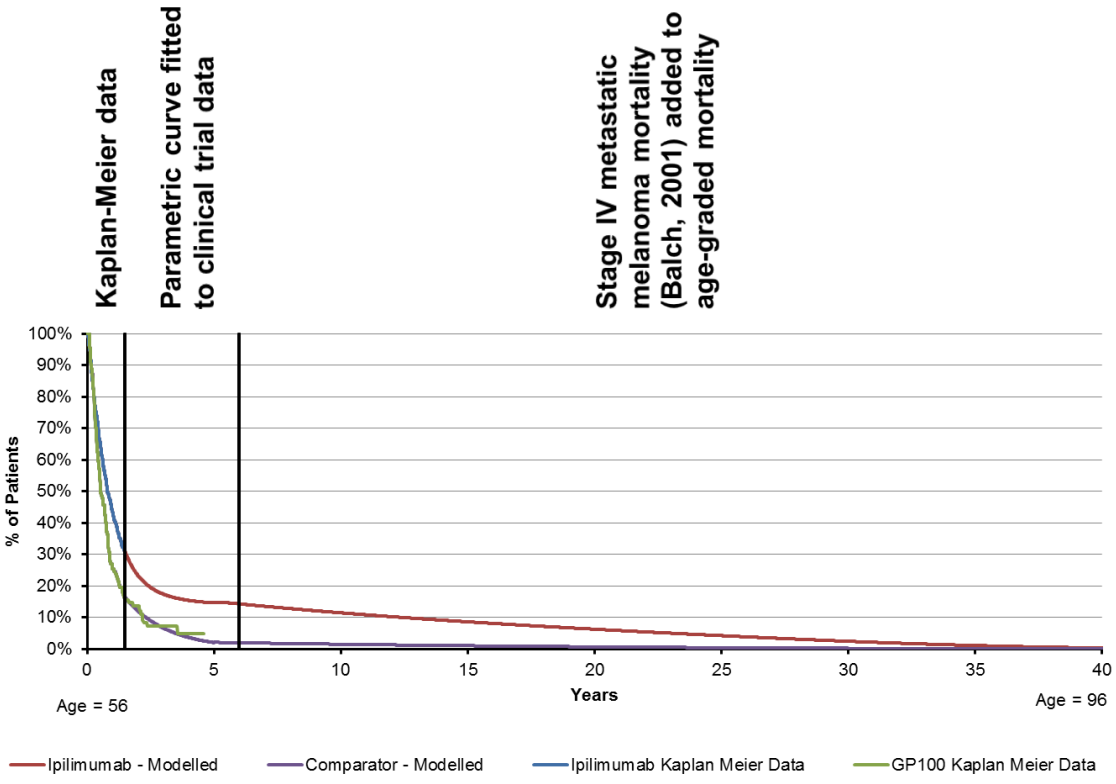


5. New base case results

Only 3mg/kg data from previously treated patients is used within the new base case analysis in line with the licence of ipilimumab.

Figure 17 provides a graphical representation of this base case model (with an identical structure to that used in the previous submission), and described in Section 4c.

Figure 17 Base Case Model, 3mg/kg Data

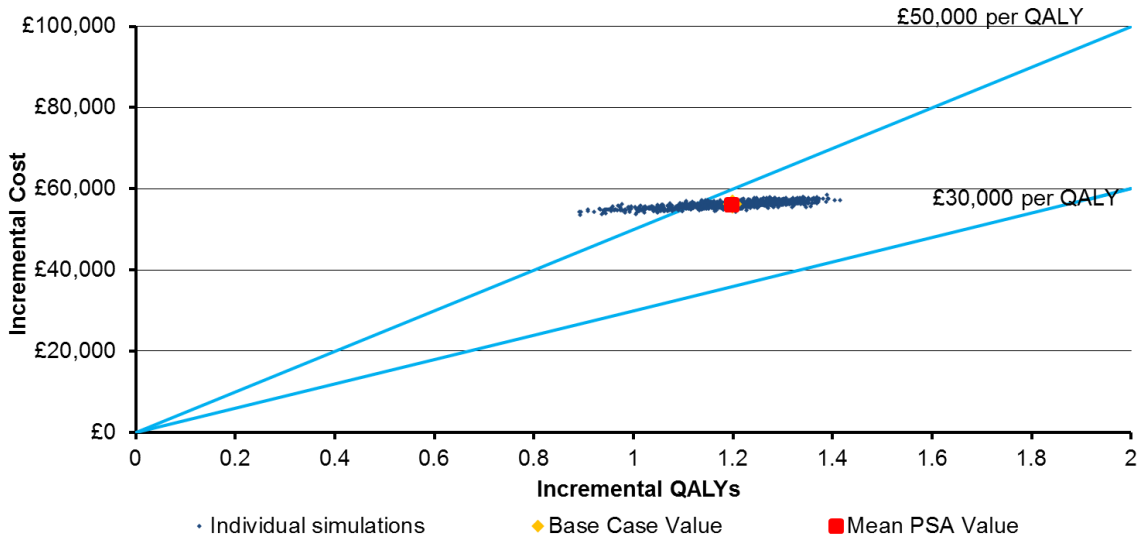


The model base case (with the new PAS, August 2012) including all available data for 3mg/kg gives an ICER of £46,739, using the most appropriate approach (3 part curve fit approach, as described within the most recent manufacturer submission).

At a threshold of £50,000 ipilimumab is cost-effective in 81% of cases as shown in Figure 18, which presents the cost-effectiveness plane for the base case, and Figure 19 which presents the cost-effectiveness acceptability curve. This probabilistic analysis shows a low level of parameter related uncertainty around the baseline ICER.

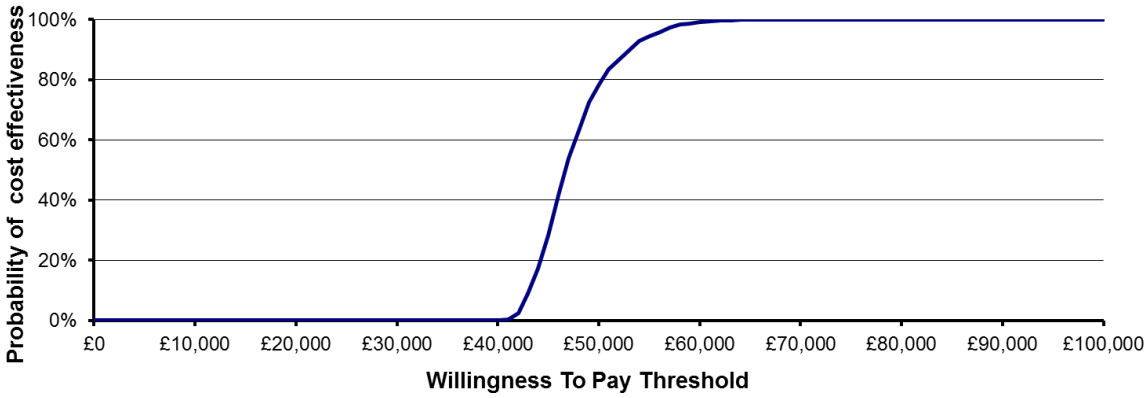
Beyond this, the analyses presented in the previous section show that the areas identified as potentially problematic by the ERG e.g. cut-off point and source of registry data, are not large sources of uncertainty. Equally the new data provides a much larger degree of certainty in the estimates, due to the increased patient numbers, and number of trials with similar results.

Figure 18 Cost-effectiveness Plane



NB: Base case value marker is obscured by the mean PSA value marker

Figure 19 Cost-effectiveness Acceptability Curve



A sensitivity analysis has been conducted using the discount rate of 1.5% for costs and benefits (Table 11). This discount rate is suggested in the draft update to the NICE methods guide with the document stating that:

> "in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)".[12]

In the case of ipilimumab, the available longer term data indicates that longer term outcomes are likely to be obtained in some patients.

The NICE Citizen's Council report recently presented at the NICE board meeting[13] also gives consideration to differentially lowering the discount rate used for benefits in the case of longer term improvements. A second sensitivity analysis was therefore conducted using a discount rate of 3.5% for costs and 1.5% for benefits, in line with that considered by the Citizens Council.

Using a discount rate of 1.5% for both costs and benefits, the ICER is £39,714, whilst using the different rates of 3.5% for costs, and 1.5% for benefits, this falls to £38,323. PSA indicates that in these scenarios (with the new PAS) ipilimumab is certain or near certain to be cost effective at a £50,000 threshold.

Table 11 Sensitivity Analysis Using 1.5% Discount Rate

Discount Rate	PAS	Treatment	Total			Incremental			ICER	% Chance Cost Effective at WTP £50,000
			Costs	LY	QALYs	Costs	LY	QALYs		
1.5% costs and benefits	No PAS	BSC	[redacted]	1.13	0.86	[redacted]	2.02	1.46	£56,706	14
		Ipilimumab	[redacted]	3.14	2.32					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	New PAS	BSC	[redacted]	1.13	0.86	[redacted]	2.02	1.46	**£39,714**	94
		Ipilimumab	[redacted]	3.14	2.32					
1.5% benefits, 3.5% costs	No PAS	BSC	[redacted]	1.13	0.86	[redacted]	2.02	1.46	£55,316	4
		Ipilimumab	[redacted]	3.14	2.32					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	New PAS	BSC	[redacted]	1.13	0.86	[redacted]	2.02	1.46	**£38,323**	100
		Ipilimumab	[redacted]	3.14	2.32					

6. Clinical Data

Presented below are synopses of the studies mentioned earlier.

a. CA184-025

CA184-025 (-025) which was cited in the original June 2011 NICE submission (Section 1.6), is an on-going, multi-centre, open-label, Phase 2 study of ipilimumab (MDX-010) extended-treatment monotherapy (re-induction or maintenance treatment) or follow-up for patients previously enrolled in ipilimumab trials (CA184-004, CA184-007, CA184-008, CA184-022, MDX010-08 and MDX010-15). The number of subjects potentially eligible for enrolment in this study was based on the number of patients enrolled in the original (parent) studies.

Details of parent studies

- **CA184-004** - Randomised, double-blind, Phase 2 study in previously treated and treatment naïve patients with Stage III (unresectable) or Stage IV melanoma. Patients were randomised into two different ipilimumab dose cohorts: 3 or 10mg/kg every 3 weeks, for 4 doses (induction), followed by additional doses of ipilimumab every 12 weeks (maintenance).[5]

- **CA184-007** - Randomised, double-blind, placebo-controlled, Phase 2 study of ipilimumab administered with or without prophylactic oral budesonide in patients with previously treated, Stage III (unresectable) or Stage IV melanoma. Each patient received 10mg/kg of ipilimumab every 3 weeks, for 4 doses (induction), followed by additional doses of ipilimumab every 12 weeks (maintenance), and was randomised in a double-blind fashion in a 1:1 ratio to 9mg of oral budesonide or placebo.[6] Study CA184007 was presented in the original June 2011 NICE submission.

- **CA184-008** - Open-label, single-arm, multi-centre, Phase 2 study in patients with previously treated, Stage III (unresectable) or Stage IV melanoma who had progressed after at least one prior treatment regimen. This was a monotherapy study of ipilimumab 10mg/kg every 3 weeks, for 4 doses (induction), followed by additional doses of ipilimumab every 12 weeks (maintenance).[7]

- **CA184-022** - Randomised, double-blind, multi-arm, multi-centre, Phase 2 fixed dose study of multiple doses of ipilimumab monotherapy in patients with previously treated, Stage III (unresectable) or Stage IV melanoma who had received prior therapy with at least one regimen containing IL-2 and/or non-experimental, experimental, or adjuvant melanoma treatment. Patients were randomized (1:1:1) to three different ipilimumab dose cohorts: 0.3, 3, or 10mg/kg every 3 weeks, for 4 doses (induction), followed by additional doses of ipilimumab every 12 weeks (maintenance).[8] Study CA184022 was presented in the original June 2011 NICE submission.

- **MDX010-08** - Randomised open-label Phase 2 study in patients receiving 3mg/kg of ipilimumab (every 4 weeks for 4 doses) alone or in combination with dacarbazine (at 250 mg/m^2 for 5 consecutive days, every 3 weeks [maximum of 6 cycles]) in the treatment of chemotherapy naïve metastatic melanoma.[9]

- **MDX010-15** - Randomised, open-label, multi-centre, Phase I dose-escalating pharmacokinetic study of ipilimumab in subjects with unresectable malignant melanoma.[10]

The primary objective of the -025 study was to monitor the safety of ipilimumab administered.

The secondary objectives included assessing overall survival from the start of ipilimumab treatment in the parent studies and assessing response to treatment.

This study allows continued treatment and/or tumour assessments of non-progressing patients as well as continued follow-up of patients previously treated with ipilimumab in prior/parent studies.

There were 3 groups the re-induction (3mg/kg or 10mg/kg), maintenance (0.3, 3, or 10mg/kg) and follow-up (no additional study treatment):

- **Re-induction**-

  All patients received open-label 3 mg/kg or 10 mg/kg (4 individual doses of ipilimumab at 3 week intervals) depending on parent study treatment arm.

- **Maintenance**

  Patients from parent studies (CA184004, CA184007, CA184008 and CA184022) entered into either a 'treatment' maintenance phase (0.3, 3, or 10 mg/kg of blinded or unblinded ipilimumab dosing in 12 week intervals) or an 'only tumour assessments' maintenance phase (without further ipilimumab treatment).

  Patients entering into this study after mixed or delayed response under the parent study received open-label 10 mg/kg regardless of the prior ipilimumab dosage.

  Patients from parent studies (MDX010-08 and MDX010-15) entered into a maintenance phase as Tumour Assessment Only. This Group could receive further treatment, either as re-induction or maintenance, if they met eligibility criteria.

- **Follow-up**

  Patients entered a follow-up phase with no additional ipilimumab treatment. Patients may also enter the study as Survival Follow-Up Only for the collection of survival data.

Study -025 is available as a poster, sub-analysis by Wolchok et al.[11] where the cut-off point for reporting was March 2011. This poster is an evaluation of the prolonged survival effect of ipilimumab in patients with metastatic melanoma through follow-up survival analyses on data from 3 of the completed Phase 2 trials (-007, -008, -022). Patients with prolonged survival included those with an objective response, stable disease, or progressive disease, according to modified World Health Organization criteria.

At the time of the poster publication, the survival follow-up data available was current in 91% of the patients at the cut-off date of March 9, 2011. The 4 year survival rates at the ipilimumab 10mg/kg dose ranged from 19.7% for heavily pretreated patients (in study -008) to >49% for treatment naïve patients (in study -007). The longest survival time for an ipilimumab patient over all the studies at the poster presentation data cut-off date was 61 months and continuing. A meaningful proportion of ipilimumab patients continued to survive beyond 4 years; most patients who were alive at 3 years were surviving at 4 years.

It must be borne in mind that a proportion of patients were lost to follow up (6%, 7% and 8% of previously treated patients in studies -008, -022 and -007 respectively, and 25% of treatment naïve patients in -007). Finally, not all sites and patients participated in this follow-up rollover study of 025.

Despite these limitations, Wolchock et al[11] considered that these Phase 2 studies of ipilimumab monotherapy in metastatic melanoma showed prolonged survival, exceeding 4 years, in a meaningful proportion of patients. This durable survival was reflected across the spectrum of heavily pre-treated to treatment-naïve patients.

This document was updated with the longest available survival data for the analysis conducted within this document (see Section 3 for plots of the updated survival data). Durability of response can be seen regardless of ipilimumab dose, through the continuing "flattened tail" of the ipilimumab overall survival curve.

a1. CA184-004

Study 004 (Hamid et al 2011)[5] was a multinational, randomised, double-blind, Phase 2 study in previously treated and treatment naïve patients with, Stage III (unresectable) or Stage IV melanoma. Patients were randomised into two different ipilimumab dose cohorts: 3 or 10mg/kg every 3 weeks, for 4 doses (induction), followed by additional doses of ipilimumab every 12 weeks (maintenance).

This study explored the association between tumour microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. The primary objective was to analyse pre-treatment characteristics of the patient and/or tumour with clinical tumour response,

82 patients (pretreated [n=62] or treatment naïve [n=20]) patients were randomised to ipilimumab treatment (n=40 in the 3mg/kg arm and n=42 in the 10mg/kg arm). Patients were followed for efficacy assessment up to 48 weeks and for up to a further 70 days post last dose for deaths.

Significant increases in post-treatment expression of various immune-response genes were seen. Consistent with other studies, no association was found between ipilimumab clinical benefit or safety, survival outcome and HLA-A*0201 genotype status.

The 1 year survival rates were 60.9% and 44.2% for the 3mg/kg and 10mg/kg groups respectively.

The Kaplan-Meier curves in Figure 20 show overall survival for this study as of April 2012 (54 months follow up).

Figure 20 Overall Survival, CA184-004

b. CA184-024

Study 024 (Robert et al 2011)[14] was a multinational, randomised, double-blind, placebo-controlled Phase 3 study of patients with previously untreated Stage III (unresectable) or Stage IV metastatic melanoma to determine whether ipilimumab (10mg/kg) plus dacarbazine, as compared with dacarbazine and placebo, improved overall survival.

In total 502 patients were assigned treatment (250 patients in the ipilimumab plus dacarbazine group and 252 in the dacarbazine monotherapy arm). 498 patients received at least one dose of the assigned drug and followed up (247 ipilimumab plus dacarbazine, 251 dacarbazine monotherapy).

Patients were randomized in a 1:1 ratio to receive either ipilimumab (10mg/kg) plus dacarbazine (850mg/m^2), at weeks 1, 4, 7 and 10 for a total of four doses, or placebo plus dacarbazine (850mg/m^2), at weeks 1, 4, 7 and 10, followed by dacarbazine alone every 3 weeks up to week 22.

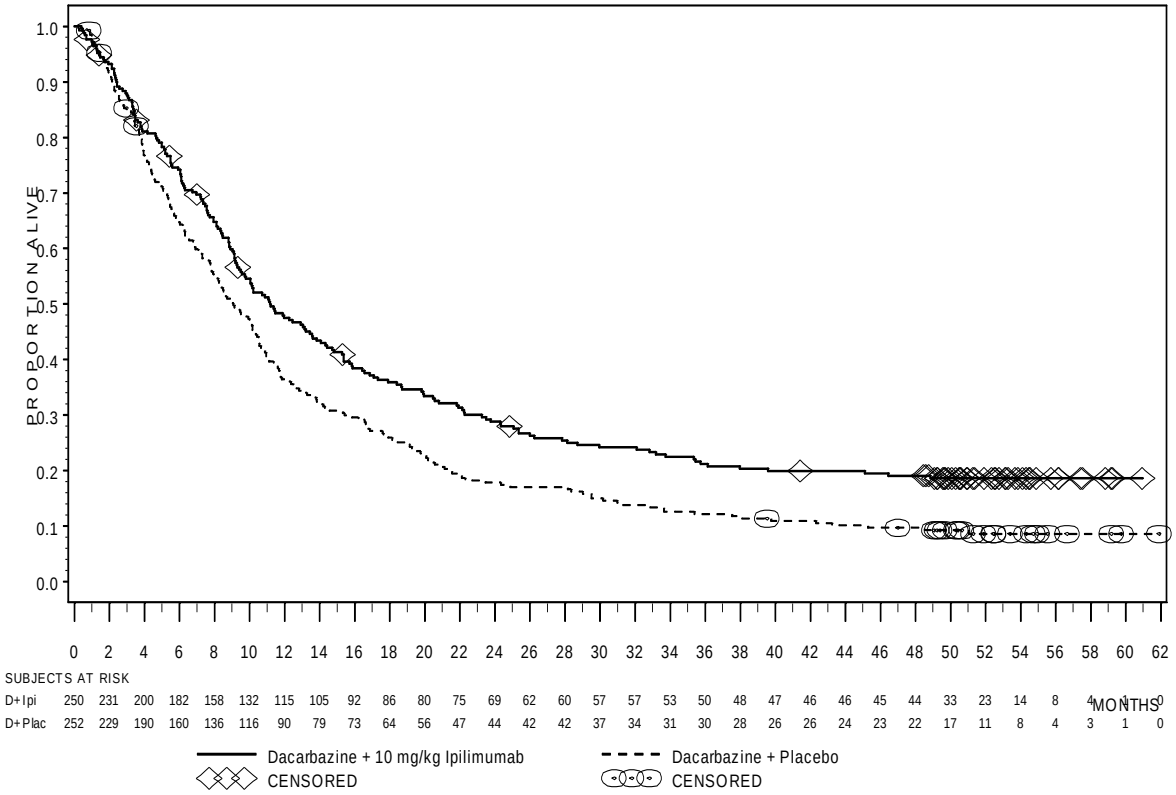
At week 24, patients with stable disease or an objective response were entered into the maintenance phase, receiving ipilimumab plus dacarbazine or dacarbazine monotherapy every 12 weeks until disease progression, development of toxic side effects or the end of the study.

Follow-up for the primary endpoint analysis was 37 months after the last subject was randomized.

The Kaplan-Meier curves below show similarity for the groups through approximately the first 4 months of treatment, after which a separation in the curves suggests a favourable overall survival advantage for the ipilimumab plus dacarbazine group.

Median overall survival was 11.2 months (95% CI: 9.4, 13.6) in the ipilimumab plus dacarbazine group and 9.1 months (95% CI: 7.8, 10.5) in the dacarbazine monotherapy group.

Figure 21 Overall Survival, (<u>unpublished recent data</u>), CA184-024



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Dacarbazine + 10 mg/kg Ipilimumab	198/250	11.2 (9.40 - 13.6)
Dacarbazine + Placebo	226/252	9.07 (7.75 - 10.5)

Prolonged survival was noted among some patients who were followed for up to 4 years (n=44). In the ipilimumab plus dacarbazine group an estimated 28.5% of patients were alive at 2 years, and an estimated 20.8% at 3 years, as compared with an estimated 17.9% and 12.2%, respectively in the dacarbazine monotherapy group.

Overall, this trial showed a significant improvement in overall survival among patients with previously untreated metastatic melanoma who received ipilimumab plus dacarbazine as compared with dacarbazine monotherapy. A long term benefit demonstrated over a minimum of 4 years follow up is unprecedented in metastatic melanoma trials. This study is still open and continues to follow up and treat patients and so further long term data collection is ongoing.

c. CA184-045

Study 045 is the Expanded Access Program in the US, Canada, Argentina, and Brazil consisting of previously treated metastatic melanoma patients. Initially patients were treated with 10mg/kg

ipilimumab; however, based on the results from the MDX010-20 Phase 3 study of 3mg/kg ipilimumab the protocol was amended to allow patients to receive ipilimumab at 3mg/kg. In total, 803 patients in

the 10mg/kg group, and 2000 patients in the 3mg/kg ipilimumab cohort were followed for survival. Thus, Study 045 provides a large safety database for ipilimumab, one which includes patients typically excluded from ipilimumab registration clinical trials (for example, patients with brain metastases, patients with ocular melanoma).

Safety and overall survival data from the 10mg/kg ipilimumab group was presented at ASCO 2012 (1-5th June 2012) [redacted]

[redacted]

Overall survival data collection for ipilimumab 10mg/kg was initiated in 2011, 2.5 years after enrolment was completed. In this analysis, patients who were lost to follow up within 2 or 3 years on the study (approximately 20%) were considered to have died; this conservative approach provides an underestimation of overall survival rates.

Based on the available data collected as of October 2011, 22% (n=183) of ipilimumab patients were alive after 2 years, and 17% (n=138) were alive after 3 years. This database captures 90% of enrolled patients.

Within the limitations of retrospective data collection for survival, overall survival was consistent with the results seen elsewhere in the ipilimumab clinical trial programme.

These data show that, in line with the survival curves already presented, a proportion of previously treated metastatic melanoma patients show durable survival - over 2-3 years after treatment with ipilimumab.

d. CA184-089

Study CA184-089 is the Italian subset of the European Early Access Programme (EAP). These data represent a European population and ipilimumab use in the context of routine practice within an EAP rather than within a randomised clinical trial.

There are 2 cohorts of patients, all of whom are previously treated metastatic melanoma patients:

- (1) 10mg/kg every 3 weeks for 4 doses (induction), followed by additional doses of ipilimumab every 12 weeks (maintenance).
- (2) 3mg/kg every 3 weeks for 4 doses (induction), followed by re-induction if necessary.

The outcome data shown in **Error! Reference source not found.** and **Error! Reference source not found.** are from 74 patients in the 10mg/kg cohort (patients enrolled from February 2008 to October 2008). Forty- three patients (58.1%) completed the induction phase, with 26 (35.1%) entering the maintenance phase.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Data for 563/848 patients in the 3mg/kg cohort (patients enrolled from June 2010 to January 2012) are available with a median follow-up of 3 months. As of April 2012 the median overall survival was 6.2 months, with a 1 year survival rate of 34%.

e. Other sources of long term data recently published: Prieto et al 2012

In addition to the BMS clinical trial database, the Prieto et al publication[1] provides further data pertinent to the durability of response to ipilimumab in patients with metastatic melanoma.

Patients with metastatic melanoma were treated in three trials from 2002 to 2005 and their longer term follow-up and survival data were analysed. The three studies involved:

- Study 1: 56 patients receiving ipilimumab with a gp100 peptide.
- Study 2: 36 patients receiving ipilimumab with interleukin-2.

- Study 3: 85 patients receiving ipilimumab with intra-patient dose escalation and were randomised to receive a gp100 peptide.

The median time of follow-up for Studies 1, 2, and 3 were 92, 84, and 71 months respectively. Median survival was 14, 16, and 13 months, with 5-year survival being 13%, 25%, and 23% respectively. All but one of the 15 complete responders from these studies were still ongoing at 54+ to 99+ months at the time of publication. Figure 5 shows the Kaplan-Meier data for overall survival for each protocol.

These data represent the longest follow-up to date of melanoma patients treated with ipilimumab and demonstrate the durability of the responses arising from this innovative agent. Although initial response rates were low (Objective Response [OR] of 7%), long-term follow-up shows that some non-responders became responders, while some Partial Responses (PRs) became Complete Responses (CRs) – this occurring over an average period of 30 months.

Importantly, Prieto et al[1] consider that ipilimumab can lead to long-term regression of metastatic melanoma which is durable and potentially curative in some patients with metastatic melanoma, as demonstrated by the flattening of the survival curves on long-term follow up (Figure 4).

7. Discussion and Conclusion

The addition of new clinical data has reduced the uncertainty around long-term survival and together with a new PAS leads to a baseline ICER that is within the acceptable range, with very little variation, reinforcing and adding more certainty to the previous findings of cost-effectiveness for ipilimumab in the treatment of metastatic melanoma.

We have demonstrated consistent overall survival (OS) curve profiles across the large number of patients treated with ipilimumab in a number of trials with different designs. From heavily pre-treated patients, to treatment naive patients, the shape of the survival curve is similar – strengthening the clinical supposition that ipilimumab has a consistent, enduring effect in a proportion of patients and increasing confidence in the clinical benefit of ipilimumab. The longer term data presented here reflect and reinforce the validity and durability of the longer term survival whilst reducing the uncertainty originally seen in the extrapolations of the shorter term data that has previously been presented to NICE.

The newly available data further confirm that the 3 part curve fit approach is the most appropriate of the methodologies presented to model OS. This is particularly so when comparing to the ERG methodology which in the new data set overestimates mortality in long term survivors in both ipilimumab and control populations. For the 3mg/kg data, this provides both internal validity (fitting the trial data well) and external validity (showing a good fit to registry data). Additional longer term data (outside the BMS trial program), provide further strong evidence that ipilimumab can induce durable, possibly a potentially curative[1], tumour regression in a percentage of patients with metastatic melanoma. This is compatible with the modelling approach used within the most recent manufacturer submission (January 2012).

In the new base case model we estimate approximately 1.2% of patients treated with ipilimumab will die of non-melanoma mortality, with the remainder dying from melanoma mortality (as would be expected for Stage IV disease), some having their lives extended (in some cases substantially) through the use of ipilimumab.

The previous submission showed an ICER of £49,844. New base case results for this model have been produced using all available 3mg/kg data and the best-fitting survival analysis. The results show an increase in the ICER to [redacted] using the previous PAS (January 2012), but a reduction in the range of uncertainty around the estimate. The increase is driven by a small reduction in predicted long term survival with the newly available trial data. The degree of uncertainty however is reduced due to increased patient numbers and increased length of follow-up. When the new PAS (August 2012) is applied, a reduction in the ICER to £46,739 is observed with all the available 3mg/kg data. If all trial data is taken into account (not just the data using the licensed dose) the ICER falls to £38,707.

The use of the new data, along with reassessment of existing trial and registry data, has reduced the uncertainty around the modelled long term survival with ipilimumab. Scenario analyses around all potential survival assumptions have shown that the majority of analyses described within this report (16/17) present an ICER of less than £50,000 per QALY.

It must be noted that the one scenario for which ipilimumab is not cost-effective at £50,000 per QALY is when the ERG's methodology is used for survival extrapolation, which shows high variability depending upon the dataset used. Whilst the ICER is lower when using only 3mg/kg trial data (£55,807 compared to £46,739), it is also higher than the 3 part curve fit approach when using all the

available trial data (£35,147 compared to £38,707). It should be reiterated that the EGR methodology does not fit the available registry data, and shows a strong tendency to over-predict survival in the short term and under-predict survival in the long term.

Sensitivity analyses around the curve fit used, the trial data-set used, the source of the registry data and the cut-off point for the 3 part curve fit analysis indicate the ICER is likely to lie within the range of £38,000–£47,000 per QALY, depending on the assumptions used. More precisely, the ICER for all trial data is £38,707 and for the new 3mg/kg trial data it is £46,739.

Adapting the approach, by changing the cut-off point selected for the 3 part curve fit approach or using alternative registry data, has little effect on the results - the ICER increases or decreases by up to 3% depending on the source of data or cut-off point used. In probabilistic analysis, with the new base case model the ICER remains cost effective (at a £50,000/QALY threshold) in 81% of cases.

The analysis conducted within this document demonstrates that the use of the 3 part curve fit approach is justified, and that, with the new PAS, ipilimumab is highly likely to be cost-effective at the threshold of £50,000 per QALY.

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