STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ipilimumab for previously treated unresectable malignant melanoma

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1 INTRODUCTION

Following the 3rd appraisal meeting for this Single Technology Appraisal (STA) the manufacturer of Ipilimumab made a request to submit additional survival data for patients who had received ipilimumab. The manufacturer's submission (MS) is directed at concerns expressed in both the Appraisal Consultation Document (ACD) that had been released for consultation and the Final Appraisal Document (FAD) that was due to be released by NICE. These concerns related to the uncertainty attached to estimates of the long-term survival benefits which may be expected from use of ipilimumab in patients who have previously been treated for malignant melanoma.

In the submission, two alternative data sets are described, based on combining selected data from several Phase II clinical studies with data from the primary randomised clinical trial.[1] The manufacturer's objective was to increase the volume of data (both number of patients and duration of follow-up) and hence to reduce uncertainty in estimates of survival benefit attributable to ipilimumab. These new data sets are then applied to the previously submitted model, together with a reduced price for ipilimumab detailed in a second PAS (approved July 2012), to generate a new set of cost-effectiveness results and sensitivity analyses.

2 ADDITIONAL DATA

The submission details a total of five phase II studies involving ipilimumab for which some results are currently available. In most cases, the patient population is too dissimilar to the MDX010-020 trial[1] to allow direct comparison. In addition, not all studies involve the dosing regimen of ipilimumab (3mg/kg) for which marketing authorisation has been granted.

The manufacturer has identified 72 patients from one arm of a dose-ranging study (CA184-022), which were considered sufficiently similar to be suitable for pooling of survival data with that of the ipilimumab treated patients in the MDX010-020 trial.[1] No pooling of patients has been proposed for comparator treatments. In addition, a broader pooling of all data from patients treated with ipilimumab regardless of dosing level and differences in patient characteristics is also suggested in the submission.

The ERG does not consider this pooling of isolated treatment arms across trials to be appropriate for the following reasons:

- it breaks randomisation and therefore invalidates any comparison between the intervention treatment and the comparator

- it undermines the stratification of the MDX010-020 trial.[1] In particular, there are only 50% of patients in the CA184-022 trial with stage M1c disease compared with 71% in the

MDX010-020 trial[1] ($p < 0.001$ for grade equivalence), which is the strongest prognostic indicator

- patients in the CA184-022 trial received ipilimumab maintenance therapy subsequent to ipilimumab induction therapy, but this was not available in the MDX010-020 trial[1]

- the additional 72 cases do not extend the range of follow-up covered in the results published by MDX010-020[1] and therefore cannot contribute to resolving uncertainty in terms of long-term outcomes

- there are no equivalent comparator treatment arms available to balance the pooling of ipilimumab arms

In addition, the broader pooling of data from all patients who received ipilimumab, regardless of dosing regimen or patient baseline characteristics, can only result in uninterpretable results of no relevance to the current decision problem.

It is therefore the ERG's view that in the absence of any additional follow-up from the MDX010-020 trial,[1] no extension of the currently available MDX010-020 data set is warranted. See Table 1 for study details and ERG reasons for considering these data inappropriate for pooling with the MDX010-020[1] trial data.

Table 1 Summary of Ipilimumab Data

Study Name	Randomised	#of Patients	Patient status	Ipilimumab Dose	ERG Reasons for exclusion
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] +maintenance	Different drug dose in two trial arms +Maintenance therapy Crossover allowed
	[redacted]	[redacted]	[redacted]	[redacted]	Non-randomised Different drug dose +Maintenance therapy
	[redacted]	[redacted]	[redacted]	[redacted] +maintenance	Mixed population (80% pre-treated) Different drug dose + Maintenance therapy

Study Name	Randomised	#of Patients	Patient status	Ipilimumab Dose	ERG Reasons for exclusion
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]+maintenance	Different population Different drug dose +Maintenance therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Non randomised Different drug dose
	[redacted]	[redacted]	[redacted]	[redacted]	Non randomised
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Non randomised Different drug dose
	[redacted]	[redacted]	[redacted]	[redacted]	Non randomised

DTIC = dacarbazine;

3 PROJECTIVE MODELLING OF OVERALL SURVIVAL

3.1 *Manufacturer's approach*

The manufacturer's latest decision model maintains the three phase approach employed in the January 2012 submission. This uses Kaplan-Meier analysis results from the MDX010-020[1] clinical trial (with pooled additions from other trials) unmodified for the first 18 months, followed by a parametric model (Gompertz) fitted to the trial data from 18 months to 5 years, and thereafter hazards derived from analysis of the AJCC patient register, modified where necessary by background mortality rates.

In their report the ERG commented on the manufacturer's approach to modelling survival in section 5.5.2 (page 57):

> "Taken together these adjustments indicate that the modellers failed to achieve a coherent and credible interpretation of the MDX010-20 trial[1] data on which to predict future outcomes, and to allow reliable estimates of patient benefit to be made. In particular, reversion to general mortality rates implies that any patient surviving beyond 5 years of second-line systemic treatment is effectively completely cured of their metastatic disease. No evidence has been submitted to support such a strong claim. It is also noteworthy that the Gompertz function employed as the basis for projecting OS in the ipilimumab arms is frequently associated with especially 'long tails' so might be expected to overstate future benefits for the intervention therapy."

3.2 *ERG consideration of evidence*

Following unsatisfactory attempts to identify an alternative rationale for projective modelling of the available data, the ERG indicated the extent of uncertainty associated with this key aspect of the decision problem in Section 6.1.2 of our original report:

> "In the absence of an obvious parametric method for projecting OS, the ERG undertook an exploration of survival data from the MDX010-20 trial[1] and its representation in the submitted model, with a view to deriving at least a simple method of projecting outcomes to illustrate the direction and approximate magnitude of future gains, even if particular estimates might only be considered approximate."

This suggested that the manufacturer's model may lead to substantially overstated survival gains, so that the true ICER could be much greater than claimed.

Subsequent to the original ERG report being completed, the ERG has carried out further analyses aimed at clarifying the possible mechanisms underlying the singular pattern of survival observed in all clinical trials and registry databases for patients with advanced malignant melanoma, and concluded that the earlier exploratory analysis could be improved by use of published results from registry data.

The starting point for this investigation was the comment made in the ERG report (section 5.5.2, page 56):

> "An initial high attrition rate is common in the later stages of advanced and metastatic disease, but the extended survival tail is problematic without suggesting that a minority of patients are effectively cured of their condition by a treatment normally expected to yield only modest benefits. The only other possible explanation is that this population is severely heterogeneous exhibiting different prospects of survival for distinct subgroups."

Although the attempt to employ known patient characteristics or outcome variables to explain this heterogeneity were unsuccessful, this did not negate the likelihood that other factors may be present leading to the observed effect. To test this possibility a simple hypothesis was proposed involving the minimum of assumptions:

- that advanced malignant melanoma patients are drawn from two distinct subgroups of unknown aetiology
- that each subgroup is characterised by a separate hazard rate which does not vary over time

This hypothesis leads to a mixed exponential distribution for overall survival, involving three parameters: the proportion of the population comprising one of the subgroups, and separate hazard rates for each of the subgroups.

This model was then tested by applying it to published results from two large patient registries (SEER[2] and AJCC[3,4]). The results were promising resulting in very strong correspondence to the observed data in both data sets and for each disease stage.

The results for Stage IV melanoma are shown in Figure 1. It is evident that the mixed exponential model performed well in both populations, and that data from the SEER[2] and AJCC[3,4] registries are mutually confirmatory. The AJCC results were selected for further analysis, since these allow adjustment of the data to match the M class casemix of patients in the MDX010-020[1] clinical trial.

Finally, the MDX010-020[1] Kaplan-Meier results were superimposed on the AJCC[3,4] data and fitted model (Figure 2). As expected, for patients with a history of previous failed systemic therapy, the survival trend for patients in the comparator arm indicates a poor prognosis when a mixed exponential curve was fitted to the comparator data. By contrast, patients treated with ipilimumab followed a trajectory almost identical to the AJCC[3,4] casemix-adjusted trend, suggesting that for these patients the AJCC fitted model could be used to project future survival directly.

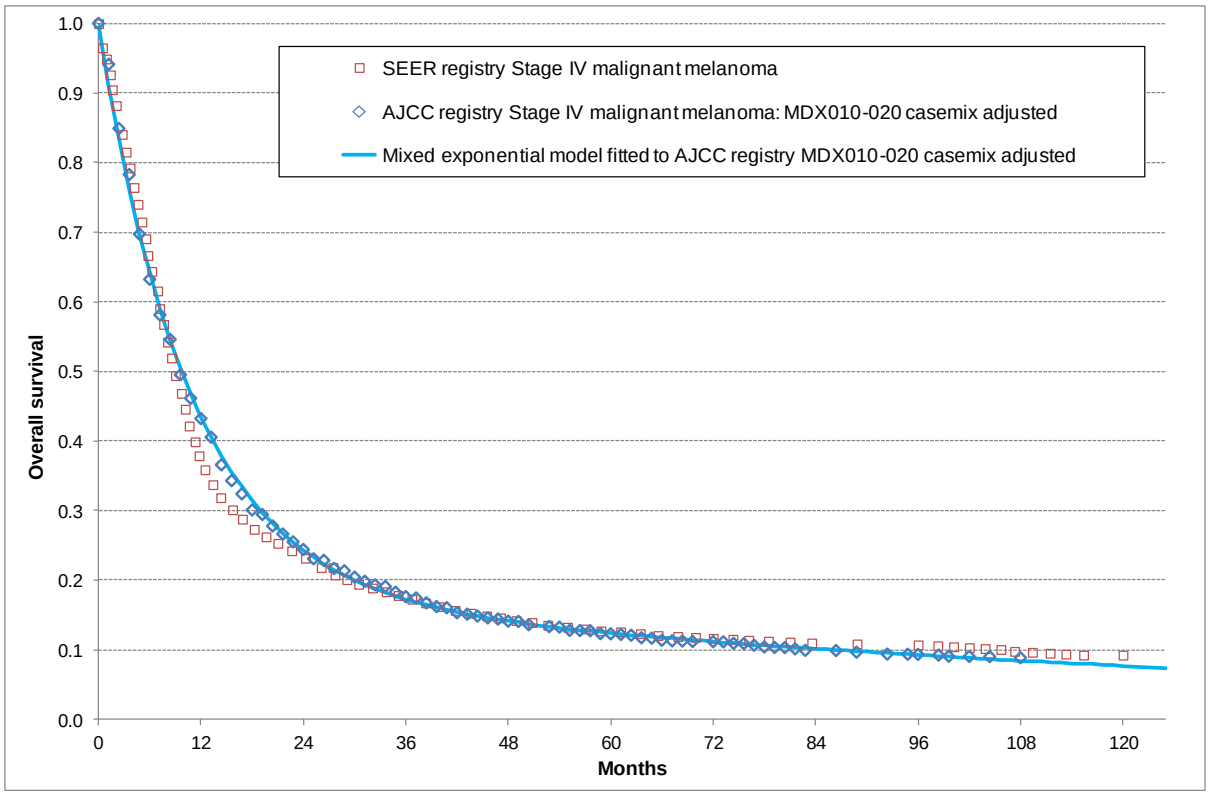

Figure 1 Survival results for Stage IV malignant melanoma from two large registries

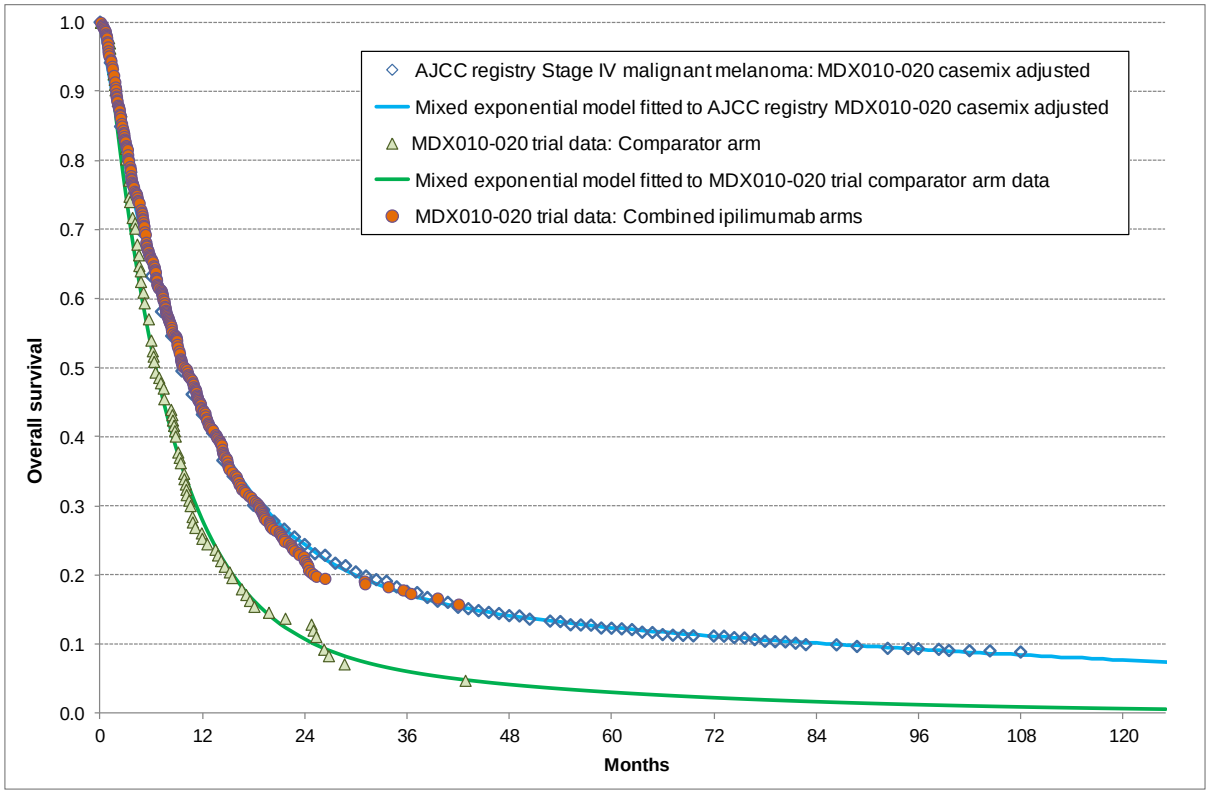

Figure 2 MDX010-020 Kaplan-Meier data compared to AJCC Stage IV fitted model

3.3 *Summary*

The inherent weakness of the manufacturer's survival modelling is that it lacks any underlying rationale to support the division of data into three time periods and the use of different methods in each period, beyond the imperative to somehow replicate the observed data. By contrast, the mixed exponential model proposed by the ERG addresses the whole dataset without any need to replicate different time periods using contrasting mechanisms. The ability of the new approach to accurately replicate the long-term results obtained from large patient registers provides external confirmation of its applicability to this patient population.

Two issues remain unresolved:

1) The mixed exponential model strongly implies that patients fall into two distinct groups in relation to mortality risk, but there is currently no direct evidence of how such a differentiation may occur.

Though this may be initially perplexing, it is not unusual for a consistent pattern to emerge from empirical observations leading to further research aimed at discovering additional causal mechanisms.

2) Both the SEER[2] and AJCC[3,4] databases feature patients from the time of diagnosis. However, their use in modelling (both by the manufacturer and by the ERG) begins at the time of randomisation at which point patients may have survived several years of treatment. It would be reasonable to suppose that the casemix of the original cohort will have changed significantly over time, so that direct use of SEER[2] or AJCC[3,4] trends could be misleading.

However, two factors may play a part in mitigating this problem.

Firstly, recruitment to clinical trials involves explicit inclusion/exclusion criteria based on a patient's physical condition and immediate survival prospects. In the MDX010-020[1] trial patients were required to have a life expectancy of at least 4 months, ECOG performance status of 0 or 1, and be free of active CNS metastases and of other treated cancers or disease–free for at least 5 years. This suggests that patients should have a better prognosis at randomisation than an unselected population. One the other hand, all included patients were required to have undergone at least one unsuccessful or relapsed prior systemic treatment. In addition the casemix of MDX010-020[1] patients shows an over-representation of M1c patients (71%) compared to those in the AJCC register at diagnosis of Stage IV disease (58%). These two factors should imply a worse prognosis. There is no way of judging how combining these opposing influences may lead to better or worse survival outcomes, compared with the published AJCC[3,4] results.

Secondly, the exponential distributions used in the ERG model to represent the two subgroups have the special characteristic of being inherently self-similar (i.e. if surviving patients are selected at any

subsequent time, and the conditional survival distribution at that time is calculated it will follow exactly the same trajectory as the original distribution). This means that if the balance of patients assigned to the two mixed model subgroups is similar in the originally diagnosed cohort and a trial sample selected from patients surviving at a later time, then the resultant trial survival curves may also prove to be similar.

4 ECONOMIC RESULTS

The ERG has confirmed that errors previously reported in the manufacturer's decision model have been corrected in the latest version.

The manufacturer's revised base case analysis is based on using trial data for patients receiving the 3mg/kg dose of ipilimumab in the MDX010-020 trial[1] pooled with 72 patients from the CA184-022 dose-ranging trial receiving the same dose. As in the previous submission, Kaplan-Meier data was used for the first 18 months, followed by a Gompertz parametric fitted model from 18 months to 5 years. Beyond 5 years hazards from the earlier (2001) Balch AJCC analysis were used.[3] On this basis the model generated a mean of 2.4 additional life years per patient, and 1.2 additional discounted QALYs per patient. Using the latest PAS discounted price the base case ICER is £46,739 (Table 2).

For comparison, the survival parameters from the ERG's initial exploratory analysis have been substituted in the manufacturer's latest model to yield economic results following the model revisions and updated ipilimumab acquisition cost. The model then estimates 1.3 additional life years per patient and 0.8 additional discounted QALYs per patient, with an ICER of £66,250 (Table 2).

The ERG has also substituted the mixed exponential model estimates of overall survival (shown above in Figure 2) in the submitted model to generate the ERG's preferred results. In this case the original MDX010-020[1] trial results (i.e. without pooling with CA184-022 ipilimumab data), and the AJCC casemix adjusted projection model (based on the Balch 2009[4] analysis) are used to represent survival in the ipilimumab arm. These changes reduce the expected gain in life years to 1.74 per patient, and the additional discounted QALYs per patient falls to 0.93. The ERG amended base case analysis results in an ICER of £58,590 per QALY gained (Table 2).

A request from NICE to the ERG was received on 6th September 2012 for economic results "using the manufacturer's 3 part curve fit approach and the new PAS but only the data from the main trial (no pooling). The ERG has been able to amend the revised model to use the original Kaplan-Meier data for ipilimumab in the first 18 months, but was not able to recalibrate the Gompertz projective model used in the second phase of the model as a complete set of pooled OS data was not available. The limited adjusted to the model resulted in a very small alteration to the model results (manufacturer's

ICER reduced from £46,739 to £46,652/QALY) suggesting that the pooling of data is not likely to be important in determining cost-effectiveness.

Table 2 Manufacturer's revised base case cost-effectiveness analysis compared to ERG base case using original exploratory analysis and mixed exponential OS analysis.

	Manufacturer's revised base case	ERG exploratory analysis	ERG preferred analysis
OS* - Ipilimumab	3.58	2.28	2.76
OS* - BSC	1.18	0.93	1.02
OS* - increment	+2.40	+1.34	+1.74
QALYs - Ipilimumab	2.02	1.51	1.68
QALYs - BSC	0.82	0.70	0.75
QALYs - increment	+1.20	+0.80	+0.93
Cost - Ipilimumab	£67,822	£64,435	£65,661
Cost - BSC	£11,747	£11,028	£11,289
Cost - increment	+£56,075	+£53,408	+£54,372
ICER (£/QALY)	**£46,739**	**£66,520**	**£58,590**

OS - overall survival, * - undiscounted,
ICER - incremental cost-effectiveness ratio (cost per QALY)

5 CONCLUDING REMARKS

In their supplemental submission the manufacturer has attempted to strengthen the case for substantial survival gains by introducing additional data. These data are derived from a number of other trials which included a variety of different patient populations and drug dosages that were inconsistent with the treatment provided within the original MDX010-020 trial,[1] including maintenance treatment. The rationale provided for the submission of these data is to address the concerns raised by NICE related to the degree of uncertainty in estimated long term survival benefits of ipilimumab. Given the noted differences noted in dosage and use of maintenance treatment the ERG do not believe that these data are applicable to the current appraisal

Therefore, the ERG rejects the pooling of data from trials with differing patient characteristics and who received a variety of treatment doses as well as maintenance treatments. The ERG have concentrated their analysis on the data from the primary study and included the new PAS as approved by the Department of Health.

It is apparent that there is patient benefit from the use of ipilimumab in terms of PFS, but the extent to which this translates into OS benefit is still not known. The evidence is difficult to interpret, for as pointed out in the previous ACD, there appears to be a sub-population of patients whom ipilimumab may benefit, corresponding to long-term survivors indicated by both the SEER[2] and AJCC[3,4]

published results. However at present no patient characteristics or biomarkers have been identified that can prospectively identify who these individuals might be and what level of benefit they could expect to receive from treatment with ipilimumab.

The mixed exponential survival model proposed by the ERG is technically simple (parsimonious) and has proved to be successful in accurately reproducing long-term survival data from two large patient registries and as well as results from several published clinical trials in patients suffering malignant melanoma (external validity). The ERG therefore considers this approach to have much to commend it compared to the available alternatives. Its use results in a lower estimated survival gain for ipilimumab than presented by the manufacturer, and therefore a considerably larger ICER (£58,590 per QALY gained) despite a further PAS reduction in the acquisition cost of ipilimumab.

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