Ipilimumab for previously treated unresectable malignant melanoma: ERG comments on the manufacturer’s response to NICE ACD

1 BACKGROUND

Following the meeting of the NICE Appraisal Committee (AC) on September 20th 2011, NICE issued an Appraisal Consultation Document (ACD) indicating that the Committee was minded not to recommend ipilimumab as a treatment for patients with previously treated unresectable malignant melanoma. Consultees and the manufacturer (Bristol Myers Squibb Ltd [BMS]) were invited to respond to the ACD by November 4th 2011 in time for any comments to be considered at the second AC meeting on the 16th November 2011. The manufacturer of ipilimumab has submitted a detailed document setting out several grounds on which the Committee is asked to reconsider their interim decision, including additional economic results. The ERG has been asked to provide commentary on this new evidence for the Committee’s consideration. A revised model was received by the ERG on November 7th 2011. Given the time limitations, this revised model has not been examined and this document is based on the written submission of the manufacturer.

2 INNOVATION

The manufacturer draws the Committee’s attention to the definition of innovation described in the NICE response\(^2\) to the recently published Kennedy Report:\(^3\)

“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.”

A case is presented by BMS for quantifying the degree of innovation in the form of a simple numeric ratio of incremental survival gain to estimated life expectancy. By reviewing past ‘End of Life’ Appraisal Committee decisions, BMS seeks to validate this ratio measure as being compatible with established practice, and then suggests that it should be used to assess innovation in the case of ipilimumab for malignant melanoma.
The ERG considers this line of argument to be unconvincing.

Firstly, the suggested ‘Innovation Index’ ratio is merely a reworking of the estimates that have already considered by the AC in two separate ways:

- by means of the estimated incremental cost-effectiveness ratio (ICER), when survival gain is modified by a measure of the value attached to health-related quality of life; and

- through the application of the ‘End of Life’ criteria which require a minimum gain in survival as well as a maximum expected life expectancy without the new treatment.

What the additional analysis presented by BMS demonstrates is that the decisions taken to date by NICE Appraisal Committees in these circumstances are mutually consistent. However there is no indication that the ‘Innovation Index’ proposed by BMS would yield any additional explanatory power or discrimination for reaching these decisions.

2.1 **What makes a health care technology innovative?**

There are indeed important questions which need to be addressed relating to the concept of innovation as it may affect NICE decision-making, but generally they are not amenable to simple quantification since they concern essentially qualitative criteria. As outlined in the Kennedy report, these are:

1. Can the treatment “be regarded as a ‘step-change’ in the management of the condition”?
2. Does the treatment offer “a significant and substantial impact on health-related benefits”?
3. Does the treatment “improve the way that a current need is met”?

The first criterion depends on seeking to delineate what might constitute a ‘step-change’ in how a condition is managed. This is especially difficult and in practice may only be achieved by the accumulation of case law over time.
It can be argued that the second criterion is largely addressed by the existing framework of decision-making. This uses common ‘willingness to pay’ thresholds applied to estimated ICERs which combine incremental benefits from extended survival and improved health-related patient utility. It therefore provides a minimum entry standard for any innovatory treatment.

The third criterion is less specific but may be viewed as recognising additional patient preference for treatment options which provide benefits in the manner or context of care delivery which are not currently available, and not directly measured through the accepted quality weighting methods. Thus, for example, the first self-administered oral therapy for a condition may have great merit for patients and their families who would normally have to cope with repeated hospitalisation at distant specialist centres.

In the current context we suggest some additional questions which may help to identify relevant aspects of the problem, the final two questions raised being taken directly from the Kennedy report: ³

a) Does the treatment change the therapeutic objective for an identifiable group of patients (e.g. does the new treatment have curative intent, rather than seeking only to manage the condition and/or palliate symptoms)?

b) Is the new treatment the ‘first of a kind’ in terms of its mechanism of action, which has been shown to offer important benefits through addressing current symptoms or through avoiding future morbidity, where these cannot be addressed/avoided by any current treatment?

c) Has the development of the new treatment led to insights into the nature of the condition and/or its natural history, which effectively render the current treatments redundant as essentially inferior or ineffective?

d) Has the appropriate research on stratification identified the population in which the product is effective?

e) Has appropriate effectiveness been demonstrated? e.g. Will the product benefit 70% of the intended group?
2.2 The case for ipilimumab

In relation to the appraisal of ipilimumab for the treatment of malignant melanoma, the ERG’s observations are as follows:

- Statistically significant benefits have been demonstrated in terms of extended survival and quality-adjusted life years for use of ipilimumab, and these are reflected in the range of ICERs estimated by the manufacturer and the ERG. The magnitude of this health gain is large enough to warrant consideration under the ‘End of Life’ criteria, but is nonetheless subject to a large degree of uncertainty.

- It does not appear that ipilimumab represents a substantial change in the way current need is met: patients still require a series of invasive administrations in a specialist hospital environment, and the treatment is subject to some severe and unpleasant side-effects which are comparable in their impact on patients to those exhibited by the existing treatments. Although the long-term treatment pattern is not wholly clear, it appears that some responding patients do suffer relapse and require additional courses of treatment, in a similar manner to those treated conventionally.

- Previous trials and observational studies have demonstrated that although the bulk of malignant melanoma patients have a very poor prognosis, a small number (5-10%) appear to achieve very long survival times on any treatment. The origin of this heterogeneity is unknown, and therefore there is no basis on which to target treatment and it is currently impossible to identify reliably and prospectively the small number of patients who would benefit from ipilimumab. The principal benefit of ipilimumab is that of increasing the response rate to therapy so that more patients fall into this fortunate group. However, the great majority of patients gain no lasting advantage from treatment but suffer the disadvantages of undergoing a very challenging treatment protocol.

- Ipilimumab cannot be considered a ‘first of kind’ treatment since immunotherapy agents have been developed and are used in various countries, most notably interleukin-2 (IL-2). At present the reasons for the apparently better performance of ipilimumab compared to existing treatments are obscure, and do not indicate an obvious pathway to the development of a new class of superior treatment options.

In summary, the ERG has not identified any convincing basis for considering that ipilimumab should be given special innovatory status in terms of NICE decision-making criteria.
3 LONG-TERM SURVIVAL PROJECTION

3.1 Background

The manufacturer acknowledges that the method used in their submitted decision model to project the gains in overall survival observed in the key clinical trial throughout patients’ remaining lifetime was incompatible with current clinical understanding and therefore over-optimistic. However, BMS contends that the simple exploratory projection presented by the ERG (which resulted in an estimated ICER of £96,717 per QALY gained) is unduly pessimistic, and offers two alternative methods of projection based on published analysis of American registry data. These result in new estimates of survival gain between the originally submitted base case analysis and the ERG estimate (Table 1).

Table 1 Modelled survival gain per patient by different methods of projection

<table>
<thead>
<tr>
<th>Projection method</th>
<th>Discounted life-years gained</th>
<th>Discounted QALYs gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS original submission</td>
<td>1.86</td>
<td>1.37</td>
</tr>
<tr>
<td>ERG exploratory analysis</td>
<td>1.07</td>
<td>0.80</td>
</tr>
<tr>
<td>BMS revision (registry data only)</td>
<td>1.54</td>
<td>1.13</td>
</tr>
<tr>
<td>BMS revision (registry data and continuing benefit assumption)</td>
<td>1.70 (new BMS base case)</td>
<td>1.24</td>
</tr>
</tbody>
</table>

3.2 Use of registry data

The registry findings used by BMS are drawn from a paper published in 2001 to support changes to the melanoma staging system included in the sixth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (2002). The analysis used data from 17,600 patients from 13 centres to derive melanoma-specific survival curves for defined sub-populations. The manufacturer used the survival curve for Stage IV patients as the basis for estimating extended survival of patients from the key ipilimumab trial. This analysis was based on 1158 patients whose first diagnosis was Stage IV disease. The 2001 paper also reported an important and statistically significant subgroup classification within Stage IV patients distinguishing between patients with only skin metastases (M1a), those with metastatic spread to the lungs (M1b), and those with metastases in other visceral sites (M1c). However no long-term survival curves were shown for these subgroups, which had small patient numbers in two of the three groups.
The manufacturer has correctly recognised that the melanoma-specific survival results exclude all other causes of death and have therefore also included background mortality in their revised model. However, there are two important issues in the use made of the AJCC registry results by BMS:

1) Use of the 2001 Stage IV survival curve to populate the revised model ignores the important differences in survival identified between the three subgroups. An updated analysis published in 2009\textsuperscript{6} was based on 7972 Stage IV patients, with sufficient numbers in each subgroup to allow survival curves up to 10 years to be estimated. In addition, these new results allow accurate case mix adjustment to be carried out to reflect the balance between subgroups in the key ipilimumab trial.

2) There appears to be a serious mismatch between the patients entered in the ipilimumab randomised controlled trial (RCT) and those in the AJCC database. All patients in the ipilimumab RCT had received previous lines of treatment during an average of 5 years since their initial diagnosis. The inclusion criteria for the RCT require only that patients are classed as suffering “a diagnosis of unresectable Stage III or Stage IV melanoma who had relapsed, failed, or were not able to tolerate at least one or more prior treatment regimens”. This does not exclude patients initially diagnosed with less advanced disease whose treatment was unsuccessful and subsequently progressed to Stage III or IV. Projection for such patients would be more correctly obtained from the AJCC survival curves for Stages I-III. Even those patients initially diagnosed with Stage IV melanoma enter the trial having survived (on average) for 5 years, so that these patients already constitute a minority of long-surviving patients. Any projection of their future life expectancy should not follow the Stage IV curve from year 6 to year 15 (as stated by BMS), but a range of later times centring around year 11 to year 15. This presents an additional problem since the larger and more reliable 2009 database results (with subgroups) has only yielded survival curves up to 10 years from diagnosis, so could not be used consistently for projection in the BMS model beyond 10 years. It is not clear to the ERG to what extent this method of projection can be considered appropriate, accurate or reliable since it seems likely that the trial population may be substantially different in terms of their initial diagnosis, prior treatment history and time from initial diagnosis from the AJCC database cohort.
3.3 **Use of hazard ratio adjustment**

In addition to using survival information from the AJCC melanoma database, BMS seeks to adjust their survival estimates to reflect the observation that long-term hazard trends are continuing to diverge at the longest observed survival times, suggesting that benefit continues to accrue beyond the trial period. This is a reasonable inference to draw; however, the method used to estimate a hazard ratio through a Cox proportional hazards regression analysis is questionable. Long-term survivors are defined as patients alive at 18 months. This is problematic for two reasons:

- the numbers of patients at risk in the analysis are very low for the GP100 trial arm (only 19) so that the confidence interval for the estimated hazard ratio is very wide encompassing unity;

- examination of the cumulative hazard plot indicates that long-term trends are established much earlier in the GP100 arm (about 300 days), but later in the combined ipilimumab arms (about 750 days) so that the estimated long-term hazard ratio is likely to be biased, and that the assumption of proportional hazard may be compromised.

The ERG’s exploratory analysis avoids these problems by using treatment-specific definitions of the long-term period.

3.4 **Summary**

The issues identified concerning the relevance and manner of use of the registry results and the derivation of a long-term hazard ratio suggest that the new base case survival projection presented by BMS is not reliable. The ERG considers that its own exploratory analysis is more robust, since it makes fewer assumptions and more directly reflects the available trial data.
4 COST OF IPILIMUMAB TREATMENT

4.1 Actual cost of treatment
The manufacturer has noted that their submitted model assumed that all patients received a full course of treatment involving four injections. Using information of the number of doses actually delivered in the key trial, BMS have calculated that on average only about 3.5 doses are delivered (taking account of discontinuations and doses missed) and therefore have reduced the modelled cost of ipilimumab treatment by 12-13%.

The ERG considers this to be a reasonable amendment which more accurately reflects experience in a clinical context.

4.2 Vial sharing
In addition, BMS present evidence that vial sharing between patients may be possible, and have included an assumption of 50% vial sharing in their revised base case calculations.

The ERG considers that although vial sharing is theoretically possible (though not recommended in the Summary of Product Characteristics), in reality it is unlikely to be generally implementable because of the low numbers of cases that are expected to require treatment. The annual number of eligible cases has been estimated at 250-300 in England and Wales. This means that the average cancer network can expected to treat less than one new case each month. With this low volume of demand the scope for organising co-ordinated treatment schedules across multiple patients must be considered extremely limited, and does not warrant any significant reduction in the expected acquisition cost of ipilimumab.

The manufacturer’s sensitivity analysis results indicate that their base case ICER increases from £62,632 to £65,303 per QALY gained if no vial sharing reduction is allowed.
5 SUMMARY

Three major topics are addressed by the manufacturer in their response to the ACD; ipilimumab as an innovatory technology, long-term survival projection methods, and the estimated cost of ipilimumab treatment.

The ERG has attempted to identify criteria which can be used to identify innovative treatments, and uses these to test their relevance to ipilimumab. It is the view of the ERG that a clear case has not been made for considering ipilimumab as offering important patient benefits which are not already reckoned within the standard methods of appraisal, and the ‘End of Life’ supplementary criteria.

The manufacturer acknowledged that the original submitted model presented an optimistic survival projection, and prepared alternative estimates based on use of published registry data results combined with a hazard ratio derived from the key ipilimumab RCT. The ERG questions the appropriateness of using the registry findings due to the clear differences between the categories of disease staging used and the prior history of treatment and extended survival already evident in the trial population. In addition the ERG considers the derivation of a hazard ratio to be subject to question and to involve substantial uncertainty due to the small number of cases in the comparator arm. The ERG considers that its own exploratory analysis is probably more robust and more closely matches the available data.

The manufacturer’s use of data on the actual number of doses given seems to be fully justified, but the ERG is not convinced that with only 250-300 new cases per year nationally, that any specialist centre could realistically count on regular savings in ipilimumab costs from organised vial sharing.

The manufacturer has provided additional information of quality of life data and estimated utility values, and also reported a range of sensitivity analyses relative to their revised base case. These suggest that other areas of uncertainty are unlikely to alter the size of the estimated ICER significantly.
References


