Ipilimumab for previously untreated advanced malignant melanoma

ERG review of manufacturer's response to NICE following ACD

10th April 2014

1. Overview

Following the first appraisal meeting of ipilimumab for previously untreated advanced melanoma (28th January 2014), the manufacturer of ipilimumab made a request to submit additional analyses and evidence to support the cost-effectiveness of ipilimumab at first-line. The manufacturer's response is based on concerns expressed in the Appraisal Consultation Document (ACD) produced by NICE. These concerns relate to the uncertainty surrounding the relative efficacy of 3mg/kg ipilimumab monotherapy compared with DTIC and vemurafenib in the first-line setting, the comparability of the patient populations at first- and second-line, the treatment sequencing of ipilimumab and vemurafenib, and the effect of DTIC when administered in combination with ipilimumab.

The ERG was requested by NICE to provide additional commentary and validity checks on the additional evidence submitted by the manufacturer in response to the ACD. Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the manufacturer's resubmission and hence does not accord with the procedures and templates applied to the original submission.

2. Comparability of 3mg/kg ipilimumab monotherapy vs. 10mg/kg ipilimumab in combination with DTIC and comparability of the populations in the first- and second-line settings

The key uncertainty for the appraisal of ipilimumab 3mg/kg alone in the first-line setting, compared with DTIC and vemurafenib, is the magnitude of the relative effectiveness estimates. The assessment of cost-effectiveness in the manufacturer's original submission was based on comparative effectiveness evidence on the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy based on the CA184-024 trial. The lack of comparative studies investigating ipilimumab as a first-line treatment in the 3mg/kg dosing regimen imposed a number of strong assumptions on the cost-effectiveness analysis. These assumptions have been outlined in detail in the original ERG report. Given the need for robust evidence on the relative efficacy of ipilimumab 3mg/kg in the first-line setting (as well as the need to establish the treatment sequence for vemurafenib and ipilimumab in BRAF V600 mutation-positive patients), the Appraisal Committee concluded that further research was required. The

additional analyses by the manufacturer attempts to address this concern without the need for further research by making use of the MDX010-20 trial, which reports efficacy data for the 3mg/kg dose of ipilimumab in a second-line setting (as used in TA268).

The manufacturer made very little use of the evidence from the MDX010-20 trial in their original submission, presumably because the trial lies outside the scope of the population with previously treated malignant melanoma. However, the ERG requested in their points for clarification a comparison of ipilimumab 3mg/kg and 10mg/kg in both the treatment-naïve subgroup population and the whole population (both previously treated and untreated). In response the manufacturer presented results from a pooled data analysis comparing overall survival (OS) profiles of ipilimumab 3mg/kg from MDX010-20 and CA184-022, and 10mg/kg from CA184-007, CA184-008, and CA184-022 (see Figure 6.8 of the ERG report). The ERG subsequently used this data, which includes the MDX010-20 trial in the second-line setting, to adjust the OS of ipilimumab 10mg/kg + DTIC from CA184-024 to provide an estimate of ipilimumab 3mg/kg in a first-line setting (see Section 6.3.1 of the ERG report). This adjustment assumes that the populations in the first- and second-line trials are the same and that the only difference considered is the variable dose of ipilimumab between trials. The Appraisal Committee considered that the ICERs from the resulting reduction in efficacy for a 3mg/kg dose were likely to be implausible.

Subsequently, in the manufacturer's response to the ACD, they quote support from the European Medicine Agency (EMA) that the populations between first-line (untreated) and second-line (previously treated) are similar:

> "*the baseline characteristics of the patients included in the pivotal studies in previously treated and previously untreated subpopulations were similar; the similar patient characteristics of the two trials [MDX010-20 and CA184-024] support the relevance of the results observed in a previously treated population to the first-line setting.*"

This highlights the central issue with this appraisal: the difficulties faced with the current evidence base in terms of appropriately quantifying the impact of deviating from the assumptions of similarity/equivalence of populations between first- and second-line and equivalence of dose (3mg/kg = 10mg/kg + DTIC). The ERG report, based on the evidence currently available, reported a series of scenarios which indicate that the cost-effectiveness results lie at different ends of the dose-population spectrum, i.e. the ICER of £42,449 (vs. DTIC) from a three-state model (removing concerns about treatment sequencing) is based on the assumption of similarity/equivalence between dosages, while the ICER of £331,091 is based on the assumption of similarity/equivalence of populations.

The manufacturer in their new analyses indicate that the 'worst case' scenario for the cost-effectiveness results is the application of the MDX010-20 data in a first-line setting, which results in an ICER of £58,593 for ipilimumab compared with DTIC. However, the ERG notes that this is not the worst case ICER as demonstrated by the ERG's additional analyses described above where the ERG considered all the available trial evidence (not just MDX010-20) for 3mg/kg vs. 10mg/kg in both previously treated and untreated patients. It is expected that the most plausible ICER lies somewhere along the spectrum between dosages assumed equivalent (i.e. the CA184-024 trial is the most appropriate source to inform the cost-effectiveness in a first-line setting and concomitant DTIC has no effect) and populations assumed equivalent at first- and second-line.

The uncertainty in the clinical effectiveness evidence does not stem from whether ipilimumab is efficacious in previously untreated patients, but instead stems from the *unknown magnitude* of the relative effectiveness of 3mg/kg ipilimumab dose compared with DTIC or vemurafenib in a first-line setting. The two randomised phase III trials of ipilimumab (MDX010-20 and CA184-024) clearly demonstrate long-term OS benefit (median OS 10.1 months for ipilimumab 3mg/kg vs. 6.4 months for gp100 vaccine in MDX010-20; median OS 11.2 months for ipilimumab 10mg/kg + DTIC vs. 9.1 months for DTIC in CA184-024). The preliminary 'Only in Research' recommendation in the ACD is in line with the conclusions of the EMA. A positive opinion from the EMA to extend the indication of ipilimumab 3mg/kg to adults with previously treated advanced melanoma was granted based on the conclusions that:

> *"The efficacy of ipilimumab in previously untreated patients has been established. The CHMP [Committee for Medicinal Products for Human Use] considers the ongoing post-authorisation measure to address issues related to efficacy of 3 mg/kg vs 10 mg/kg ipilimumab (study CA184169) was also applicable to this extension of indication."*

Therefore, despite a positive opinion, the uncertainty surrounding the magnitude of effect from a 3mg/kg dose in a first-line setting remains and the ongoing trial (CA184-169), which is directly comparing ipilimumab at a 3mg/kg dose and 10mg/kg dose, is expected to shed light on whether ipilimumab at a dose of 10mg/kg is superior, in terms of OS, compared with a 3mg/kg dose.

Given that the EMA considered the results of both the MDX010-20 and CA184-024 trials to make its regulatory decision to approve the drug in the first-line indication at a 3mg/kg dose, the manufacturer now considers that the evidence available for ipilimumab second-line from MDX010-20 should be formally used to address the decision problem for 3mg/kg in

previously untreated patients. In the manufacturer's response to the ACD they support the statement by clinical experts that there is no biological reason why the efficacy of ipilimumab should be different between first- and second-line settings in UK clinical practice. However, they argue that there are underlying differences in the patient populations with those treated in MDX010-20 presenting with more severe disease than those treated in CA184-024 and BRIM-3 (vemurafenib). Therefore, the manufacturer presents additional analyses which adjust the overall survival for 3mg/kg ipilimumab second-line from MDX010-20 to predict outcomes for 3mg/kg ipilimumab in a first-line setting based on the prognostic characteristics of an untreated patient population in CA184-024. This adjustment represents one component of the manufacturer's new base-case analysis, which is critiqued below.

2.1 Critique of the method of adjustment of the OS curve for 3mg/kg ipilimumab second-line (MDX010-20) to predict outcomes for 3mg/kg dose in first-line

The manufacturer adjusted the OS curve from the MDX010-20 trial for incorporation into the first-line model (i.e. replacing the OS curve from CA184-024) by predicting outcomes based on differences in patient baseline characteristics between CA184-024 and MDX010-20 using a Cox proportional hazards model. A comparison of baseline characteristics in these trials is shown in Table 5 of the manufacturer's response. Most notable is the difference between ECOG performance status (PS), stage of melanoma, brain metastases, and level of lactate dehydrogenase (LDH). The manufacturer's model estimated survival in the first-line setting after adjustment for the following five explanatory prognostic factors: i) gender; ii) ECOG PS; iii) visceral disease status; iv) brain metastases; and v) LDH. The manufacturer provides limited explanation for the choice of these variables. In particular, it is not clear why baseline disease stage was excluded from the model despite a notable difference between trials (e.g. M1c stage 56.2% in CA184-024 vs. 71.4% in MDX010-20). The adjustment by means of a Cox proportional hazards model is appropriate; however, without access to the individual patient level data, the ERG cannot verify the resulting model and the reasons for the exclusion or choice of particular prognostic variables. The predicted OS curve was estimated by taking a weighted average of the survival curves obtained by different combinations of the five prognostic variables based on the proportion of patients in each combination from study CA184-024. The resulting OS curve, which is used to represent an approximation for the efficacy of 3mg/kg ipilimumab monotherapy in a first-line setting, is shown in Figure 6 of the manufacturer's response.

In order to incorporate the new OS curve within the model, the manufacturer applied the adjusted Kaplan-Meier (K-M) curve directly in the model for the first 4.5 years and then

extrapolated the curve beyond 4.5 years by switching it to the modelled OS curve from CA184-024. The manufacturer's justification for the extrapolation is based on the observation that the proportion of patients alive at 4.5 years in the CA184-024 trial is equal to the estimated proportion alive in the adjusted K-M curve. Hence it appears that the manufacturer has used a non-parametric adjusted survival curve between time 0 and 4.5 years, a parametric analysis of CA184-024 data between 4.5 and 5 years, followed by a parametric analysis of registry data from AJCC for 5 years and onwards.

The ERG has a number of concerns about the approach used by the manufacturer. Firstly, it is noted that the approach taken is inconsistent with that used in TA268. In TA268, the OS from MDX010-20 was incorporated within the model using a three-part curve fit, where K-M data were applied directly in the model for the first 18 months before switching to a parametric curve from 18 months to 6 years (the last point at which data were available from the trial), at which point registry data from the AJCC was then used – this is summarised in Table 3 of the manufacturer's response[1]. The manufacturer does not provide the rationale for using a new cut-off point of 4.5 years or present an exploration of alternative cut-off points or curve fits, whereas in the original submission for first-line ipilimumab the cut-off points were based on the point at which the hazard changes in the OS data.

Secondly, there are a number of additional uncertainties arising from the non-parametric adjustment of the K-M data from MDX010-20:

i. The manufacturer appears to have adjusted the K-M data from MDX010-20 based on the set of covariates described above in order to estimate a K-M function in a first-line setting. It is not clear from the manufacturer's response how this adjustment was achieved in order to estimate a new K-M function. In particular, the manufacturer does not specify how censoring of the data was considered in the adjustment.

ii. There is a significant amount of uncertainty in the K-M curves beyond year 3 of the MDX010-20 trial. Of the 540 patients randomised to the ipilimumab arms (3mg/kg ipilimumab only and 3mg/kg ipilimumab + gp100), only 37 patients were still at risk at 3 years. Hence there is significant uncertainty surrounding the K-M data between 3 and 4.5 years which is not captured in the manufacturer's analysis.

[1] Note that the cut-off point of 6 years presented in Table 3 of the manufacturer's response does not agree with the cut-off point of 5 years presented in the 'Updated analysis with revised patient access scheme for ipilimumab for previously treated unresectable malignant melanoma' document dated 17th August 2012 for TA268 (available at http://guidance.nice.org.uk/TAG/208/FAD).

iii. It is not clear from the manufacturer's response why the adjustments and predictions were not based on parametric models, which would allow the higher censoring in the latter part of the K-M curves to be taken into account.

A third concern is that the inconsistency between the approaches used for previously treated and untreated patients extends to an inconsistency between the methods used to model OS for the comparator treatment arms. For example, a three-part curve fit for the DTIC arm of the CA184-024 trial (as presented in the manufacturer's original submission) was used to compare the relative efficacy of the 'predicted' ipilimumab 3mg/kg curve with DTIC. In addition, the use of separate, independent arms from different clinical trials to inform the relative efficacy of ipilimumab and DTIC (MDX010-20 for ipilimumab and CA184-024 for DTIC) breaks randomisation.

The manufacturer assumed that no adjustment was required for the progression-free survival (PFS) curve for ipilimumab from MDX010-20 since PFS was similar in both trials. The ERG is satisfied that the impact on results of introducing an adjustment to the PFS curve is expected to be minimal. In order to allow for the reduced toxicity associated with ipilimumab 3mg/kg alone (i.e. the use of concomitant DTIC in the ipilimumab arm of the CA184-024 trial was expected to have resulted in increased toxicity and therefore reduced the chance of patients receiving all 4 scheduled doses of ipilimumab), the manufacturer adjusted the number of ipilimumab doses to the higher number in the MDX010-20 trial (mean doses during induction 3.4 in MDX010-20 compared with 2.9 in CA184-024).

The impact of the new OS curve on the cost-effectiveness results for the comparison with DTIC is shown in Table 1 for the three-state model and sequential model. The results for the new base-case three-state model presents a higher ICER compared with the manufacturer's original three-state model (ICER of £47,899 in the new base-case vs. £42,449 in the original model). The increase in the ICER is due to a lower relative efficacy, in terms of OS, between the adjusted 3mg/kg ipilimumab and DTIC compared with the higher OS curve from CA184-024, which is partly compensated by an increase in the mean number of doses of ipilimumab received. The ICER from the manufacturer's new sequential model for the same comparison is £41,016, which is driven by assumptions surrounding OS on second-line and best supportive care (BSC) with DTIC.

In presenting the results for the new sequential model, the manufacturer has addressed a number of important limitations identified by the ERG in their original modelling of sequential treatments. The first of these relates to the arbitrary downward adjustment of the first-line survival curves to obtain second-line curves. The ERG is pleased to see that the manufacturer has now applied the survival curves from MDX010-20 directly in the model for

second-line treatment on ipilimumab. However, no details are presented on how the manufacturer has implemented this approach within the model. Previously, the manufacturer argued that the incorporation of the time-dependent OS curves from the previous submission (TA268) would be very difficult to implement in the cohort model structure since patients progressed to second-line therapy at different time points. Therefore, in order to avoid the additional complexity and uncertainty associated with attempting to model hazards individually, second-line outcomes were implemented as an adjustment to first-line curves. Given that no details of the new implementation have been provided in the manufacturer's response to the ACD, the ERG cannot verify the approach used. The second important limitation of the original sequential analysis related to the switching of OS curves between lines of treatment. The manufacturer has partly addressed this concern by assuming that the mortality hazard for third-line BSC is the same as second-line ipilimumab.

Table 1: Manufacturer's new base-case results for the comparison of ipilimumab with DTIC (results include the PAS)

Manufacturer's new base-case			**Ipilimumab**		**DTIC**		**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
			Mean costs (£)	**Mean QALYs**	**Mean costs (£)**	**Mean QALYs**			
Three-state model									
	Ipilimumab	DTIC							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS DTIC 1st line OS	£[redacted]	2.2566	£[redacted]	1.4611	£[redacted]	0.7955	£47,899
Sequential model									
	Ipilimumab	DTIC							
1st line 2nd line BSC	Ipi 1st line OS Ipi 1st line OS Ipi 1st line OS	DTIC 1st line OS Ipi 2nd line OS Ipi 2nd line OS	£[redacted]	2.2566	£[redacted]	1.9959	£[redacted]	0.2607	£41,016

In addition to the concerns highlighted above regarding the method of adjustment for the estimation of ipilimumab 3mg/kg, the ERG would like to add a number of important caveats which concern the validity of the cost-effectiveness results. The first of these relates to the assumptions used to model OS on BSC; once patients progress to BSC, different OS curves are followed depending on treatment received at first-line (in the three-state model) and second-line (in the sequential model). For example, in the three-state model patients who receive ipilimumab continue to receive the long-term survival benefits of ipilimumab despite progression to BSC, while patients who receive DTIC first-line continue to receive the long-term survival associated with DTIC upon progression to BSC. In the ERG report (Section

6.2.2), a number of scenarios explore the implications of this assumption. A second, and perhaps more important caveat, relates to whether the adjustment of the OS curve from MDX010-20 to estimate survival on ipilimumab 3mg/kg alone in a first-line setting addresses the Appraisal Committee's need for more precise and accurate estimates of the relative magnitude of effectiveness compared with DTIC (and vemurafenib). The approach used by the manufacturer only addresses the observed differences between the trial populations. It does not control for all the other unobservable differences between patients presenting at first- and second-line in UK clinical practice.

3. Treatment sequencing of ipilimumab and vemurafenib

A second component of the manufacturer's additional analyses relates to the comparison of ipilimumab with vemurafenib. The relative efficacy was informed by using independent arms of different clinical trials; the adjusted OS curve from the MDX010-20 trial (as described above) was used for ipilimumab, while the BRIM-3 trial which investigated the efficacy of vemurafenib compared with DTIC in BRAF V600 mutation-positive patients was used for vemurafenib. In the manufacturer's original analysis, no adjustment was made for differences in baseline patient characteristics between the BRIM-3 and CA184-024 trials based on the observation that the OS curves for the DTIC arms of the trials were similar. However, an update of the follow-up data from BRIM-3 (new evidence available since the date of the manufacturer's original submission), shows differences in the DTIC OS curves between the trials. In addition, new published data cuts from the BRIM-3 trial show that a proportion of patients (~20%) received ipilimumab after both vemurafenib and DTIC. As a consequence, the manufacturer's new analyses have adjusted the OS curve for vemurafenib in order to take account of differences in baseline characteristics and by removing the effect of patients receiving ipilimumab second-line. This adjustment represents a second component of the manufacturer's new base-case analysis, which is critiqued below.

3.1 Critique of the method of adjustment of the OS curve for vemurafenib

The manufacturer adjusted the OS curve for vemurafenib by firstly removing the effects of second-line therapy. This involved estimating the proportion of patients in the vemurafenib arm of BRIM-3 who received second-line ipilimumab based on three data points (at 6, 12.5 and 13.5 months). The time-dependent survival for these patients was derived from the second-line ipilimumab OS curve from MDX010-20. The manufacturer states that this was achieved via a set of tunnel states which track patient survival based on time of treatment

initiation. The approach used by the manufacturer is appropriate within the cohort model structure and the implementation within the model is well structured based on validity checks by the ERG. This approach assumes that the efficacy of ipilimumab is independent of prior therapy with vemurafenib. In order to generate the OS curve for patients treated with vemurafenib only, the 14 months of K-M OS data from the BRIM-3 trial was adjusted by removing the patients who died during or after second-line ipilimumab. The resulting curve was then compared with the unadjusted OS curve for vemurafenib in order to compute an implied hazard ratio of 0.92. This hazard ratio was then applied to the complete unadjusted vemurafenib OS curve from TA269 in order to allow equal adjustment of the extrapolated tail of the curve beyond the 14 months of available K-M data. The assumption underpinning this approach is that proportional hazards hold across all time periods, i.e. the effect on OS of second-line ipilimumab after prior therapy on vemurafenib is the same regardless of time of treatment initiation. The resulting adjusted OS curve for vemurafenib is shown in Figure 8 of the manufacturer's response.

The second adjustment to the OS curve for vemurafenib takes account of differences in patient baseline characteristics between the trials (see Table 5 of the manufacturer's response). For the adjustment of differences between CA184-024 and MDX010-20 described above, the manufacturer had access to individual patient-level data. However, this was not the case for the BRIM-3 trial. Consequently, the manufacturer used an alternative source of patient-level data from Korn et al. This is referenced as data on file to the manufacturer but appears to be referring to the same data used in Korn et al, 2008[2]. The manufacturer used this data to predict outcomes, in terms of OS, for metastatic melanoma patients based on four prognostic characteristics: i) gender; ii) ECOG PS; iii) tumour stage; and iv) presence of brain metastases. However, without access to the data, the ERG cannot verify the resulting model and the reasons for the choice of particular prognostic variables. More importantly, any adjustment to the OS curve of vemurafenib is based only on these prognostic factors, which do not control for all the observed and unobserved differences between patients presenting for first-line treatment in UK clinical practice. Furthermore, since the comparison of ipilimumab with vemurafenib comes from independent arms of separate clinical trials, the adjustment to the vemurafenib curve was made via the common comparator arm of DTIC in the trials. The DTIC arms of BRIM-3 trial and CA184-024 were reproduced based on the prognostic characteristics of the Korn model. A comparison of

[2] Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, Moon J, Sondak VK, Atkins MB, Eisenhauer EA, Parulekar W, Markovic SN, Saxman S,Kirkwood JM. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008 Feb 1;26(4):527-34.

these arms was then used to estimate an implied hazard ratio of 0.96, which was used to quantify the effect of differences in baseline characteristics between the trials. This hazard ratio was then applied to the vemurafenib arm of the BRIM-3 trial. However, it is not clear from the manufacturer's response whether the hazard ratio was applied to the unadjusted vemurafenib OS curve, which included a proportion of patients who received ipilimumab second-line, or the adjusted curve which removed the effects of second-line therapy. The ERG presumes that it must be the latter to enable the manufacturer to incorporate both changes to the vemurafenib OS curve in the cost-effectiveness analysis. This method also assumes that the prognostic factors included in the model have the same effect on the OS of vemurafenib and DTIC in both trials.

The impact of the new vemurafenib OS curve on the cost-effectiveness results for the comparison of ipilimumab with vemurafenib is shown in Table 2 for the three-state model. The results are very similar to the manufacturer's original three-state model (ICER = £28,980) because the impact of the adjustments to both the vemurafenib OS curve and the ipilimumab OS curve based on MDX010-20 have a similar relative effect on OS. An important caveat to these results (similar to the one mentioned in Section 2) is that the results are based on the use of different OS curves representing BSC, i.e. once patients progress on ipilimumab they continue to receive the long-term benefits of treatment, while patients who progress on vemurafenib continue to receive the long-term survival of vemurafenib (see Section 6.2.2 of the ERG's report for an exploration of the implications of this assumption). It is also important to emphasise that the new analysis does not control for differences in prognostic characteristics observed and unobserved between patients presenting for first-line treatment in UK clinical practice. To date, no patient characteristics or biomarkers have been identified that can prospectively identify the people most likely to benefit from treatment with ipilimumab.

The manufacturer's additional analysis no longer compares ipilimumab and vemurafenib used in sequence. The manufacturer acknowledges the limitations in the evidence for sequencing and lists a number of ongoing sequencing and combination trials, which will provide important evidence (see Section 3 and Appendix 2 of the manufacturer's response).

Table 2: Manufacturer's new base-case results for the comparison of ipilimumab with vemurafenib (results include the PAS)

Manufacturer's new base-case			Ipilimumab		Vemurafenib		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
			Mean costs (£)	Mean QALYs	Mean costs (£)	Mean QALYs			
Three-state model									
	Ipilimumab	Vemurafenib							
1st line BSC	Ipi 1st line OS Ipi 1st line OS	Vem 1st line OS Vem 1st line OS	£[redacted]	2.2566	£[redacted]	2.0550	£[redacted]	0.2016	£28,642

4. The effect of concomitant DTIC on the clinical efficacy of ipilimumab

In Section 4 of the manufacturer's response to the ACD they provide additional clarification on the effect of concomitant DTIC on the clinical efficacy of ipilimumab. The manufacturer argues that although the efficacy outcomes for DTIC are not supported by clinical evidence, it is reasonable to assume that the use of concomitant DTIC did not enhance the efficacy of ipilimumab in CA184-024. They also argue that it is more likely that increased toxicity associated with ipilimumab 10mg/kg in combination with DTIC reduced the observed efficacy of ipilimumab since increased toxicity reduced the likelihood of patients receiving all 4 scheduled doses of ipilimumab. This latter issue has been addressed in the manufacturer's additional analysis as part of the adjustment to the OS curve for ipilimumab 3mg/kg alone, described in Section 2.1 above. It is worth noting, however, that the results of the MDX010-08 trial (phase II, open-label study[3]), which compared ipilimumab 3mg/kg in combination with DTIC to ipilimumab 3mg/kg alone in a chemotherapy-naïve population, showed an improved median OS for combined therapy with hazard ratio = 0.75 (95% CI, 0.45 – 1.24) – See Table 16 of the manufacturer's original submission.

5. End of life considerations

The manufacturer's response to the ACD assumes that NICE End of Life (EOL) considerations hold for the appraisal of ipilimumab compared with DTIC in a previously untreated population. Although no discussion of EOL considerations is provided in the response, the manufacturer concludes that the new base-case results (presented in Table 1 and 2 above) indicate that ipilimumab compared with DTIC is cost-effective at a threshold of

[3] Hersh EM, O'Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. *Invest New Drugs*. 2011; 29:489-98.

£50,000 per additional QALY (end of life), while the cost-effectiveness of ipilimumab relative to vemurafenib is established at a threshold of £30,000 per additional QALY.

For EOL considerations to hold, the following criteria must all be met[4]:

i. The treatment is indicated for patients with a short life expectancy, normally less than 24 months;
ii. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment;
iii. The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

In addition, the Appraisal Committee must be satisfied that the estimates of the extension of life are robust and that the assumptions used in the model are plausible, objective and robust.

The ERG is satisfied that the first and third criterion above are likely to be met; advanced melanoma patients have a short life expectancy with a median OS of 6 - 9 months, while the estimated population eligible for first-line therapy is ~340 in 2014 (according to the manufacturer's submission, p30). However, the second criterion is not met based on estimates of median OS. In the CA184-024 trial, median OS for ipilimumab 10mg/kg + DTIC was 11.2 months (95% CI, 9.4 – 13.6) compared with 9.1 months (95% CI, 7.8 – 10.5) with DTIC alone, i.e. an increase of 2.1 months. In the new analyses by the manufacturer, the estimated median OS for ipilimumab 3mg/kg alone based on MDX010-20 was approximately 10.8 months[5], i.e. an increase of 1.7 months over DTIC. This is in contrast with the EOL considerations for the use of ipilimumab at second-line, where ipilimumab increased median OS by approximately 3.7 months (see TA268). In the manufacturer's original submission for first-line ipilimumab, it is stated that ipilimumab meets the second criterion based on mean OS estimates at 5 years, where a restricted mean analysis of CA184-024 shows a survival gain of 5.7 months over the 5 year trial. Based on the adjusted OS curve for ipilimumab 3mg/kg alone from MDX010-20, the ERG has estimated that the corresponding mean OS gain over 5 years is 4.3 months.

[4] The National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013.
[5] Derived from manufacturer's model, worksheet 'OS Curves', column AN.