Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Ipilimumab for previously treated advanced (unresectable or metastatic) malignant melanoma

Prepared by:

Bristol-Myers Squibb Pharmaceuticals Limited

28th October 2011

CONFIDENTIAL VERSION

Response to the Appraisal Consultation Document: Ipilimumab for previously treated advanced (unresectable or metastatic) malignant melanoma

Confidential information is highlighted and underlined, e.g. [redacted]

Approved Name of Medicinal Product:	ipilimumab
Brand Name:	Yervoy
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd
Submitted by:	[redacted]
Position:	Associate Director Health Economics and Outcomes Research
Date:	28th October 2011

Dear Dr Adam,

BMS is in receipt of the Appraisal Consultation Document (ACD) for ipilimumab for previously treated unresectable malignant melanoma. We are obviously disappointed that the ACD does not recommend the use of ipilimumab in this indication.

Of singular importance, in our view, is the lack of credit that this highly innovative product has been given by the Appraisal Committee. In Section 4.2, the AC recognises that the treatment represents a step change in the treatment of advanced melanoma and that it is the first treatment development in this area for 30 years.

Section 4.13 of the ACD considers *"...whether the innovative nature of the technology may not have been adequately captured in the QALY measure."* We believe that while the treatment effects have been captured in the QALY measure, the mechanism of action of ipilimumab – which represents a paradigm shift in the treatment of malignant melanoma, and is the essence of the highly innovative nature of ipilimumab – has not been appropriately and comprehensively captured.

Innovation is one of the factors that the methods guidance recognises as relevant to whether a product represents a good use of NHS resources, so this is a crucial point. The AC says that it "considered that the magnitude of additional weight that would need to be assigned to the QALY gains….would be too great…to be…a cost effective use of NHS resources". This implies that it was applying the same end of life cut off point that it has used with other oncology products, many of which have been significantly less innovative than ipilimumab. It is unclear from the ACD what methodology the AC used to reach this conclusion and, in particular, what value it is ascribing to various degrees of innovation to decide what is, and isn't, an acceptable magnitude of additional weight.

The end of life criteria allows NICE to recommend treatments with an ICER over £30,000 per QALY if a substantial improvement in overall survival is demonstrated. This captures the unmet need for a treatment. However, society should put additional value on innovation benefits not captured by the QALY and therefore the NHS, as the organisation dealing with the health interests of society, should be willing to pay more for medicines offering a paradigm shift in the treatment of a disease through such non QALY captured benefits.

BMS has conducted further work on the value of innovation within the NICE 'End of Life' guidance. This work is set out in **Section 1** on **page 6** (Valuation of innovation within NICE 'End of Life' guidance) and outlines a method to quantify the level of innovation inherent in an end of life product, defined as the 'innovation ratio'. This work shows ipilimumab to be one of the most innovative drugs assessed by NICE under the 'End of Life' criteria. Please note that it is provided as Academic in Confidence (AIC). BMS is clear that this drug has the ability to produce substantial survival benefit in a sizeable group of patients, for whom rapid and painful death would be their only other option. The AC states:

- *"…the manufacturer showed a survival advantage for ipilimumab, it was unable to reliably quantify the long-term survival benefit beyond 2 years."* **(Section 3.15).** This statement is not correct, as the pivotal MDX010-20 study provides outcomes up to 4.5 years. In addition poster presentations are included with this submission, showing survival data from patients in Phase 3 studies.

The ACD also states:

- *"When the cost of administering the full course (four doses) of ipilimumab in line with the UK marketing authorisation was included in the model, the manufacturer's base-case ICER increased to £70,200 per QALY gained."*

  An error has been recognised in the model for this scenario analysis. The model allowed all patients to receive 4 doses of ipilimumab even if they were deceased. Re-running the scenario analysis to allow only living patients to receive a dose of ipilimumab reduces this value to **£60,556**

BMS have also conducted other additional modelling and provided further information to assist the appraisal committee. This is presented below.

- **Revision of the modelling methodology in using registry data on long term survival rates (see page 13)**

BMS recognise the limitations of the original modelling – the ACD states *"the ERG considered that the manufacturer's model is likely to have substantially overestimated the extent of survival benefit associated with treatment with ipilimumab"* (Section 3.17), and the inherent positive bias – the ACD also states *"The ERG noted that this approach implied that anyone surviving beyond 5 years of second-line systemic treatment was effectively cured"* (Section 3.16).

In order to model the effectiveness of both ipilimumab and best supportive care, the initial modelling submitted by BMS to NICE used:

- Kaplan-Meier data from months 0 – 18
- Parametric curve fitting for months 18-60
- Background mortality beyond month 60

However, to inform better the cost-effectiveness of ipilimumab, BMS revised its modelling methodology based upon feedback from clinical experts. Rather than assume patients are effectively cured should they survive to month 60, we have used registry data (available for up to 15 years post diagnosis) to predict disease specific mortality for Stage IV melanoma in addition to background mortality. This addresses the issue that patients after 5 years were effectively cured, and uses real world data to support the number of patients dying of relapsed melanoma.

The impact of the changes is to increase the ICER from the original model of around £54,500, to approximately **£65,303.** Although the SmPC does not allow for vial sharing of ipilimumab, discussions with clinicians have indicated that vial sharing may occur in a proportion of patients in practice (Appendix 1). BMS endorses the use of ipilimumab as outlined in the SmPC (Appendix 2). However based on the feedback from clinicians BMS is providing ICERs incorporating vial sharing for the Appraisal Committee's consideration. The ICER including 50% of patients sharing vials is **£62,632** if all patients vial share the ICER lies at £59,961.

- **Revised economic model results and sensitivity analyses (see page 2121)**

BMS believes that the revised approach addresses the comments by the ERG and Appraisal Committee on the original modelling, and provides a more realistic estimate of both the effectiveness and cost-effectiveness of ipilimumab. As such, the key results and sensitivities are provided in **Table 1**, with a full set of results and sensitivity analyses presented later on page23.

In the revised model, survival gain is estimated to be 30 months (44.1 months vs. 14.1 months), which generates an ICER of **£65,303**, implementing 50% vial sharing reduces this ICER to **£62,632.**

Table 1: Key results and sensitivity analyses of the revised economic modelling

Technology	Total			Incremental			ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Revised Base Case - 50% vial sharing							
BSC	£11,747	1.07	0.82				
Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Sensitivity analysis – full vial sharing							
BSC	£11,747	1.07	0.82				
Ipilimumab	£86,286	2.77	2.06	£74,539	1.70	1.24	£59,961
Sensitivity analysis – no vial sharing							
BSC	£11,747	1.07	0.82				
Ipilimumab	£92,928	2.77	2.06	£81,181	1.70	1.24	£65,303

- **Further information on utilities used in the submission (see page 33)**

In the Appraisal Committee meeting it was highlighted that BMS should provide further information on the utilities used within the submission. This Section contains a full report on the methods used to value the utility of patients in the MDX010-20 clinical trial, and is also provided as Academic in Confidence.

- **Utility of progressive disease patients (see page 44)**

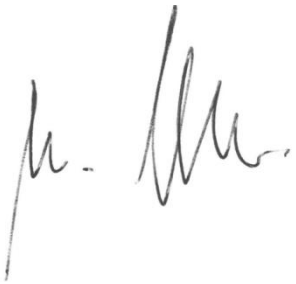
In the Appraisal Committee meeting, questions were asked as to whether the pre- and post- progression utilities were appropriate, as only a small decrease was seen between health states.

Analysis of the utilities data by time to death highlights that patients do not experience a marked decrease on progression, but do experience a rapid fall in utility immediately prior to death; these values are 0.85 in measurements taken in patients over 400 days from death, but 0.64 in patients experiencing death in the following 50 days.

Unfortunately this analysis was conducted too late to be included in the economic modelling, however given the long term survival exhibited by ipilimumab patients (remaining in the post-progression state for longer), this biases the result against ipilimumab, as the post-progression utility reported is artificially low.

BMS hopes that the information provided in this response will help to inform best estimates of the value to patients of ipilimumab, the methods by which this value is calculated, and to reinforce the high degree of innovation that ipilimumab shows. We look forward to meeting with NICE on 16th November, and to developing a mutually acceptable way in which to bring this valuable medicine to patients in the NHS.

Yours sincerely



Maximilian Lebmeier
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Section 1: Valuation of innovation within NICE 'End of Life' guidance

Summary of key points regarding valuing innovation in End of Life treatments

- In the Appraisal Committee meeting for ipilimumab, and in the Appraisal Consultation document, the Appraisal Committee acknowledged that ipilimumab represents a significant innovation and that the QALY estimates were unlikely to have fully captured the benefits of this innovation.
- NICE Methods Guide suggests that innovation and the benefits from innovation should be considered in a *proportional fashion* to the extent to which a treatment's ICER exceeds the £20-£30K per QALY threshold.
- NICE End of Life guidance recognises that treatments that meet certain criteria, around life expectancy and survival gain, represent particular innovations and should be approved at higher ICERs than normal.
- BMS have evaluated previous End of Life guidance using an 'innovation ratio' of incremental survival divided by life expectancy in the patient population. BMS believes this is a good proxy for innovation in the oncology area.
- When reviewing previous End of Life guidance, it appears that Appraisal Committees have been recognising the level of innovation (as measured by the innovation ratio) in their decisions.
- Ipilimumab represents a significant innovation and is at the far end of the spectrum of End of Life treatments as measured by this innovation ratio.
- If NICE were to consider the level of ICER threshold proportionately to the level of innovation for End of Life treatments, it would suggest that ipilimumab is approvable at an ICER up to £70K per QALY.
- Given that the most plausible ICER estimates for ipilimumab sit within this range, BMS believes that a positive decision would be in keeping with NICE's Method's Guide and remit to reward innovation.

Ipilimumab represents a significant innovation in the treatment of unresectable or metastatic malignant melanoma.

- There is a very large degree of unmet need in this relatively young patient population and life expectancy is one of the worst of all the End of Life treatments appraised by NICE (Figure 10)
- It is the first new treatment for this condition in approximately 40 years
- Ipilimumab has a novel mechanism of action, representing a paradigm shift in not only malignant melanoma but also cancers in general (T cell mediated immuno-potentiation)
- Society should put additional value on innovation benefits not captured by the QALY and therefore the NHS, as the organisation dealing with the health interests of society, should be willing to pay more for medicines offering a paradigm shift in the treatment of a disease through such non QALY captured benefits.

This was acknowledged in the Appraisal Committee meeting for ipilimumab, and in the Appraisal Consultation document. It was also observed that the QALY estimates were unlikely to have fully captured the benefits of this innovation. In the section below, BMS has sought to understand how the innovation value of ipilimumab should affect the ICER threshold at which the Appraisal Committee deems it approvable.

[redacted]

1. NICE has stated that a step-change innovation is justification for a higher ICER threshold and that the level of acceptable ICER is proportionate to the level of innovation.

Innovation is central to NICE's remit and processes. In founding the Institute, the Secretary of State for Health mandated that it should consider the long-term impact of innovation on the NHS when formulating guidance.

NICE has developed further the manner in which innovation is incorporated into the review process in the Guide to Methods of Technology Appraisal (NICE, 2008) and also in its Response to the Kennedy Report (NICE, 2009a). As discussed in these documents, NICE views innovation with regard to the level of therapeutic benefit that is accrued from a novel scientific intervention, in relation to the unmet need in the patient population in question.

'The Appraisal Committee, in reviewing a product argued to be 'innovative', should establish both that it has ***a significant and substantial impact on health-related benefits*** *and improves the way that* ***a current need is met*** *…..and that it can be regarded as a* ***'step-change'*** *in the management of the condition'*

For such innovative treatments, NICE's Methods Guide (NICE, 2008) provides the Appraisal Committee with the scope to make positive recommendations when the most plausible ICER is in excess of £20K. For this to happen, certain criteria must be fulfilled, one being specific to the innovative nature of the treatment:

'The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure.' [6.2.23]

Further, above a most plausible ICER threshold of £30K per QALY, the Methods Guide states that:

'...the Committee will need to identify ***an increasingly stronger case*** *for supporting the technology as an effective use of NHS resources, with regard to the factors listed above.'* [6.2.25]

The above statement implies therefore that there ought to be a continuous and proportional relationship between an acceptable ICER threshold and the innovative nature of the new treatment. Importantly, it does not state that there should a finite level beyond which innovation cannot be rewarded.

2. Within EoL products, ipilimumab represents a substantial level of innovation, and in keeping with NICE's proportionate methodology, deserves a higher ICER threshold than less innovative products

Thus, the supplementary End-of-Life guidance [NICE, 2009b] reflects NICE's willingness to approve innovative oncologic treatments at a higher ICER threshold than less innovative treatments. Therefore this End-of-Life guidance provides the Appraisal Committee with the opportunity to approve innovative new products at a higher ICER than normal:

'...the Institute has taken account of its responsibility to recognise the potential for long term benefits to the NHS of innovation. In this context, it considers it appropriate for its Appraisal Committees to have ***regard to the importance of supporting the development of innovative treatments*** *that are anticipated to be licensed for small groups of patients who have an incurable illness.'*

In keeping with the Methods Guide recommendation to view relationship between innovation and ICER threshold as proportional, those treatments that offer the greater level of innovation – as defined by the End of Life criteria – should be recommended at higher ICER thresholds than products that have less innovation.

BMS has undertaken an analysis of the previous drugs that been deemed to meet the End of Life criteria (regardless of final NICE appraisal decision) and compared the level of innovation offered compared with ipilimumab NICE's criteria for End of Life stipulation (NICE, 2009b):

'The treatment is indicated for patients with a short life expectancy, normally less than 24 months and [2.1.1]

'There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and; [2.1.2]

No alternative treatment with comparable benefits is available through the NHS, and; [2.1.3]

The treatment is licensed or otherwise indicated, for small patient populations. [2.1.4]'

These criteria reflect key elements of innovation for oncologic treatments, most importantly the combination of a short life expectancy in the patient population (<24 months) and a substantial improvement in survival with treatment (>3months). Together, these two factors represent a crucial measure of the *relative* therapeutic advance provided by these innovative oncologic treatments. Considering both the life expectancy and the survival benefit together reflects the fact that it is more challenging to demonstrate absolute improvements in survival in patients with the greatest morbidity. Accordingly, products that provide larger relative survival benefits in patients with shorter life expectancies can be viewed as being more innovative (in keeping with NICE's view of innovation) than treatments that provide similar benefits in patients with a better prognosis.

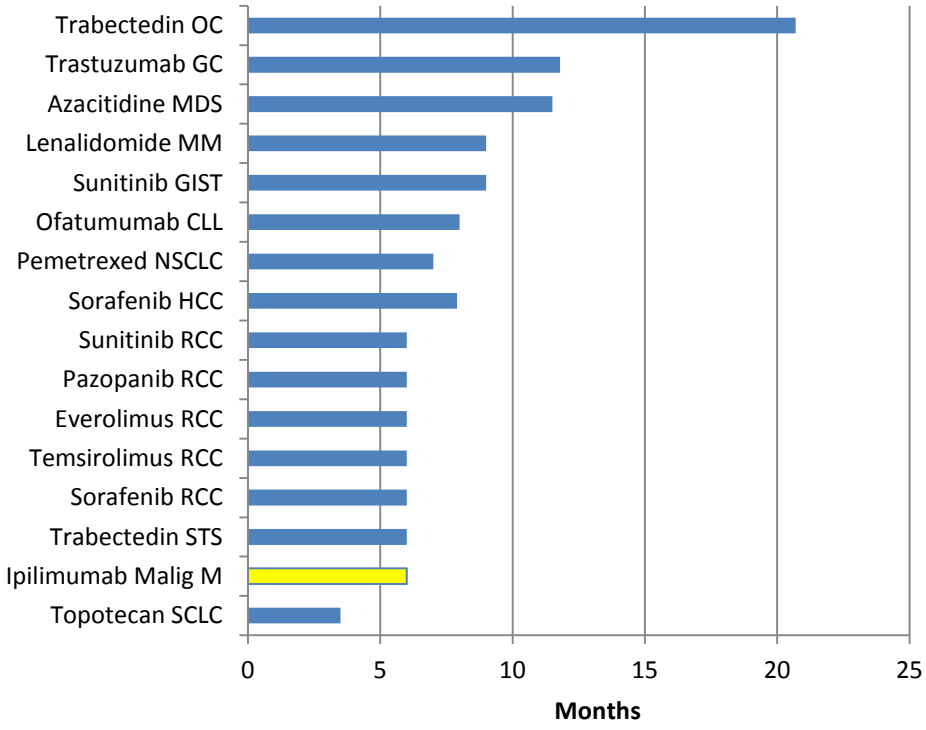
As a proxy of innovation for oncologic drugs, BMS has looked at the ratio of treatment survival benefit to life expectancy of those End of Life products that can be compared with ipilimumab using this ratio:

$$\text{Measure of Innovation (as per EoL criteria)} = \frac{\text{Therapeutic benefit}}{\text{Population Need}} = \frac{\text{Incremental Survival Gain}}{\text{Life expectancy in patient population}}$$

This 'Innovation Ratio' was estimated for ipilimumab and treatments that NICE judged to meet End of Life criteria using the data for each product that was available to NICE at the time of each review. Specifically, in the base case analysis, the following source data was used.

Life expectancy. The denominator in the equation was obtained from estimates of life expectancy in the disease, in the absence of the new treatment, that were cited by the Appraisal Committee in the NICE when ruling whether a product met the End of Life criteria. Where ranges were cited, the lower estimate was used. Where an exact estimate of life expectancy (prior to the introduction of the new technology) was not cited in the Guidance, the lower estimate from the manufacturer's submission was used. The life expectancy estimates for each of End of Life treatment are depicted in **Figure 1** below.

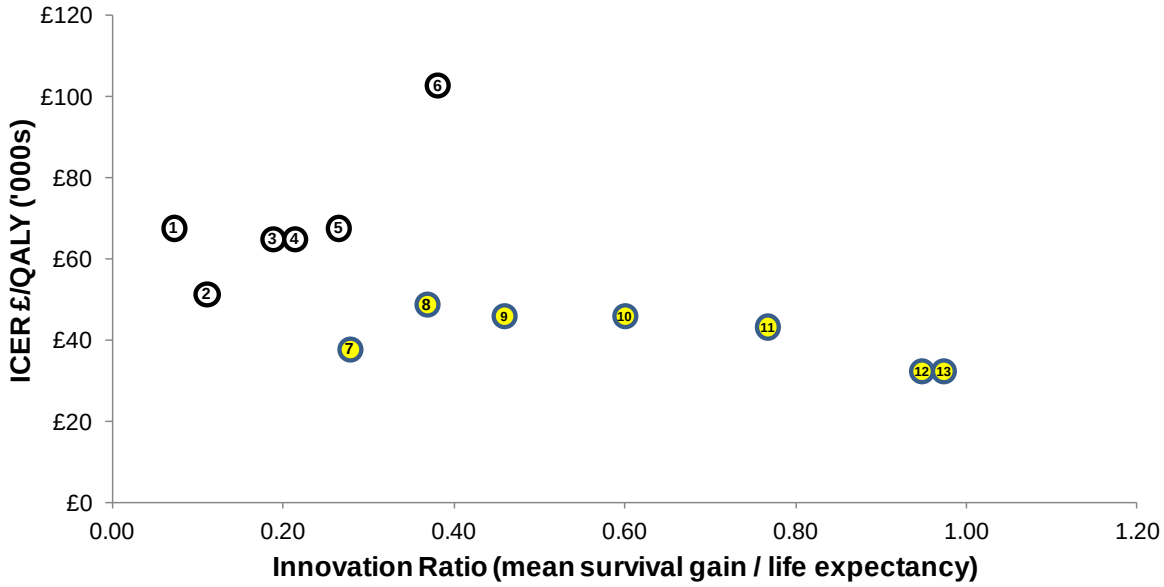
Figure 1: Life expectancy for End of Life disease as cited by NICE in Guidance



Incremental mean survival. Estimates of incremental mean survival were derived for each treatment based upon survival demonstrated in the pivotal Phase III studies referenced in the manufacturers' submissions to NICE. Only treatments that had survival benefits demonstrated from randomised controlled trials were included in the analysis (thereby excluding ofatumumab in chronic lymphocytic leukaemia and trabectedin in soft tissue sarcoma). Restricted mean survival benefits were estimated using all data reported overall survival data available at the time of the NICE review. No adjustments were made for crossover design.

Figure 2 depicts the innovation ratio for each previously assessed End of Life product against the base case ICER at which NICE made its decision (as reported in the NICE Guidance). This analysis suggests that historically, NICE decisions have recognised a distinction in the level of innovation between treatments that it approves under End of Life criteria (those points to the south east of the graph) and those it rejects (points to the north west of the graph). Therefore NICE has appeared to consistently rewarded products with greater innovation within End of Life guidance. However, despite this difference between treatments that were accepted and rejected, there is no clear evidence that Appraisal Committees have been differentiating between treatments according to the level of innovation. Instead there appears to be a £50K ICER threshold for all End of Life treatments, regardless of the level of innovation.

Figure 2: Distribution of innovation ratios and ICERs for all End of Life drugs



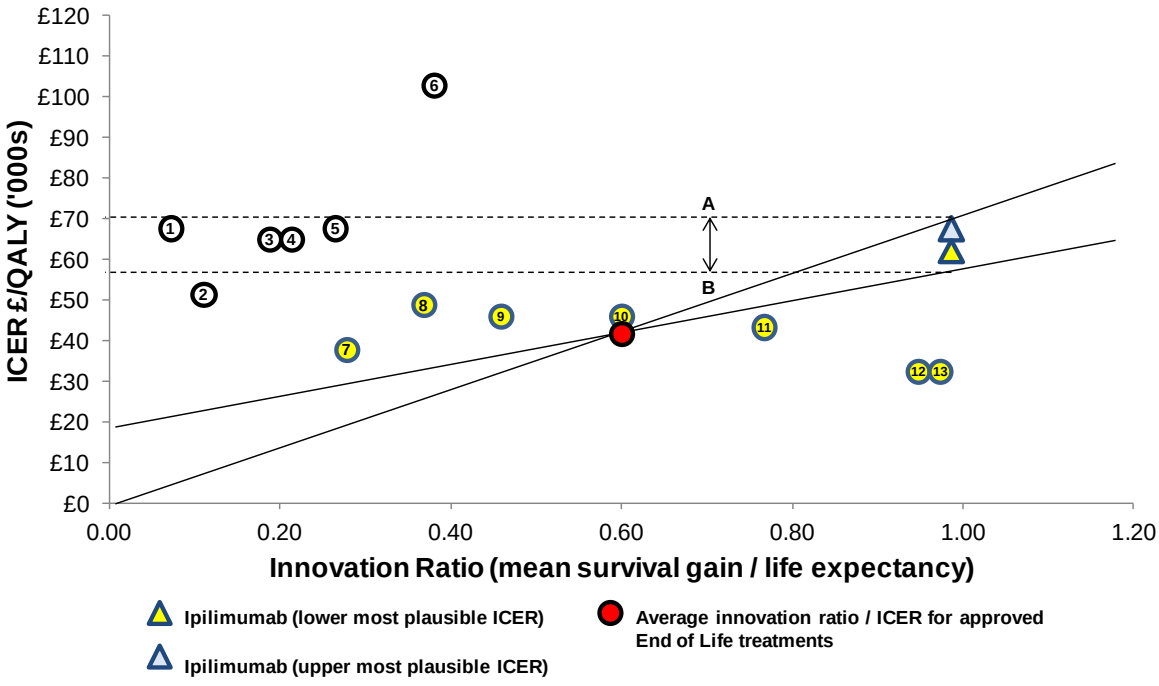
1	Trabectedin ovarian cancer	6	Temsirolimus renal cell carcinoma	11	Lenalidomide mutiple myeloma
2	Everolimus renal cell carcinoma	7	Pazopanib renal cell carcinoma	12	Topotecan small cell lung cancer
3	Sorafenib heptacellular carcinoma	8	Sunitinib renal cell carcinoma	13	Sunitinib gastrointestinal stromal tumours
4	Sorafenib renal cell carcinoma	9	Pemetrexed non-small cell lung cancer (maintenance)		
5	Trastuzumab gastric cancer	10	Azacitidine myelodysplastic syndromes		

(Note: White circles: negative final recommendation, Yellow circles: positive final recommendation)

When ipilimumab is considered within this spectrum of previous End of Life drugs, it can be seen to represent one of the more innovative treatments amongst this cohort. **Figure 3** superimposes on this graph two points that represent the ipilimumab innovation ratio against the range of most plausible ICER's which should be considered by the Appraisal Committee for ipilimumab (£59,961 - £65,303).

Also superimposed on **Figure 3** are two lines that represent the potential relationship between innovation ratio and acceptable ICER threshold. Both lines are bisecting the average innovation ratio/ICER of the End of Life treatments approved by NICE. The choice of the Y axis intercept value is subjective, to some extent, but the two lines represent two plausible scenarios. The first is an intercept at the origin, second at the £20K ICER threshold for non-innovative treatments. Using the latter, more conservative approach, the ICER threshold at which a highly innovative treatment like ipilimumab would be acceptable is £57K per QALY (point B) and using the former threshold line this would be £70K per QALY (point A). The most plausible ICER's for ipilimumab fall between these two estimates, suggesting that at the level of innovation that ipilimumab represents, the current ICERs would be deemed acceptable the Appraisal Committees to consider the relative level of innovation between End of Life treatments when making appraisal decisions.

Figure 3: Distribution of innovation ratios and ICERs for all End of Life drugs (including ipilimumab)



Conclusion

- In the Appraisal Committee meeting for ipilimumab, and in the Appraisal Consultation document, the Appraisal Committee acknowledged that ipilimumab represents a significant innovation and that the QALY estimates were unlikely to have fully captured the benefits of this innovation.
- NICE Methods Guide suggests that innovation and the benefits from innovation should be considered in a *proportional fashion* to the extent to which a treatment's ICER exceeds the £20-£30K per QALY threshold.
- NICE End of Life guidance recognises that treatments that meet certain criteria, around life expectancy and survival gain, represent particular innovations and should be approved at higher ICERs than normal.
- BMS have evaluated previous End of Life guidance using an 'innovation ratio' of incremental survival divided by life expectancy in the patient population. BMS believes this is a good proxy for innovation in the oncology area.
- When reviewing previous End of Life guidance, it appears that Appraisal Committees have been recognising the level of innovation (as measured by the innovation ratio) in previous decisions.
- Ipilimumab represents a significant innovation and is at the far end of the spectrum of End of Life treatments as measured by this innovation ratio.
- If NICE were to consider the level of ICER threshold proportionately to the level of innovation for End of Life treatments, it would suggest that ipilimumab is approvable at an ICER up to £70K per QALY.
- Given that the most plausible ICER estimates for ipilimumab sit within this range, BMS believes that a positive decision would be in keeping with NICE's Method's Guide and remit to reward innovation.
- BMS hope that the Appraisals Committee will give serious consideration to the points set out above with regard to innovation. In doing so, BMS hope that the Appraisal Committee understands and accepts the rationale behind our thinking in developing a method by which different degrees of innovation can be recognised and rewarded.

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2: Revision of the modelling methodology in using registry data on long term survival rates

Summary
The ERG raises an important issue about the validity of extrapolation without long term data. In rerunning the analysis the ERG performed we demonstrate that the results are much more favourable if certain, equally valid cut-off points or equally valid datasets are used than the 'pragmatic' methods used by the ERG.

We do however recognise that there is still methodological development ongoing in this area. The work presented here has been accepted as a podium presentation at ISPOR Europe 2011, precisely because of the interest in methods of modelling survival with novel oncology agents.

In order to better inform the effectiveness and cost-effectiveness modelling of ipilimumab, published registry data was used. These support the hypothesis of long term survival. The final results from this analysis suggest that both the best estimates of survival, and the ICER, lie somewhere between the original submission, and the values proposed by the ERG, with an estimated survival of 14.1 months for GP100, and 44.1 months for ipilimumab. This generates a survival gain of 30.0 months.

Although the SmPC does not allow for vial sharing of ipilimumab, discussions with clinicians have indicated that vial sharing may occur in a proportion of patients in practice. BMS endorses the use of ipilimumab as outlined in the SmPC. However based on the feedback from clinicians BMS is providing ICERs incorporating vial sharing for the Appraisal Committee's consideration. The ICER including 50% of patients sharing vials is £62,632 if all patients vial share the ICER lies at £59,961. With no vial sharing the ICER lies at £65,303.

Methods

The ERG and ACD have stated that there are substantial uncertainties regarding the modelling of long-term survival for ipilimumab patients based upon the available clinical data. Approaches to estimating survival for this group of patients are complex and open to debate.

The ERG conducted a *'pragmatic exploration of survival differences'* using survival data from the MDX010-20 clinical trial; however, it should be noted that within this exploration the long term survival hazards for ipilimumab are based upon an analysis of only 9 patients.

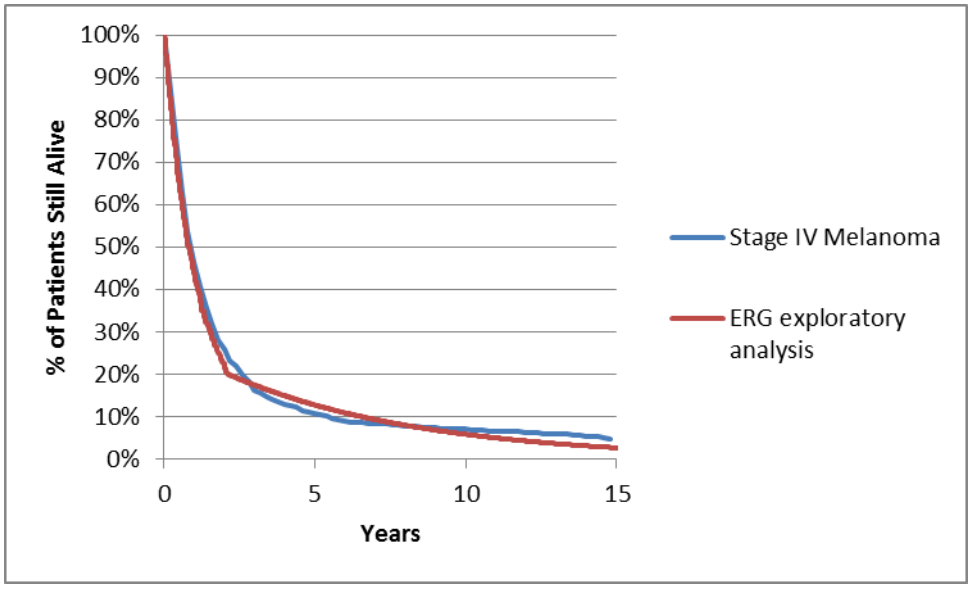
It should also be noted that a different cut off point for extrapolation is used for GP100 than for ipilimumab for Overall Survival (OS) (GP 100 assumed around 365 days, compared to ipilimumab 770 days) – as can be seen in the plot provided **(Figure 10, Page 66 ERG report)**. BMS accept that the selection of these cut off points by the ERG has been done for pragmatic reasons, however the use of slightly different, but equally valid data, could substantially influence results. For example:

- The addition of a point at the final data available date for both arms (which represents the end of known survival [1676 days]) increases the difference in survival between the arms from 16.3 months to 20.4 months.
- The use of ipilimumab only data (excluding the ipilimumab + GP100 dataset) to perform the same analysis using the 770 day cut off point gives a survival of 66.2 months for the ipilimumab arm.

This variability can be explained by the inherent difficulty in fitting a model to a small number of patients in order to understand a long term trend. For this reason the extrapolation performed by the ERG has an equal level of uncertainty to that performed by BMS within the original submission, this is also acknowledged by the ERG.

In addition comparing to registry data from Balch (2001) the ERG analysis underestimates survival in the long-term compared to Stage IV melanoma without treatment with ipilimumab as can be seen in **Figure 4**. This indicates that the ERG analyses are likely to overestimate the rate of death, particularly in the long term.

Figure 4: Comparison of ERG Analysis to Natural History of Disease



"…evidence available from the key clinical trial is inadequate to furnish a firm basis for discriminating between alternative long-term projection models." (**Page 69, ERG report**)

However, BMS do accept that, as stated by the ERG, ipilimumab patients are likely to experience some level of mortality associated with metastatic melanoma in the long-term,. Consultation with clinicians following the original submission has suggested that although this level of mortality is uncertain at present, it is likely to be above the level of mortality seen in the general population (i.e. the level that was used by BMS in the original submission), but below the level seen for patients with stage IV metastatic melanoma patients, based upon the natural history of the disease.

The limitation of not only what was presented by BMS in the original submission, but also the work performed by the ERG, is that it is based on an extrapolation of 25 years from the original 4.5 year trial. In addition the low death-rate of patients in the final years of the study adds to the difficulty in firmly predicting long-term survival, but suggests that there is the potential for good long term survival in those patients still living at the end of the trial.

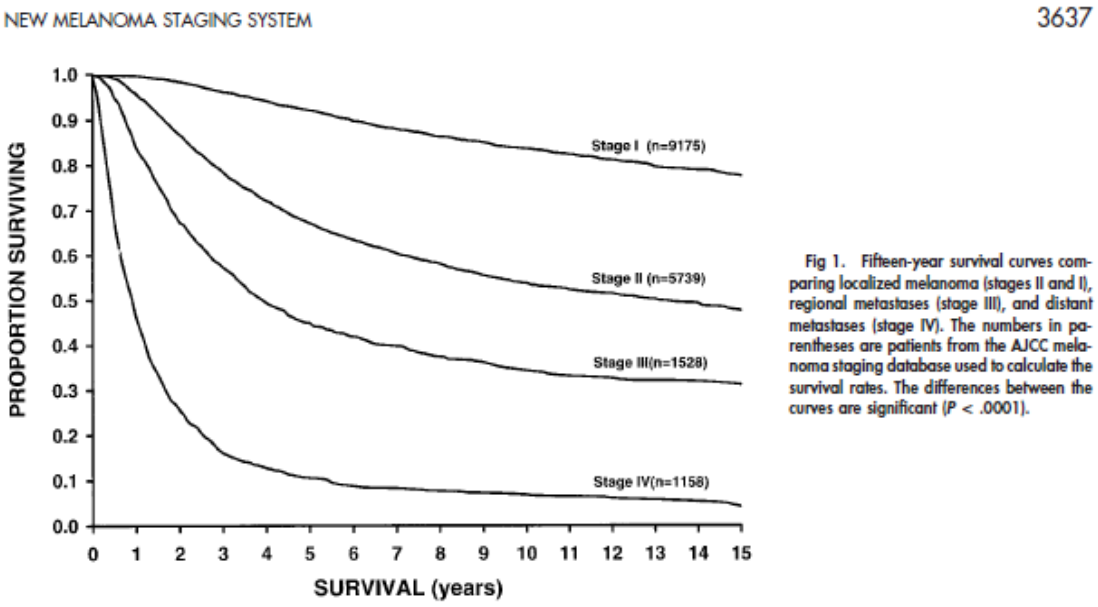
BMS has undertaken further discussions with clinicians who have identified work presented in the AJCC as a potential data source (Balch, 2001). This paper presents survival outcomes for different stages of melanoma to 15 years from diagnosis.

These clinicians indicated that the information for Stage IV melanoma was most relevant to the patients within the MDX010-20 trial (only 10/676 patients within the trial had Stage III melanoma and the clinicians indicated that these were likely to be more severe patients than a standard Stage III diagnosis).There is a more recent version of the AJCC data available (Balch, 2009),; however this only presents 10 year survival data for patients with stage IV melanoma, which makes the data less useful for the estimation of long-term survival.

Figure 5 shows the diagram extracted from Balch (2001) which shows long-term survival for Stage IV patients based on a sample of 1,158 patients. The information presented within this paper represents death from metastatic melanoma only (patients dying without melanoma are censored out); therefore this has been added to the model in addition to background mortality.

The method presented in Section 6.3 of the main submission has been used to predict survival up to the end of 5 years. Background mortality has been included separately within the model using the 3 year mortality averages from the Interim Life Tables for 2007 – 2009 (ONS, 2011) based on the MDX020-10 trial observation that patients' average age at the start of the model is 56, and 59% are male patients.

Figure 5: Natural History of Disease – Metastatic Melanoma



The Stage IV melanoma curve shown in **Figure 5** has been digitised, and the proportions surviving at each time point taken from this digitisation for 0 to 15 years. This curve was advised by leading clinicians to be most relevant to the ipilimumab trial population.

The hazard rates for 6 to 15 years have been calculated from the digitised graph for survival using the natural history for Stage IV metastatic melanoma. These latter years are seen to be representative of long-term survival for the patient population.

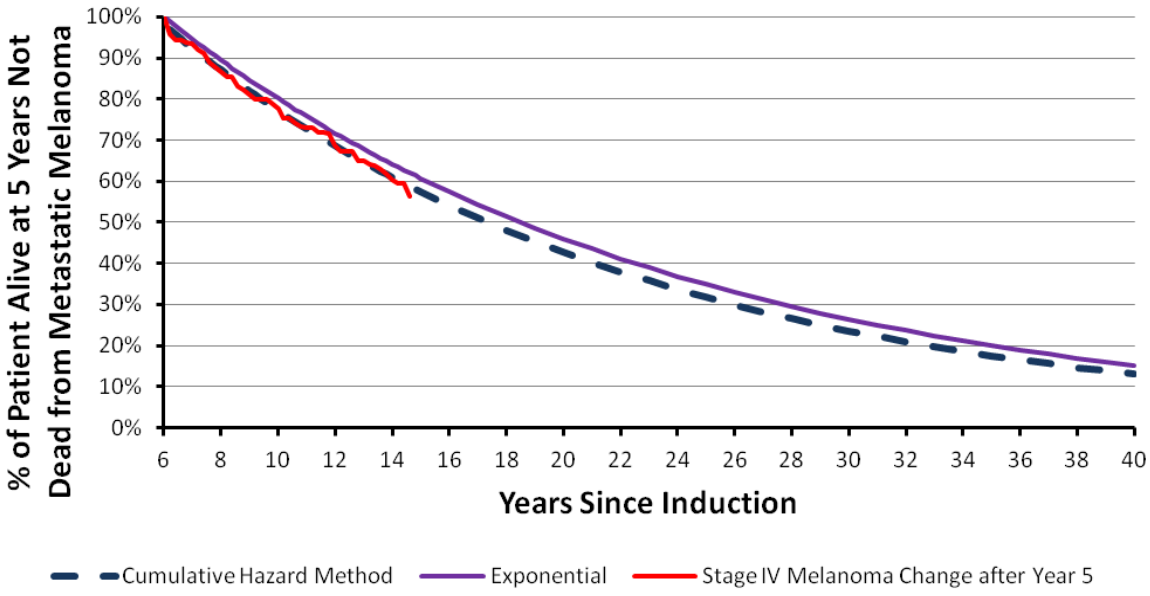
Two methods have then been used to calculate the future hazard rates from 5 years to 40 years:

- Fitting of a parametric survival curve to model the long term trend
- Plotting the cumulative hazard and fitting a trend line to the values observed

Figure 6 shows the survival curves fitted to the data using either a parametric curve fit (using the curve fit with the best AIC, which is the exponential), or the cumulative hazard approach. The results from the methods are very similar in their predicted survival for ipilimumab and GP100 patients (ipilimumab: 40.1 months using both methods, GP100: 14.1 months for both methods).

It can be seen that the best fit visually is the cumulative hazard method; therefore this method is used within the base case model and is described from this point.

Figure 6: Curve Fit to Stage IV Melanoma Natural History Data



The equation for the curve plotted cumulative hazard method is given as follows:

Where t is the time in years.

Applying this method, which assumes ipilimumab has no continued benefit for long-term survival beyond the end of the trial, produces costs and QALYs as shown in **Table 2**.

Applying this method assumes ipilimumab has no continued benefit for long-term survival beyond the end of the trial. This is a very conservative approach however, as the clinical data available contradicts this assumption regarding longer-term clinical response, and should therefore be viewed as an upper bound for the ICER and the least plausible ICER.

Table 2: Summary costs and QALYs implementing all ERG changes and conservative survival analysis

Treatment Arm	Totals			Discounted Totals			Incremental Costs	Incremental Life Years Gained	Incremental QALYs	Cost per LYG	Cost per QALY
	Costs	Life Years Gained	QALYs Gained	Costs	Life Years Gained	QALYs Gained					
BSC	£12,372	1.18	0.90	£11,747	1.07	0.82					
Ipilimumab	£92,979	3.34	2.47	£88,918	2.61	1.95	£77,171	1.54	1.13	£50,013	£68,105

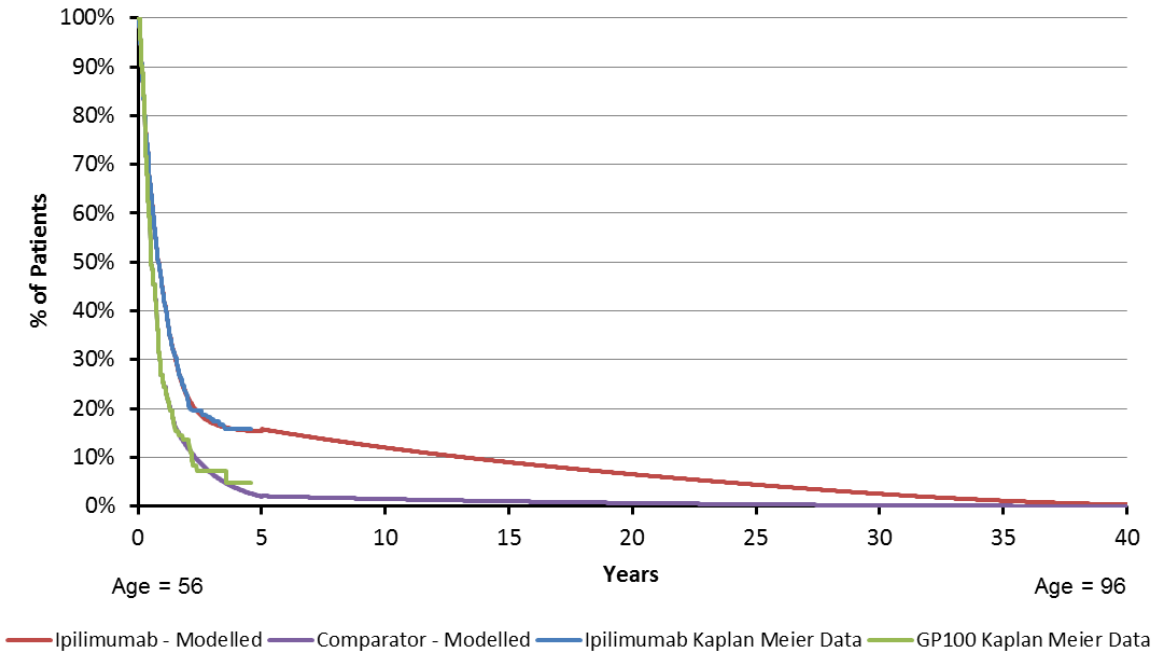
A Cox Proportional Hazard model has then been used to determine the difference in OS for long-term survivors (>18 months) between the combined arms and the GP100 arm of the MDX010-20 trial. The hazard ratio given is 0.782 (the hazard ratio for ipilimumab +

GP100 is 0.806 and for ipilimumab only is 0.735). This indicates that long-term survivors (>18 months) taking ipilimumab are 22% less likely to die within the trial period.

Using this estimate within the model is also a conservative assumption, as the cumulative hazard for GP100 continues to increase substantially beyond 18 months, whereas this is not the case for ipilimumab. However, this is more likely to reflect a real-life scenario than an assumption of no benefit.

The results of these analyses are presented graphically in **Figure 7** using the model's 40-year time horizon. As it is to be expected that all patients will die before the age of 100, curve fits that generate credible results should show this to be the case.

Figure 7: Overall Survival – Modelled Data vs Kaplan Meier Data, two-part curve fit with adjustment for background and melanoma mortality



The proportion of patients expected to remain alive by time point is shown in **Table 3**. The poor prognosis for metastatic melanoma patients can clearly be seen – more than half of patients within both arms of the trial have died within the first year. Ipilimumab is, however, estimated to extend life significantly for a group of patients with 15.3% of patients still alive at 5 years compared to 2% in the BSC arm and 6.6% of patients still alive at 20 years compared to only 0.7% in the BSC arm.

Table 3: Proportion of Patients Expected to Remain Alive

Years	Ipilimumab (%)	BSC (%)
1	44.1	25.3
2	22.5	12.1
3	17.1	6.7
5	15.3	2.0
10	12.0	1.5
20	6.6	0.7
30	2.6	0.2
40	0.3	0.0

Table 4 shows the ICER using the assumption of a 0.782 hazard ratio. Although this ICER is higher than the ICER put forward in our original submission (£54,500), based on ERG and clinician feedback on incorporating the mortality (above background mortality) expected in the long term, we think it is more plausible. Using the hazard ratios calculated from the different trial arms (including 50% vial sharing) produces the results given in **Table 5**, which are provided for completeness.

Table 4: Summary costs and QALYs implementing all ERG changes and more proportional hazard survival analysis

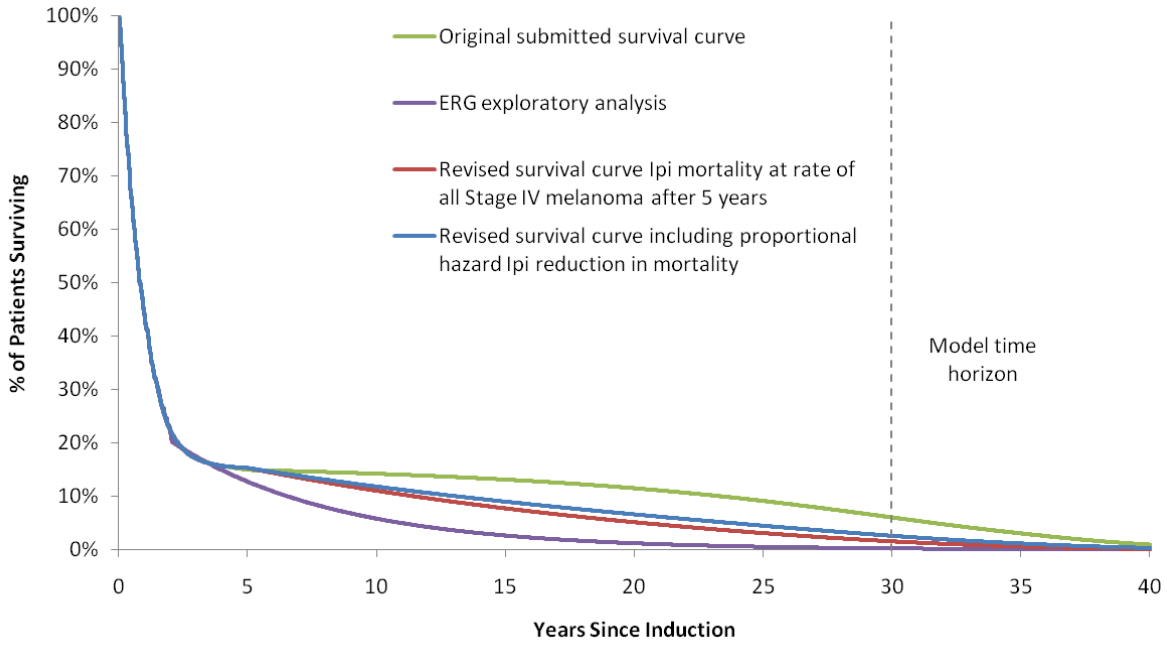
Treatment Arm	Totals			Discounted Totals			Incremental Costs	Incremental Life Years Gained	Incremental QALYs	Cost per LYG
	Costs	Life Years Gained	QALYs Gained	Costs	Life Years Gained	QALYs Gained				
BSC	£12,732	1.18	0.90	£11,747	1.07	0.82				
Ipilimumab	£94,986	3.68	2.69	£89,607	2.77	2.06	£77,860	1.70	1.24	£45,745

Table 5: Summary costs and QALYs implementing all ERG changes and proportional hazard survival analysis – impact of hazard ratios

Hazard Ratio	Cost per QALY
0.7818547 – combined data	£62,632
0.8061771 – ipilimumab + GP100	£63,185
0.7353992 – ipilimumab only	£61,605

The results of these analyses are presented graphically in **Figure 8**, which allows the ipilimumab survival curves estimated using the various different methods up to this point to be easily compared. It can be seen that mortality estimated using the natural history of disease lies above the ERG estimated survival curve, but below that from the originally submitted analysis, which took only background mortality into account.

Figure 8: Comparison of survival curves



Section 3: Revised economic model results and sensitivity analyses

Summary of main findings from sensitivity analysis
The probabilistic sensitivity analysis shows that the model has relatively equal levels of upside and downside risk with the majority of the uncertainty in the model being associated with the model outcomes rather than costs. There is a 100% probability of ipilimumab being cost effective at a £100,000 threshold.

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

- The curve type selected – as many of the potential curve fits do not fit the trial data well
- The patient's starting age – as this affects the length of time over which the survival associated with ipilimumab can be accrued
- The curve fit parameters assumed for overall survival for ipilimumab and BSC - as the majority of the benefits associated with ipilimumab come from increased survival over BSC

Base case results

Using the revised economic model (taking account of ERG amendments and the new modelling of survival described in the previous section) this section presents revised economic results and sensitivity analyses.

The sensitivity analysis for 4 doses has also been updated as the original model simply multiplied the cost by 4 – allowing patients to receive doses even if they had died.

Within the base case model the percentage of living patients receiving each dose is shown in **Table 6,** which gives an average of 3.5 doses received for living patients. It should be noted that there are various clinical reasons as to why doses after the first dose may not have been given, including adverse events and disease progression to the point where clinicians would suggest withdrawing treatment.

Table 6: Percentage of patients receiving each dose

Dose	% of Alive Patients Receiving Dose	% of Total Patients Receiving Dose
1	100%	100%
2	94%	92%
3	83%	77%
4	72%	64%

Base case results for the revised model are presented in

Table 7.

Table 7: Base-case results

Technology	Total			Incremental			ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£11,747	1.07	0.82				
Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632

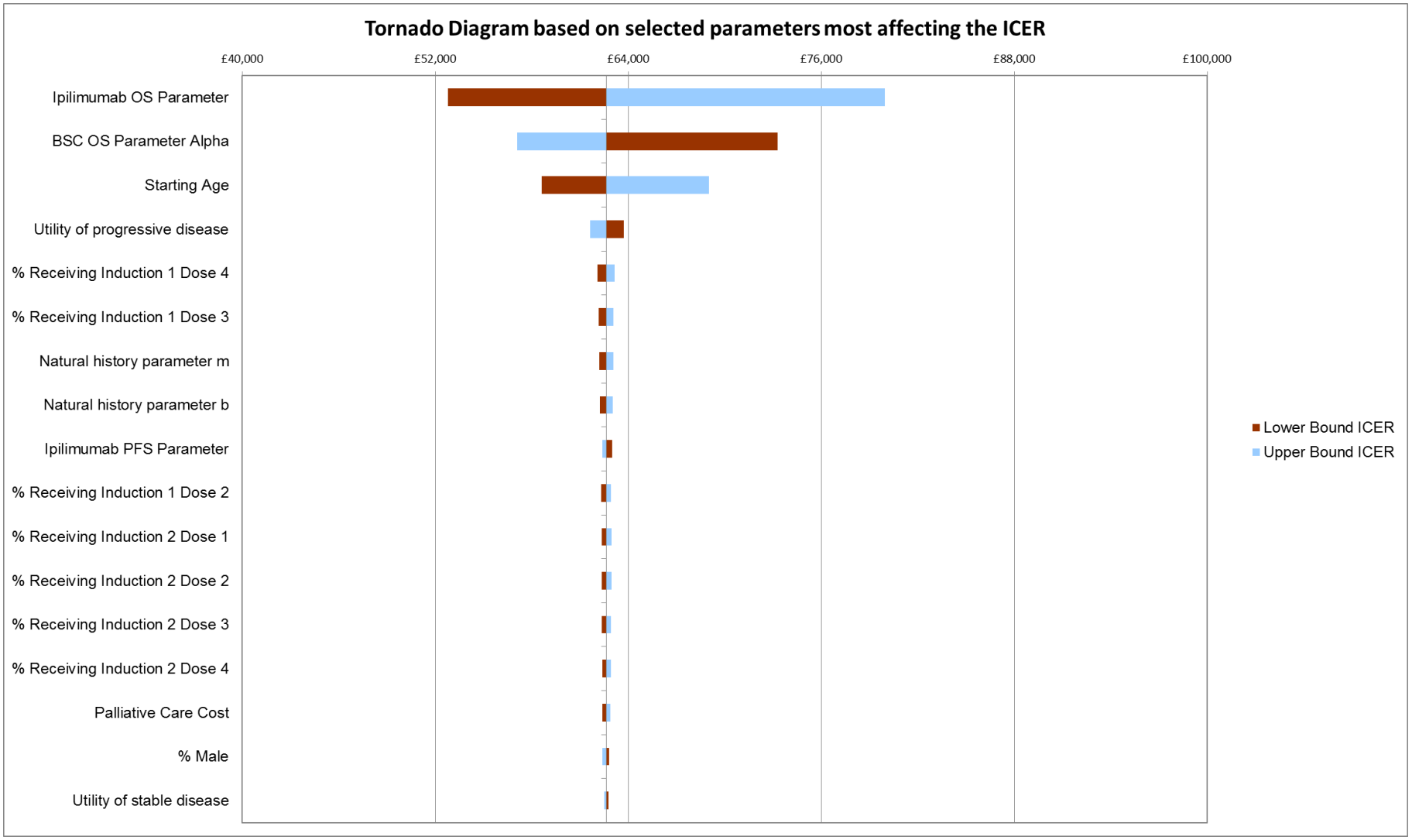
Deterministic sensitivity analysis

Figure 9 shows the results of the deterministic sensitivity analysis for all variables that produced a change of greater than or equal to £500 in the ICER. The results remain as were presented in the original analysis. The input which most affects the ICER is the utility assumed for progressive disease (PD). An increase in the utility assumed for PD reduces the ICER (as patients live longer in PD in the ipilimumab arm) and conversely a reduction in the utility assumed for PD increases the ICER.

Other variables which significantly affect the ICER are:

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

Figure 9: Tornado diagram presenting results of sensitivity analysis for all variables that cause a change of ≥ ± £500



Deterministic sensitivity analysis is shown separately in **Table 8** to **Table 10** for key variables:

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

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

The dose of ipilimumab given per patient per induction also has a large impact on the ICER, with the minimum dose given in the trial and compassionate use programme resulting in an ICER of £38,387 and the maximum dose given resulting in an ICER of £88,788. The risk surrounding the dose is evenly distributed between both upside and downside risk. Vial sharing has the potential to reduce the ICER by approximately £4,900 if 100% vial sharing occurs, by £2,671 if 50% vial sharing occurs and the use of the closest vial size has the potential to reduce the ICER by approximately £4,800. Vial sharing is likely to happen in normal clinical practice (**Appendix 1**).

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

Table 8: Impact of Vial Sharing Assumptions

Vial Sharing Assumptions with Average Dose	**ICER**
No Vial Sharing - Round Up	£65,303
50% Vial Sharing	**£62,632**
No Vial Sharing - Round Down	£59,737
100% Vial Sharing	£59,631

Table 9: Impact of Dose Required

Number of Vials	**ICER**
3 x 50mg	£51,470
1 x 200mg	£56,521
1 x 200mg + 1 x 50mg	£61,572
5.21 x 50mg	**£62,632**
1 x 200mg + 2 x 50mg	£66,623
1 x 200mg + 3 x 50mg	£71,674
2 x 200mg	£76,725

Table 10: Impact of the Utility of Progressive Disease

Utility of Progressive Disease	ICER
0.6	£76,838
0.625	£74,261
0.65	£71,850
0.675	£69,592
0.7	£67,471
0.725	£65,475
0.75	£63,594
0.763	**£62,632**
0.775	£61,818
0.8	£60,139

Probabilistic sensitivity analysis (PSA)

A scatter plot of PSA results is shown in **Figure 10**. The main source of variance in the model remains within the QALYs gained between the two treatment arms. This is consistent with the key sources of uncertainty identified in the deterministic sensitivity analysis (relating to the efficacy of treatment).

The cost effectiveness acceptability curve (CEAC) shows that: at the £100,000 per QALY threshold, there is 100% chance ipilimumab is cost-effective. At a £60,000 per QALY threshold there is a 25% chance ipilimumab is cost-effective; at a £70,000 per QALY threshold this rises to 88%. The mean ICER produced via PSA was £63,859.

Figure 10: Scatterplot of PSA results (1,000 simulations)

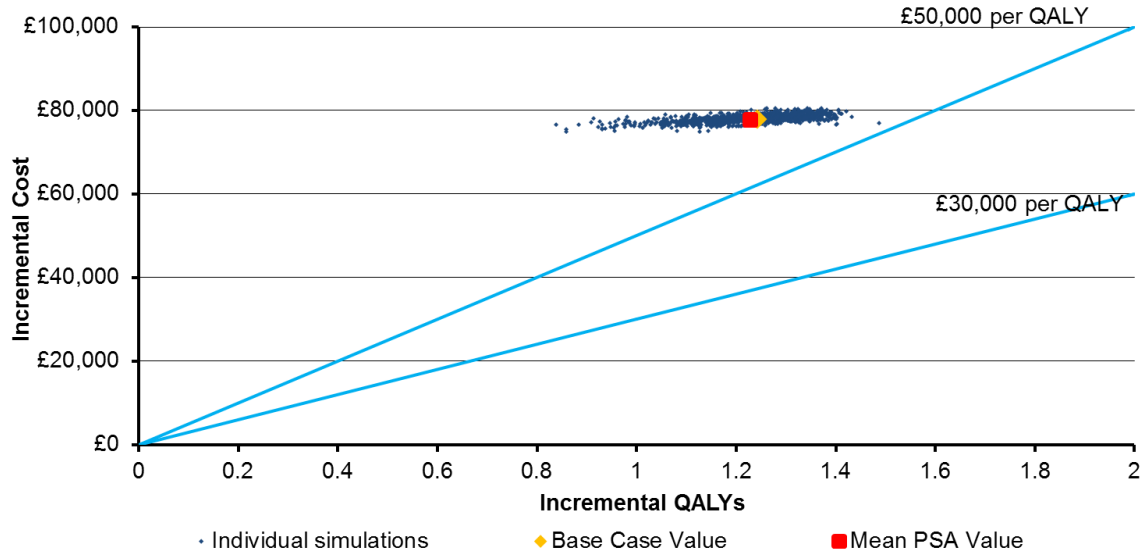


Table 11 to **Table 18** present the results of the structural sensitivity analysis and analyses for several different scenarios:

- Scenario 1: No discounting,
- Scenario 2: Alternative comparators
- Scenario 3: Alternative utility estimates
- Scenario 4: Maximum dosing assumption
- Scenario 5: Alternative curve fits
- Scenario 6: Use of alternative data for ipilimumab
- Scenario 7: Use of alternative time horizons
- Scenario 8: Use of alternative weight data

Scenario 1: No discounting

Table 11 shows that decreasing the discount rate reduces the ICER – as the benefits of ipilimumab in the longer term in the base case are discounted to a large degree, while costs are incurred within the 1st year of the model, and therefore are unaffected by discounting.

Table 11: Scenario 1: No discounting, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Discount 0%	BSC	£12,372	1.18	0.90				
	Ipilimumab	£94,486	3.68	2.69	£82,114	2.50	1.80	£45,743

Scenario 2: Alternative comparators

Table 12 shows the ICERs when comparing the various different estimates of current practice and the suggested alternative comparators of paclitaxel, paclitaxel + carboplatin and carboplatin. In all cases the ICER is reduced as Korn et al (2008) indicate than none of the current potential comparators have an efficacy greater than best supportive care (BSC), therefore the use of an alternative comparator increases the cost associated with treatment in the comparator arm without increasing efficacy.

Table 12: Scenario 2: Alternative comparators, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Collinson	Current Practice	£19,103	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£70,503	1.70	1.24	£56,714
IMS	Current Practice	£13,473	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£76,133	1.70	1.24	£61,243
MELODY	Current Practice	£13,020	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£76,587	1.70	1.24	£61,608
Oxford Outcomes	Current Practice	£15,221	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£74,385	1.70	1.24	£59,837
Paclitaxel	Paclitaxel	£23,423	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£66,184	1.70	1.24	£53,239
Paclitaxel + Carboplatin	Paclitaxel + Carboplatin	£35,825	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£53,782	1.70	1.24	£43,263
Carboplatin	Carboplatin	£17,973	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£71,634	1.70	1.24	£57,624

Scenario 3: Alternative utility estimates

Table 13 presents the differences in the ICER dependent on the source of utilities used. Use of the utilities from the SF-6D and Beusterien et al (Beusterein, 2009) increases the ICER by approximately £16,000 and £17,000, respectively. It can be seen that the use of drug specific utilities would decrease the ICER by approximately £3,200 (as utilities are marginally higher for ipilimumab patients), while the effect of adjusting the utilities for age (as within the base case) is to increase the ICER by over £3,000. Including separate adverse events utilities has little impact upon the ICER.

Caution should be used with the Beusterein utilities however, as due to differences in the observed utility, health states may not have been described accurately, particularly given the introduction of ipilimumab, which is likely to change the patient experience of disease (rather than a short post-progression stage, patients experience long term survival at a healthy level of utility, as seen in Section 4.

Table 13: Scenario 3: Alternative utility estimates, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Beusterien et al UK Utilities	BSC	£11,747	1.07	0.68				
	Ipilimumab	£89,607	2.77	1.65	£77,860	1.70	0.98	£79,562
SF-6D Utilities	BSC	£11,747	1.07	0.66				
	Ipilimumab	£89,607	2.77	1.65	£77,860	1.70	0.99	£78,455
Drug Specific EORTC Utilities	BSC	£11,747	1.07	0.78				
	Ipilimumab	£89,607	2.77	2.09	£77,860	1.70	1.31	£59,456
EORTC Utilities with additional decrement for AEs and no AEs for BSC	BSC	£11,590	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.05	£78,017	1.70	1.23	£63,391
EORTC Utilities unadjusted for age	BSC	£11,747	1.07	0.83				
	Ipilimumab	£89,607	2.77	2.14	£77,860	1.70	1.31	£59,419

Scenario 4: Maximum dosing assumption

Table 14 presents the differences in the ICER if all patients who are alive receive all 4 doses of ipilimumab during the first induction. This represents a scenario of maximum dosing beyond what which would be expected in clinical practice (due to adverse events toxicity and irreversible disease progression). The ICER does not increase substantially, while increasing or decreasing the proportion of patients receiving re-induction also does not affect the ICER substantially.

Table 14: Scenario 4: Maximum dosing assumption, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Patients Receive all 4 Doses of Ipilimumab	BSC	£11,747	1.07	0.82				
	Ipilimumab	£96,483	2.77	2.06	£84,737	1.70	1.24	£68,164
50% more patients receive each reinduction	BSC	£11,747	1.07	0.82				
	Ipilimumab	£92,828	2.77	2.06	£81,081	1.70	1.24	£65,223
50% less patients receive each reinduction	BSC	£11,747	1.07	0.82				
	Ipilimumab	£86,385	2.77	2.06	£74,639	1.70	1.24	£60,041

Scenario 5: Alternative curve fits

Table 15 presents the ICERs associated with various possible curve fits. It can be seen that curve fit does have a substantial effect on the ICER, particularly in the case of utilising the one part curve fit in the ipilimumab arm (which as discussed previously does not fit the trial data well).

Using a one part curve fit for the BSC arm reduces the ICER by approximately £4,000 – a result which is not substantially impacted by the curve type selected and indeed may be appropriate.

The use of melanoma mortality to model survival after 5 years also has a large impact. Assuming that patients who live to past 5 years on either arm do not experience further mortality from melanoma reduces the ICER by £11,600.

The melanoma mortality hazard has less of an impact upon the ICER. Assuming equal hazards for long-term survivors (>5 years) for BSC and ipilimumab increases the ICER by £5,400, whereas assuming that ipilimumab reduces the chance of re-occurrence of melanoma by 50% reduces the ICER by £5,700.

Table 15: Scenario 5: Alternative curve fits, results of structural sensitivity analysis and scenario analysis

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
One Curve Fit Both Arms – Best AIC	BSC	£11,023	0.92	0.71				
	Ipilimumab	£83,396	1.66	1.26	£72,374	0.74	0.55	£130,655
One Curve Fit Both Arms – Weibull	BSC	£10,840	0.89	0.69				
	Ipilimumab	£82,182	1.40	1.08	£71,342	0.51	0.39	£183,622
One Curve Fit BSC Arm – Best AIC	BSC	£11,023	0.92	0.71				
	Ipilimumab	£89,607	2.77	2.06	£78,584	1.85	1.35	£58,160
One Curve Fit BSC Arm – Weibull	BSC	£10,840	0.89	0.69				
	Ipilimumab	£89,607	2.77	2.06	£78,767	1.88	1.37	£57,435
Two Part Curve Fit – Best AIC without Melanoma Mortality (assumes cure after 5 years)	BSC	£12,157	1.17	0.88				
	Ipilimumab	£92,075	3.34	2.45	£79,919	2.18	1.57	£51,008
Two Part Curve Fit –Mortality Hazard one between arms	BSC	£11,747	1.07	0.82				
	Ipilimumab	£88,918	2.61	1.95	£77,171	1.54	1.13	£68,015
Two Part Curve Fit – Mortality Hazard 0.5 between arms	BSC	£11,747	1.07	0.82				
	Ipilimumab	£90,497	2.98	2.20	£78,750	1.91	1.38	£56,928

Scenario 6: Use of alternative data for ipilimumab

Table 16 presents the ICERs using data from the individual ipilimumab trial arms as opposed to the combined data used in the base case. The use of ipilimumab data alone reduces the ICER as greater efficacy was seen in the ipilimumab only arm.

Table 16: Scenario 6: Use of alternative data for ipilimumab

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Data for Ipilimumab only arm	BSC	£11,747	1.07	0.82				
	Ipilimumab	£97,672	3.24	2.44	£85,926	2.17	1.62	£53,129
Data for Ipilimumab + GP100 arm	BSC	£11,747	1.07	0.82				
	Ipilimumab	£86,846	2.31	1.73	£75,099	1.24	0.91	£82,463

Scenario 7: Use of alternative time horizons

Table 17 shows the impact of the use of alternative time horizons on the ICER. As expected, reducing the time horizon increases the ICER because one of the benefits of ipilimumab is increased long term survival. Reducing the time horizon to 15 years increases the ICER to £77,938, at which time approximately 9% of ipilimumab patients are expected to still be alive.

Table 17: Scenario 7: Use of alternative time horizons

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case – 40 years	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
Lifetime for all patients	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,617	2.77	2.06	£77,870	1.70	1.24	£62,595
15 years	BSC	£11,523	1.03	0.79				
	Ipilimumab	£87,323	2.33	1.76	£75,801	1.30	0.97	£77,938
20 years	BSC	£11,639	1.05	0.80				
	Ipilimumab	£88,399	2.54	1.91	£76,760	1.49	1.10	£69,500
25 years	BSC	£11,701	1.06	0.81				
	Ipilimumab	£89,039	2.67	1.99	£77,338	1.61	1.18	£65,487
30 years	BSC	£11,731	1.07	0.82				
	Ipilimumab	£89,389	2.73	2.04	£77,658	1.67	1.22	£63,614

Scenario 8: Use of alternative weight data

Table 18 shows that the source of the weight data used in the model has little effect upon the ICER.

Table 18: Scenario 8: Use of alternative weight data

Scenario	Technologies	Total			Incremental			ICER (£) versus baseline
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Base Case	BSC	£11,747	1.07	0.82				
	Ipilimumab	£89,607	2.77	2.06	£77,860	1.70	1.24	£62,632
UK Patients from MDX010-20 trial only	BSC	£11,747	1.07	0.82				
	Ipilimumab	£92,260	2.77	2.06	£80,514	1.70	1.24	£64,767
Compassionate use programme patients only	BSC	£11,747	1.07	0.82				
	Ipilimumab	£88,877	2.77	2.06	£77,130	1.70	1.24	£62,045

Section 4: Further information on utilities used in the submission

Summary of key points regarding the utility analysis

The utility analysis is based upon trial data from the EORTC-QLQ-C30 and SF-36 as follows:

- Questionnaires were completed predominantly at Week 12 and baseline with some questionnaires completed at Week 24 and beyond (questionnaires beyond Week 24 were only completed for patients receiving reinduction)

EORTC trial data shows:

- There is only one statistically significant differences between the three treatment groups (constipation)
- This demonstrates that concerns regarding ipilimumab toxicity impacting on patients' quality-of-life are not borne out by the patient responses within the trial
- For ipilimumab and GP100 functional scales do decrease between baseline and Week 12 and symptom scales increase between baseline and Week 12. This indicates that the medication toxicity is impacting upon quality-of-life, although not significantly (as above).
- Quality of life improves at Week 24 compared to baseline for both GP100 and ipilimumab showing that the effects of toxicity are short-lived
- After Week 24 quality-of-life seems to be maintained at a similar higher than baseline level for ipilimumab whereas long term survivors receiving GP100 see a reduction in their quality of life over the long-term – a time scale compatible with PD

Utility data were aggregated for use in the economic model using the following methods:

- Utilities were calculated for each individual observation.
- The average utility for each patient pre- and post-progression was calculated (where data were available) irrespective of the time period in which data was collected.
- The average utility within each health state was calculate as the average of the average patient utilities in each health state

In response to ACD questions regarding the raw EORTC data, we have provided the following information for clarity.

Analysis of EORTC QLQ-C30 Scores

Six hundred and sixteen patients completed EORTC QLQ-C30 questionnaires (1,190 observations). Some patients completed more than one questionnaire either pre or post-progression.

Table 19 shows the completion rates for the EORTC questionnaire by time period. The majority of questionnaires were completed at baseline or in Week 12.

Table 19: Completion Rates for EORTC Questionnaire

	Ipi + GP100	Ipi Only	GP100
Total Number of Patients	381	131	131
Course 1 Day 1	365	126	125
Course 1 Week 12	236	85	81
Course 1 Week 24	50	18	8
Course 2 Day 1	27	7	2
Course 2 Week 12	26	6	2
Course 2 Week 24	7	3	
Course 3 Day 1	4	3	
Course 3 Week 12	3	3	
Course 4 Day 1	1	1	
Course 4 Week 12	1		

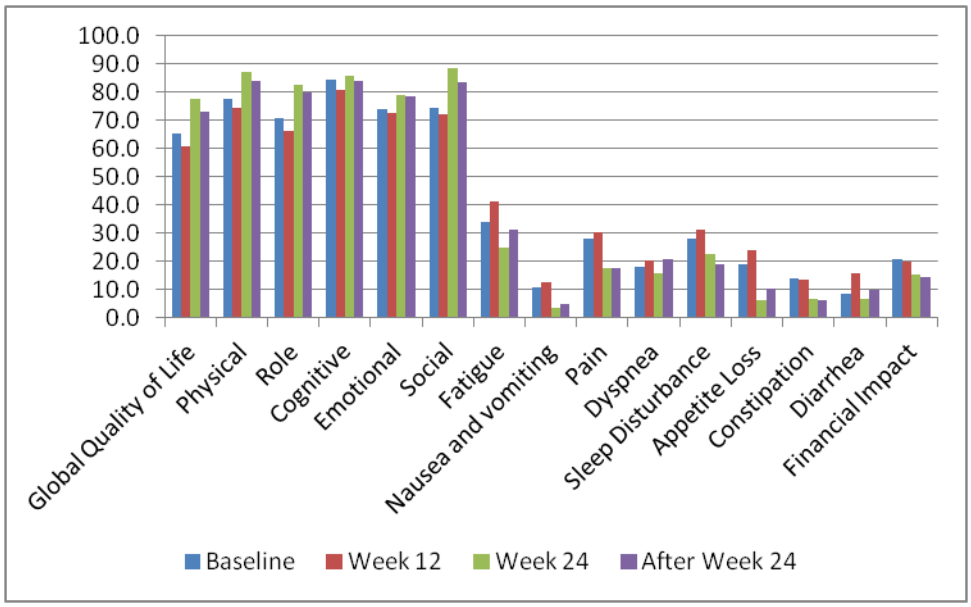
The HRQL scores for ipilimumab patients are summarized in **Figure 12** using the grouping from the original 30 questions defined within the statistical analysis plan and shown in

Table 19

Table 20: Grouping of EORTC-QLQ-C30 Questions for Analysis

Category	**Items from the questionnaire**
Global quality of life	29, 30
Functional scales	
Physical	1-5
Role	6, 7
Cognitive	20, 25
Emotional	21-24
Social	26, 27
Symptom scales and/or items	
Fatigue	10, 12, 18
Nausea and vomiting	14, 15
Pain	9, 19
Dyspnea	8
Sleep disturbance	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial impact	28

Figure 12: EORTC QLQ-C30 Scores – average over all ipilimumab patients[1]



It can be seen that all functional scales decrease between baseline and Week 12 and symptom scales increase between baseline and Week 12. This indicates that the medication toxicity is impacting upon quality-of-life. This is the case particularly for fatigue levels and diarrhoea. By Week 24, however, quality-of-life has improved compared to baseline with: large increases in the social and role limitations functional dimensions; a large increase in global quality-of–life; and a large decrease in many of the symptom scales – particularly fatigue, nausea and vomiting, pain, appetite loss, constipation and diarrhoea.

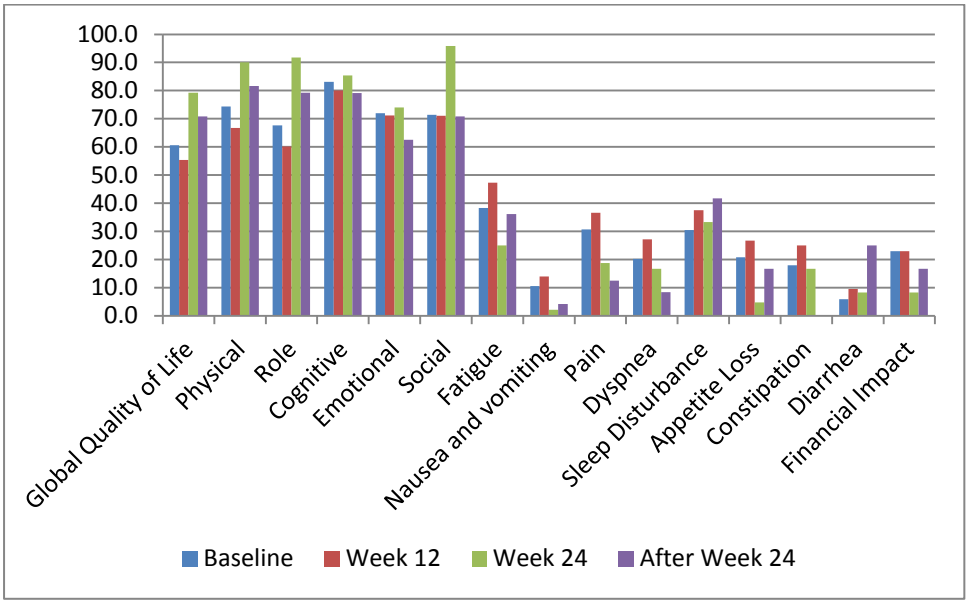
These results indicate that while toxicity has some impact on quality -of-life within the first 12 weeks of treatment, quality-of-life improves after this initial effect with increases over baseline by Week 24. After Week 24 quality-of-life seems to be maintained at a similar level (however, it should be noted that only 92 questionnaires were completed after Week 24, by patients receiving re-induction, so there may be some selection bias).

The HRQL scores for GP100 patients are summarised in **Figure 13**.

[1] Global QoL score is a transformation of the average raw scores of items 29 and 30, with 0 the worst and 100 the best. Functional scales: Physical (1 to 5), Role (6, 7), Cognitive (20, 25), Emotional (21 to 24), Social (26, 27). Each score is the transformation of the average raw scores with 0 the worst and 100 the best.

Symptom scales and/or items include: Fatigue (10, 12, 18), Nausea and vomiting (14, 15), Pain (9, 19), Dyspnea (8), Sleep disturbance (11), Appetite loss (13), Constipation (16), Diarrhoea (17), Financial impact (28). Each score is a transformation of the item score(s) with 0 as no symptom at all and 100 very much severe.

Figure 13: EORTC QLQ-C30 Scores – average over GP100 patients



As was the case with ipilimumab, all functional scales decrease between baseline and Week 12 while symptom scales increase between baseline and Week 12. By Week 24, (again, was the case with ipilimumab), quality-of-life improved compared to baseline. However, after Week 24, (in contrast to the quality-of-life results for ipilimumab), GP 100 quality-of-life seems to decrease again (only 4 questionnaires were completed after Week 24 by patients receiving re-induction, as most GP100 patients had died by the timepoint where reinduction applicability was determined).

These data indicate that while long term survivors receiving ipilimumab therapy appear to show a good quality-of-life (higher than baseline), long term survivors receiving GP100 see a reduction in their quality of life over the long-term – a time scale compatible with PD.

The clinical significance of these changes in scores is determined by comparing QLQ-C30 scores with an independent measure of HRQL, the Subjective Significance Questionnaire. No clinically meaningful changes were classified as <5 points.

For patients indicating a “little” change (for either improvement or worsening), the mean change in scores was 5 to 10 points; for a “moderate” change the mean change in scores was 10 to 20 points; and for a “very much” change, the mean change in scores was greater than 20 points.. This methodology was not defined in the statistical analysis plan (SAP) but is widely accepted (Osoba 1998).

Most changes from baseline in HRQL domains were “no change” to “moderate” across the three treatment groups. The trend in global health status was towards a return to baseline. Across the three treatment groups, none of the changes were in the “very much” category.

The only statistically significant differences seen in the changes from baseline between the three treatment arms was in the mean baseline to 12 week constipation scores for the ipilimumab + GP100 versus GP100 monotherapy group (5.2 vs. 11.8, p=0.043) and the ipilimumab monotherapy versus the GP100 monotherapy group (1.9 versus 11.8, p=0.010). No other statistically significant differences were seen between the three treatment groups.

This is an important result as it demonstrates that concerns regarding ipilimumab toxicity impacting on patients' quality-of-life are not borne out by the patient responses within the trial.

Analysis of SF-36 Scores

As with the EORTC QLQ C-30 questionnaire, the SF-36v2 questionnaire was completed by the majority of patients at baseline and Week 12 and by some patients at Week 24 and upon re-induction.

Five hundred and ninety-nine patients completed SF-36 questionnaires (1,157 observations). Some patients completed more than one questionnaire either pre or post-progression.

Table 21 shows the completion rates for the SF-36 questionnaire by time period. Once again, as with the EORTC QLQ C-30 questionnaire, the majority of questionnaires were completed at baseline or in Week 12.

Table 21: Completion Rates for SF-36 Questionnaire

	Ipi + GP100	**Ipi Only**	**GP100**
Total Number of Patients	381	131	131
Course 1 Day 1	362	123	126
Course 1 Week 12	235	84	82
Course 1 Week 24	50	18	8
Course 2 Day 1	21	5	1
Course 2 Week 12	19	2	1
Course 2 Week 24	8	2	
Course 3 Day 1	3	2	
Course 3 Week 12	2	2	
Course 4 Day 1		1	

Method for Aggregation of Data

Utility data were aggregated for use in the economic model using the following methods:

- Utilities were calculated for each individual observation.
- The average utility for each patient pre- and post-progression was calculated (where data were available) irrespective of the time period in which data was collected.

- The average utility within each health state was calculate as the average of the average patient utilities in each health state

This approach uses all of the data collected, and minimises the potential bias of patients with more observations being given greater weight.

Mapping of EORTC Scores to EORTC-8D

Following on from analysis of the EORTC QLQ-C30 scores the trial observations were mapped to the EORTC-8D (which is similar in nature to the EQ-5D with 3 additional cancer specific domains).

EORTC QLQ-C30 values have been mapped from the 971 observations which were produced using the aggregation method described above using the mapping algorithm defined in Rowen et al. (Rowen, 2011). The Rowen et al mapping study used a clinical trial dataset of 655 patients with multiple myeloma who completed the EORTC-QLQ-C30 questionnaire at each of 1-9 cycles of treatment. The mapping algorithm uses a validation dataset using a mid-cycle treatment point with 471 responses.

Using this data, a health state classification system was valued by 350 members of the UK general population using time trade-off method (TTO) implementing the protocol used to derive the UK EQ-5D preference weights. When valuation was carried out respondents were not told which cancer the valuation related to in order to make the mapping applicable to cancer in general rather than just multiple myeloma.

The mapping uses all EORTC dimensions except shortness of breath and cognitive functioning. The authors of the paper suggest that the algorithm should be applicable to cancers (with the proviso that it may not be as applicable for cancers that are significantly affected by the two dimensions which are not included). As metastatic melanoma is unlikely to have a significant impact on either of these dimensions, an assumption which is supported by the analysis of the results for these dimensions which show little change over time (shown in the above figures as dyspnea and cognitive), the algorithm is therefore likely to be applicable.

The authors of the paper are currently undertaking research into the impact of the use of alternative datasets from other cancers on the mapping algorithm and have so far found little difference in the algorithms produced.

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

1. A low mean absolute error (0.046)

2. No inconsistencies within the model

3. The lowest number of large errors (>5 or 10% out)

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

The results are split by progression status and treatment arms, as shown in **Table 22**. These have not changed from the original NICE submission.

Table 22: Utility Values Mapped from EORTC QLQ-C30 Trial Data

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

The average utility for patients who have not progressed is similar across all treatments, and consistent with the UK and Australian health state utilities for stable disease found by Beusterien et al (2010). The utilities for progressive disease are also similar across treatments. The difference between the EORTC-8D utility scores in the non- progressed (stable disease) and progressed disease states is very small (0.80 versus 0.76, averaging 0.04 lower in progressive state than that in stable disease).

According to clinical experts, it is clinically plausible to expect such results, i.e. small utility decrement when patients are defined as having progressive disease when treated with immunotherapy such as ipilimumab (as discussed in the clinical section). Indeed, these results may be due to the unique kinetics of response associated with treatment with ipilimumab. Saenger et al. (2008) state that patients treated with ipilimumab have a significantly different kinetics of response from those of chemotherapy and other immunotherapy with responses observed weeks to months after therapy initiation which may be preceded by apparent early disease progression, or may occur simultaneously with different progressing lesions within the same patient (a 'mixed' response).

This response kinetics becomes apparent when looking at long term survival for patients taking the drug. Although follow-up tumour assessments after progression were not mandated by the protocol, 14 subjects had such additional tumour assessments performed. Of these 14 subjects, 3 demonstrated stable disease (relative to baseline) after Week 24, all in the ipilimumab plus GP100 group. In the absence of uniform follow-up, assessment of response after progressive disease is incomplete and may be underestimated. Long-term survivors include patients with progressive disease according to modified World Health Organization (mWHO) criteria. The average time from progression to the last date of follow-up for long term survivors defined as ‘patients still alive at last follow-up who have lived at least 3 years’, was 783 days (approximately 26 months).

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

Additional analyses are presented below to clarify the relationship between progression and utility within the data.

Figure 14 shows the relationship between time since progression and the utility of patients. It can be seen that there is little correlation (0.1949). It appears to some extent that patients with a greater time since progression are showing a higher quality of life (as patients who live longer following progression are likely to be the healthier patients this is not surprising).

Figure 14: Relationship between Time Since Progression and Utility Produced Using Mapping from EORTC QLQ-C30

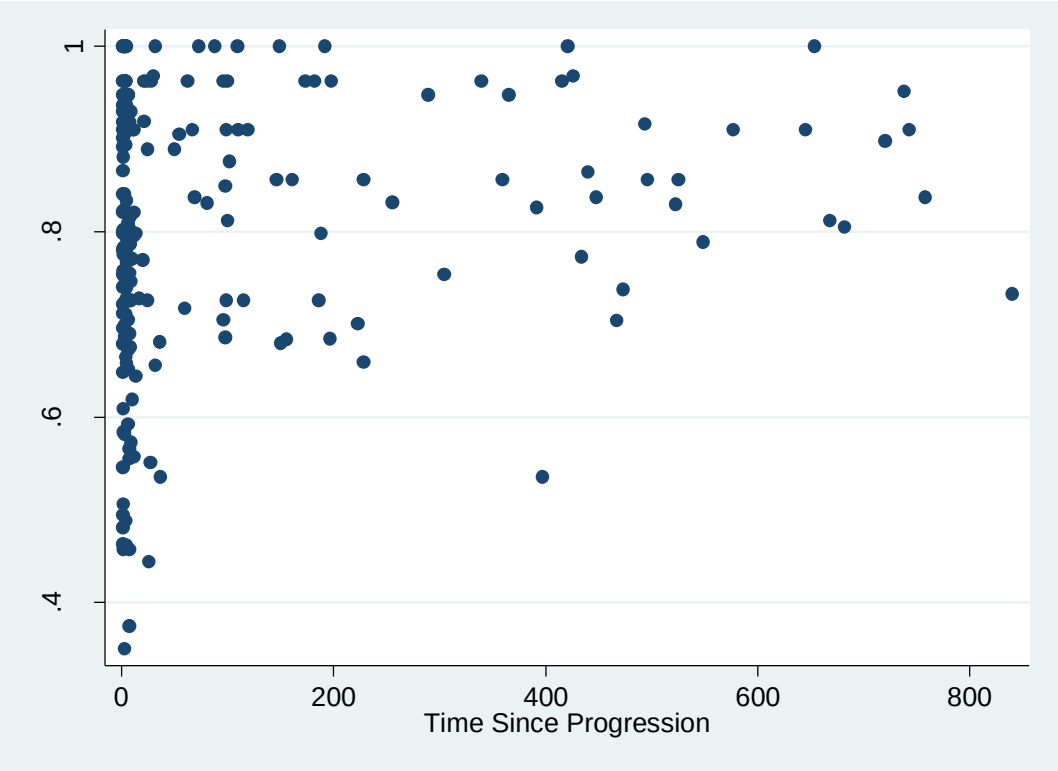


Figure 15 shows the utilities derived from the mapping by time since study start for each of the trial arms. There is no correlation for any of the trial arms between time since the study start and the utility value (as for time since progression and also for time to progression as explained in the original submission).

This is likely due to 2 factors:

- Progression as defined within the study not being a true marker for actual disease progression with clinical symptoms resulting in premature death (the majority of the long-term survivors in the study were classified as having progressive disease before responding)

- A short duration of real symptoms of true progression which affect a patients quality of life before death making these difficult to detect using quality of life assessment measures

The first factor relates solely to patients treated with ipilimumab, whereas the second relates to both trial arms and is likely to be the cause of a lack of detection of significant decreases in quality of life association with progression for patients with GP100.

As the same utilities are used for progressive and non-progressive disease for ipilimumab and BSC in the submission this may in fact bias against ipilimumab for the following reasons:

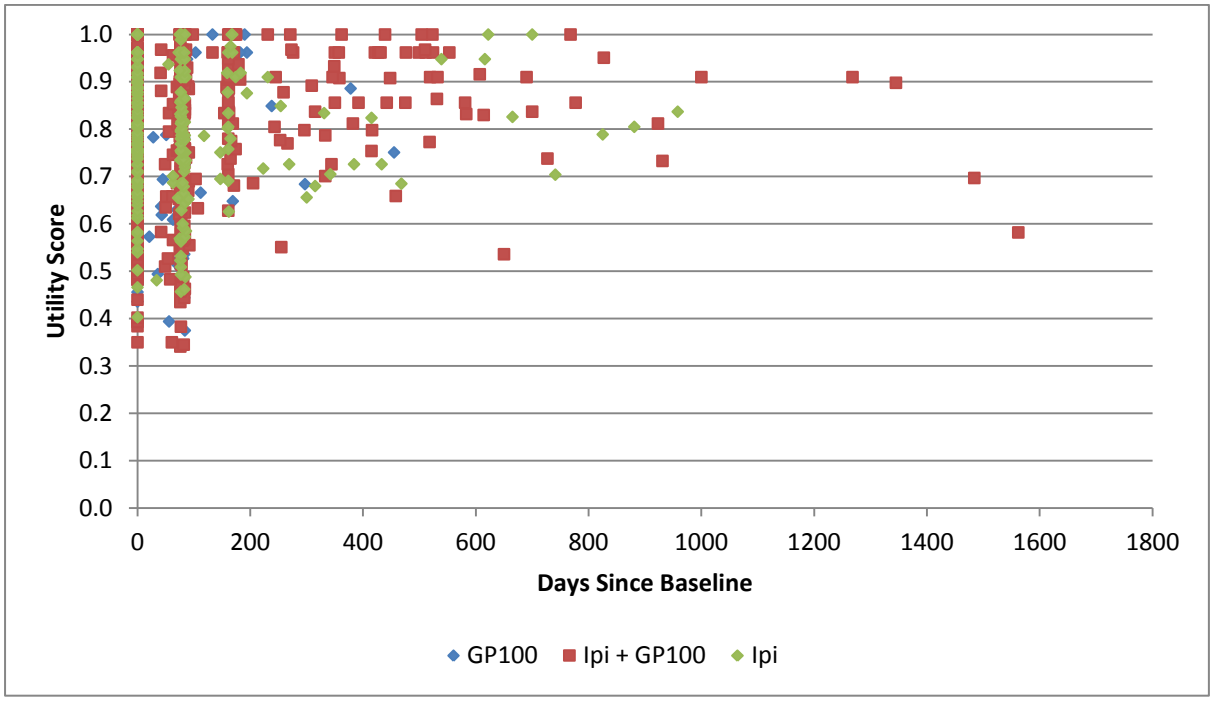
- Patients dying from metastatic melanoma may experience a loss of utility at the later stages of progression, this may not be accounted for in current modelling as the duration of this period is unknown and likely to be short in nature

- More patients die from metastatic melanoma on BSC than on ipilimumab therefore this decrease would be applied to more patients on the BSC arm and would also be applied to these patient sooner (as patients in the BSC arm die more swiftly from metastatic melanoma than within the ipilimumab arm)

This means that any decrease in utility associated with the final stages of progression would apply more to the BSC arm and would also be less heavily discounted on this arm of the trial.

As evidence is not available for utility decreases in the final stages of progression from the trial and what duration these might apply for, and also the methodology for how to account for apparent progression on the ipilimumab arm is unclear this potential benefit for ipilimumab is not included within the model at present.

Figure 15: Utility by Time Since Start of the Study



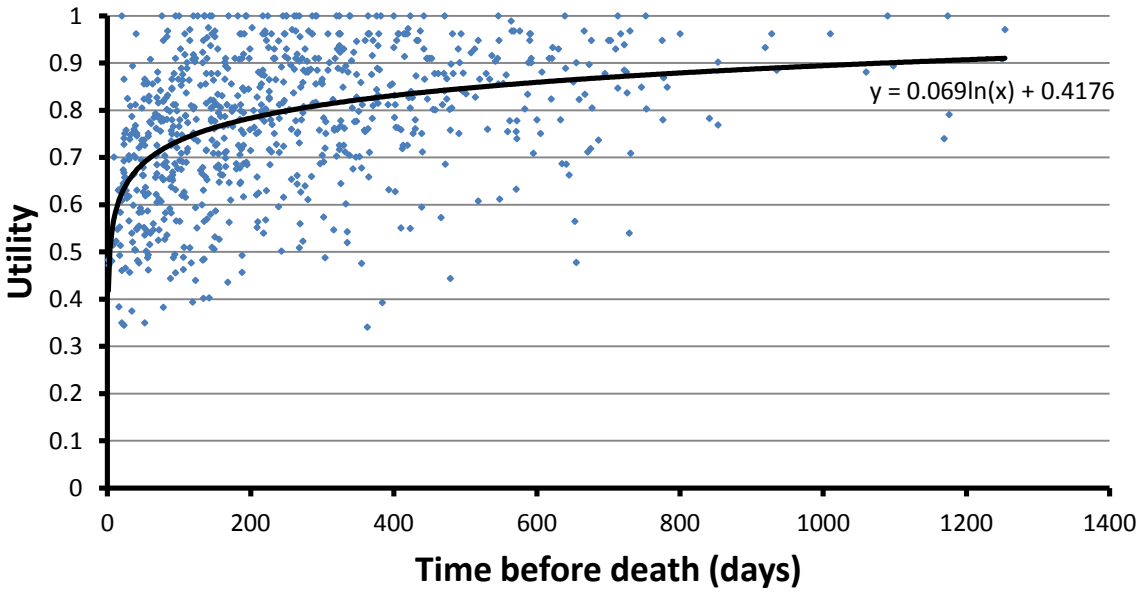
Section 5: Utility of progressive disease patients

Summary of key points

- Patients not close to death (>400 days) experience utility levels comparable with the general population of that age (0.85 vs 0.84)
- Patients experience sharply reduced utility (0.64) in the 50 days immediately prior to death
- Although not built in to the model, as the mean utility is taken from progressive patients, the model exhibits a bias against ipilimumab treated patients, who are further from death than suggested – incorporating this data would lead to a reduction in the ICER

When analysing the data presented in Section 3, along with the endpoint of death, the relationship seen **Figure 16** emerges. Patients exhibit normal utilities until approximately 2 months before death, at which point there is a sharp fall.

Figure 16: Utility & time before time measurement was taken



Full results are presented in **Table 23**. Based on Kind et al., the mean utility for a member of the general population (age 56) is approximately 0.84. This compares to the 0.85 seen in patients who do not die during the study period, and the 0.85 seen in measurements taken over 400 days before death.

That the values are similar indicates that patients do not experience significant symptoms throughout the course of the disease.

Of patients who died during the study period, utilities were lower, at 0.78, however this headline figure masks important differences; from a level comparable with background population, the utility of patients drops, eventually falling to a level of 0.64 in the 50 days before death.

Although not included in the economic modelling, these results would improve the cost-effectiveness of ipilimumab, as patients surviving would generally be experiencing higher utility than the crude mean (including patients close to death) would suggest.

Table 23: Utility values by time to death

	Average Utility	**n**
Not Dead During Study Period	0.855319	389
Dead During Study Period	0.776128	776
Less than 50 days before death	0.637397	78
50 to 100 days before death	0.70672	118
100 to 200 days	0.765649	185
200 to 400 days	0.815538	223
more than 400 days	0.846831	172

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APPENDIX 1: [redacted]

[redacted]