National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ipilimumab for previously untreated unresectable malignant melanoma [ID74]

You are asked to check the ERG report from **NHS Centre for Reviews & Dissemination and Centre for Health Economics, University York** to ensure there are no factual inaccuracies contained within it.
If you do identify any factual inaccuracies you must inform NICE by **5pm** on **9th January 2013** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.
The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Overview

Issue 1 Comparability of ipilimumab 3mg/kg and 10mg/kg alone or in combination with DTIC 2
Issue 2 Non-RCT evidence (real-world data and pooled chemotherapy-naïve analysis) 5
Issue 3 Mixed treatment comparison and indirect comparisons 9
Issue 4 Treatment sequencing approach and ERG exploratory analysis 10
Issue 5 Modelled treatment pathways 13
Issue 6 Utilities 15
Issue 7 Willingness to pay (WTP) threshold of £50,000 for end of life therapies 15
Issue 8 Weekly acquisition cost of ipilimumab in first and second line 16
Issue 9 Search strategy - Conference proceedings 17
Issue 10 Search strategy - Non-RCT evidence 17
Issue 11 Inclusion criteria 18
Issue 12 Clarification of significance and difference in patient populations 19
Issue 13 Typographical error in summary 20
Issue 14 Restricted means analysis described as not presented 20

Issue 1 Comparability of ipilimumab 3mg/kg and 10mg/kg alone or in combination with DTIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the survival benefit of ipilimumab 3mg/kg may be overestimated. As a scenario, the ERG calculated an implied hazard ratio for 3mg/kg relative to 10mg/kg. This was subsequently applied to the ipilimumab 10mg/kg + DTIC OS curve from the CA184-024 trial (which is used in the base-case analysis) to estimate the 3mg/kg OS curve for ipilimumab. This is found on pages 115-118. Although we agree with the ERG that a definite conclusion relative to the clinical equivalence in efficacy between ipilimumab 3mg/kg and ipilimumab 10mg/kg alone or in combination with DTIC cannot be supported at this time, the assumption that the clinical efficacy of ipilimumab 10mg/kg + DTIC and ipilimumab 3mg/kg monotherapy are similar - an assumption which was utilised for our economic modelling - is based on the multiplicity of clinical arguments accepted by CHMP and EMA conclusions (Reference: European Public Assessment Report (EPAR)) and is thought to be more appropriate than the ERG proposed scenario of applying an implied hazard ratio for ipilimumab 3mg/kg relative to 10mg/kg using	Remove section 6.3.1 Amend all sections that imply that BMS is claiming that there is definitive equivalence between 3mg/kg ipilimumab monotherapy and 10mg/kg ipilimumab monotherapy alone or in combination with DTIC to reflect the positioning: "Although a definite conclusion relative to the clinical equivalence in efficacy between ipilimumab 3mg/kg and ipilimumab 10mg/kg alone or in combination with DTIC cannot be supported at this time, the manufacturer states that such assumption, which was utilised for the economic modelling, is based on the multiplicity of clinical arguments accepted by CHMP and EMA conclusions (Reference: EPAR)."	The ERG calculated an implied hazard ratio for ipilimumab 3mg/kg relative to 10mg/kg, using information available outside of the manufacturer's submission. The data that the ERG used contributed to the pooled 3mg/kg vs. 10mg/kg analysis and was not derived from a randomised study. It pooled mixed patient populations, multiple treatment regimens and doses outside of the UK licence terms (3mg/kg every 3 weeks for a total of 4 doses). We do not believe relative treatment effect of ipilimumab 3mg/kg vs. ipilimumab 10mg/kg can be inferred using this analysis and believe that the pooled OS curve can only be interpreted descriptively by treatment arm. Moreover, there are two issues with the ERG calculated hazard ratios of 3mg/kg versus 10mg/kg: 1. The application of the implied hazard ratio results to an OS curve for ipilimumab 3mg/kg in untreated advanced melanoma, that falls below the OS observed in randomised trials for ipilimumab 3mg/kg in pre-treated advanced melanoma (as seen in MDX010-020). This is not clinically plausible given the potentially more severe disease state of pre-treated patients. 2. There were underlying differences in the patient populations included in the pooled analysis with those treated with ipilimumab 3 mg/kg presenting in a more severe disease state that those treated with ipilimumab 10 mg/kg. We agree with the ERG that the datasets do not	This is not a factual inaccuracy. As acknowledged by the manufacturer, the clinical equivalence in efficacy between ipilimumab 3mg/kg and ipilimumab 10mg/kg alone or in combination with DTIC cannot be supported at this time. The ERG simply states that the survival benefit of ipilimumab 3mg/kg **may** be overestimated based on the evidence from the CA184-022 trial of previously treated and untreated patients and from the pooled data analysis comparing OS profiles of ipilimumab 3mg/kg (MDX010-20; CA184-022) and 10mg/kg (CA184-077; CA184-008; CA184-022) for a mixed (both previously treated and untreated) patient population. Given that the manufacturer has assumed clinical equivalence in the economic modelled, the ERG has simply undertaken a scenario analysis in Section 6.3.1 to show the implications of this assumption. The ERG has not stated that the implied hazard ratio for ipilimumab 3mg/kg

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information available outside of the manufacturer's submission. This is found on pages 14, 15, 33, 54, 55.		support a definite conclusion at this time on the relative equivalence in efficacy between ipilimumab 3mg/kg and ipilimumab 10mg/kg alone or in combination with DTIC. As specified in our original submission, the ongoing trial CA184-169 is specifically designed to address the question of the optimal dose in patients with advanced melanoma. Whether the combination of ipilimumab with DTIC offers value to patients with untreated advanced melanoma is not investigated in the CA184-169 trial but there is a large evidence base available that concludes DTIC does not offer survival benefit in advanced melanoma. (See section 6.10 of our submission) The assumption that the clinical efficacy of ipilimumab 10mg/kg + DTIC and ipilimumab 3mg/kg monotherapy are similar - an assumption utilised for the economic modelling - was based on a qualitative synthesis of studies providing clinical evidence for the first-line use of ipilimumab as part of the multiplicity of clinical arguments accepted by CHMP and EMA who concluded that sufficient evidence of the efficacy of ipilimumab 3mg/kg in previously untreated patients was provided, which is also stated in the EPAR: "*For patients with advanced melanoma without BRAF mutation currently only DTIC is approved as first line treatment from which only a limited increase in PFS can be expected.* *Efficacy of 3mg/kg ipilimumab in second line treatment was already proven by the phase III MDX010-20 study. From a pharmacological or biological point of view it is not rational to suspect a different activity for ipilimumab treatment in the first or the next line setting, because the mechanism of action of ipilimumab is general stimulation of the immune-system,*	relative to 10mg/kg, which was calculated based on the pooled data analysis comparing OS profiles for a mixed patient population (and which was supplied to the ERG by the manufacturer in response to the points for clarification) provides a definitive estimate. Instead, the ERG states that there is currently no conclusive evidence and that the ERG scenario represents an exploratory analysis of the implications of the manufacturer's assumption of clinical equivalence on the results of the cost-effectiveness analysis.

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[EPAR; available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002213/human_med_001465.jsp&mid=WC0b01ac058001d124]		*which is rather aspecific. Efficacy of 3mg/kg ipilimuamb in previously untreated patients was supported by two retrospective studies performed in patients with untreated advanced melanoma treated with 3mg/kg ipilimumab, a median OS of 14.4 months (CA184332) and 11.5 months (CA184338) was observed. An overall survival benefit has never been shown with DTIC, while the median OS observed with ipilimumab is consistently at least > 2 months longer regardless of the line of therapy used as shown by the results from the pivotal and the supportive studies. The efficacy of the 10mg/kg ipilimumab + DTIC regimen in the CA184-024 study was considered to support the efficacy of ipilimumab in previously untreated patients.* *The data of the retrospective observational studies are useful for assessing the safety of 3mg/kg ipilimumab for the treatment of previously untreated patients. Based on the data provided, the results do not indicate additional safety issues for first line ipilimumab in comparison to second line ipilimumab treatment for key safety issues."* *"Overall, the benefit/risk of 3mg/kg ipilimumab treatment in patients with advanced melanoma without restriction regarding the line of treatment is considered positive. Estimation of the effect in previously untreated patients was based on several factors; similarity between patient characteristics of previously treated and untreated patients, the pharmacological rationale assuming similar activity for ipilimumab in different treatment setting and consistent beneficial effect on OS in comparison to DTIC observed in the clinical trials regardless the line of therapy."* [EPAR; available from	

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		http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002213/human_med_001465.jsp&mid=WC0b01ac058001d124]	

Issue 2 Non-RCT evidence (real-world data and pooled chemotherapy-naïve analysis)

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The ERG implies "absence of evidence for the licensed dose of ipilimumab 3mg/kg in previously untreated advanced melanoma". This does not reflect the submitted evidence. This is found on pages 17, 67 and 111.	Amend all respective statements to "absence of **comparative efficacy evidence** for 3mg/kg in previously untreated patients"	Evidence for the licensed dose of ipilimumab 3mg/kg in previously untreated advanced melanoma is presented in our submission from the following studies: MDX010-08; pooled chemotherapy-naïve dataset; CA184-332; CA184-338.	The ERG has amended the respective statements to include 'comparative efficacy' evidence on pages 17, 67 and 111.
The ERG fully disregards the importance of the real-world data (CA184-332; CA184-338) and the pooled chemotherapy-naïve analysis. This is found on pages 14 and 41 to 44.	The ERG should reconsider the importance of the real-world data and the pooled chemotherapy-naïve analysis in the ERG report given the importance of this evidence for the license extension, as explained.	The real-world data (CA184-332; CA184-338) and the pooled chemotherapy-naïve analysis (pooled Phase II and III studies) represent key data on which the license extension to previously untreated patients was granted. The positive opinion of the CHMP testifies to the acceptance of this same non-RCT evidence and, generally, the increasing acceptance of the value of real-world data in the scientific community. BMS propose that the ERG reconsider the importance of the non-RCT data given for 1) the robustness of long term data in these trials (based on the numbers of patients in pooled dataset, extent of follow-up, consistency of findings), 2) the importance of long-term survival as a benefit to patients with advanced melanoma given the often terminal nature of this disease	This is not a factual inaccuracy. We did not disregard this evidence, we appraised it. However, it was not as robust as the RCT evidence and the results were similar, therefore, we did not consider that these studies provided additional relevant data.

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		(i.e., usual survival < 1 year, it is rare that patients are alive beyond 3 years with alternative therapy), 3) the existence of historical data from various sources which provide evidence to support the long term benefits of ipilimumab, and the scientific basis to extrapolate benefits in previously treated patients to those patients with untreated advanced melanoma.	
The ERG claim that it is not possible to determine the reliability or generalisability of the pooled analysis for previously untreated patients eligible for ipilimumab first-line, "particularly since this pooled analysis was primarily in previously treated patients" (p. 42).	Remove respective statement on p. 42: "it is not possible to determine the reliability of the results of the pooled analysis or the generalisability of results to previously untreated patients eligible for ipilimumab first-line therapy; ~~**particularly since this pooled analysis was primarily in previously treated patients**~~" Revise wording and conclusions around pooled analysis given the justification provided and acknowledge that the long-term OS benefit of ipilimumab is independent of prior therapy, i.e. in previously treated or untreated patients.	The ERG claim does not make sense, as determining the 'reliability' of a pooled analysis does not depend on the content. We believe that the pooled analysis was reliable and even though it did contain a majority of previously treated patients, we provided in the submission data sets that showed there is a similarity in efficacy between previously treated and untreated patients. Therefore we believe the pooled analysis is of additional value for untreated patients. The hallmark of ipilimumab OS benefit is the long term durable OS benefit which has been demonstrated for both previously treated (MDX010-20) and previously untreated patients (CA184-024). In our submission's Kaplan-Meier OS plots of ipilimumab), the OS curves plateau around the same time point (i.e. after 2 years) and in a similar proportion of patients (approximately 20%), regardless of whether the studies were Phase II or Phase III or whether the patients were chemotherapy-naïve, previously treated or untreated patients. The fact that OS curves reach a plateau at similar time points and there is a similarity in the proportion of long-term survivors at 2 and 3 years, supports the long-term OS benefit of ipilimumab that is independent of prior therapy.	This is not a factual inaccuracy. We were unable to determine the reliability of the pooled analysis due to the lack of reporting of methods for the pooled analysis. The pooling of both previously treated and untreated patients reduces the generalisability of the results to an untreated population.

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		Please also note that an independent meta-analysis of 42 Phase II advanced melanoma trials demonstrated that prior therapy status (yes vs. no) was not prognostic for OS (Korn et al., 2008) (presented on page 105 of our submission).	

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The ERG states on p. 14: "The manufacturer compared the results of the non-RCT studies with the DTIC arm of the CA184-024 trial, however this is problematic due to the differences in patient characteristics and study design; (...)." The language used suggests that BMS chose a favourable comparator arm for the non-RCT data, which is not the case.	Amend text on p. 14 to: "The manufacturer compared the results of the non-RCT studies with the DTIC arm of the CA184-024 trial, however this is problematic due to the differences in patient characteristics and study design. **It has to be noted though that differences in the trial design are countered at least partially by the fact that the non-RCT data included patients with unfavourable prognostic factors ineligible for participation in CA184-024. Based upon the analysis conducted in response to the CHMP ipilimumab at 3mg/kg would be expected to be more effective in the CA184-024 trial population than in the non-RCT data trial population."**	It should be considered by the ERG that the non-RCT data include patients with unfavourable prognosis who could not have been included in clinical trials, e.g. for brain metastases, lab abnormalities etc. To compare these patients against the upper end of the historical data for DTIC in a selected population without the cited unfavourable prognostic factors suggests that BMS chose a favourable comparator arm for the non-RCT data. The ERG omitted to consider the real-world data which BMS compared against a selected clinical trial population. However the real-world data we provided is vital evidence and is very relevant in the context of how ipilimumab performs in 'real' patients, outside of a clinical trial setting and therefore should be included in the ERG's considerations. The non-RCT data provided included a comparison with best supportive care (for example DTIC) in previously untreated patients using analysis from the Korn paper (page 91 of our submission, and as presented to the CHMP) where the performance of previously untreated patients on current care is adjusted for the prognostic characteristics of the patients in the non RCT dataset. For chemotherapy-naïve patients the expected performance is considerably worse than the performance of DTIC in the CA184-024 trial (where patients had more favourable prognostic characteristics). This implies that using the non-RCT data to directly compare to the DTIC arm in the trial will underestimate rather than overestimate the benefits of ipilimumab (see Figure 1 at the end of this response).	This is not a factual inaccuracy. We have not suggested that the manufacturer purposefully chose a favourable comparator arm, just that the analysis is problematic given the difference in patient characteristics and study design.
The ERG claim that since the	Revise wording to correctly reflect	Patients treated with ipilimumab 3 mg/kg	We have amended the

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MDX010-08 trial was also included in the MS separately, there is some double-counting of patients between the results presented for the MDX010-08 trial and the pooled chemotherapy-naïve dataset. This is found on pages 14, 40 and 43.	that ipilimumab 3 mg/kg treated patients from MDX010-08 are also a subgroup of patients that make up the pooled chemotherapy-naïve dataset.	monotherapy in MDX010-08 were included in the pooled chemotherapy-naïve dataset analysis presented, but this does not represent double-counting, i.e. an error by which data is counted twice in the same analysis.	wording in the report to clarify that the MDX010-08 data were used twice in the manufacturer's submission, rather than twice in the pooled dataset.

Issue 3 Mixed treatment comparison and indirect comparisons

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The ERG considers the mixed treatment comparison (MTC)/ indirect comparisons as inappropriate because of the differences in trial populations between the included trials. Despite this conclusion the ERG present cost-effectiveness analysis using the MTC/ indirect comparisons which the ERG concluded were inappropriate. Additionally ERG statements imply that bias exists solely in one direction (i.e. that the efficacy of vemurafenib would be greater in the CA184-024 trial population) this conclusion is not supported by the available evidence – the direction of any bias is unknown. This is found on pages 14, 18, 19, 23, 31, 54-56, 117 and 118.	Provide consistent analysis within the report i.e. if the MTC is inappropriate it is also inappropriate to conduct sensitivity analysis using the MTC. Acknowledge the limitations surrounding the MTC and update information on BRAF prognostic value to include a balanced conclusion of all the relevant literature rather than one paper.	There is no RCT data available for ipilimumab's efficacy in BRAF mutation positive patients to allow any direct comparison to vemurafenib. However, the subgroup analyses of CA184-338 demonstrated that BRAF tumour mutation status does not impact on the clinical activity of ipilimumab with no statistically significant differences (p=0.23) in survival observed between BRAF mutation positive and BRAF mutation negative patients. Conducting an MTC/ indirect comparisons and identifying its limitations is more useful than not presenting an MTC/ indirect comparisons, and hence we believe these analyses should not have been disregarded as 'inappropriate' by the ERG, but rather these limitations acknowledged by the ERG. The ERG considers the MTC/ indirect comparisons as inappropriate because of the differences in trial populations between the included trials. However, there appears to be no difference in the outcome of the control patients	This is not a factual inaccuracy. The ERG considers the mixed treatment comparison (MTC)/ indirect comparisons as inappropriate because of differences in baseline characteristics between the populations included in the trials. However, the ERG also considers that the manufacturer's approach of using separate, independent arms from different clinical trials (i.e. breaking randomisation) to establish the relative efficacy of ipilimumab with vemurafenib to be highly inappropriate as well. As a consequence, the ERG simply undertook an exploratory analysis using the results from the indirect comparison

		(DTIC) between the CA184-024 trial and the BRIM-3 trial (page 129 of the submission), thus it would seem apparent that trial population differences are not contributing to a fundamental difference to the prognosis of the two groups (otherwise we would expect a notable difference in the outcome of the respective DTIC arms). The ERG noted that the presence of a BRAF mutation in metastatic melanoma has been associated with inferior survival (Long et al. 2011; Houben et al. 2004; von Moos et al. 2012). However, this is not a consistent observation with further trials reporting no significant difference in overall survival according to BRAF mutation status in multivariate analysis (Ugurel et al. 2007) and disease-free survival times reported not to be significantly impacted by the absence/presence of BRAF mutation in metastatic melanoma (Kumar et al. 2003; Long et al. 2011).	analysis for the relative efficacy of ipilimumab and vemurafenib only. This exploratory analysis was used to show the implications of the manufacturer's assumption on the cost-effectiveness results.

Issue 4 Treatment sequencing approach and ERG exploratory analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG (page 16) state that "the OS for patients who survived to receive third-line therapies was assumed to be the same as those on first-line treatment who had not progressed to next line of therapy." This statement is incorrect.	Amend the text on p.16 to: "The OS for patients who survived to receive third-line therapies was assumed to be the same as those on first-line treatment **independent** of progression status. **This does not include the effects of follow-on active treatments within the analysis of the benefits of ipilimumab or DTIC but may overestimate the benefit of vemurafenib from the BRIM-3 trial as patients were allowed to receive ipilimumab after**	The ERG's statement is technically incorrect given the OS for patients who survived to receive third-line therapies was assumed to be the same as OS from the CA184-024 trial in its entirety, which includes patients who have progressed to the next line of therapy, e.g. BSC, but does not include patients who progress to active treatments such as ipilimumab and vemurafenib. This is an important distinction. It should be noted by the ERG that no benefit from active follow-on treatments is included within either the CA184-024 trial or the submitted non-RCT data. Analysis of the BRIM-3 trial carried out by Roche in TA269 includes patients following on to receive ipilimumab after	The ERG has amended the statement on p16 to include 'independent of progression status'.

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	vemurafenib."	vemurafenib and has been used by Roche to calculate the benefit of vemurafenib first line without follow on to ipilimumab.	
The ERG scenarios presented around second line efficacy do not include an assessment of their clinical plausibility. This is found on pages 20 and 98 to 117.	Inclusion of comparison of the life years gained (i.e. estimation of OS) with OS for: • Mean predicted life years using OS for ipilimumab followed by BSC (i.e. from CA184-024) - 3.352 • Mean predicted life years using OS for vemurafenib followed by BSC (i.e. from CA184-024) - 3.013 • Mean predicted life years using OS for DTIC followed by BSC (i.e. from CA184-024) - 2.002 • Mean predicted life years using OS for ipilimumab 3mg/kg at second line followed by BSC (i.e. from TA268 - MDX-010-020) - 3.325 Clarification is needed in the ERG report on page 20 around how plausible the ICERs are based on how clinically viable the associated presented ERG scenarios are.	Whilst we accept the ERG's comments regarding the arbitrary nature of the assumptions for third-line efficacy and the assumptions around efficacy from CA184-024 being applicable to 3mg/kg, we would respectfully request that the scenario analyses presented by the ERG are provided alongside an assessment of their clinical plausibility. This affects for example the following scenarios presented by the ERG: • Scenarios 4 to 6, 14 and 15: The efficacy of ipilimumab is assumed by the ERG to be negatively affected by the subsequent use of vemurafenib at second line - Scenarios 4 to 6 include substantial decreases in the life years assumed for ipilimumab when it is followed by vemurafenib compared to ipilimumab alone. Scenarios 14 and 15 also imply this assumption. It cannot be clinically plausible that adding an active treatment reduces survival. • Scenarios 2 and 3: The efficacy of ipilimumab is assumed by the ERG to be negatively affected by the continuation onto BSC. OS in our analysis already includes progression onto BSC and this was already included in the survival curves presented from the clinical trial. Therefore the clinical trial evidence has been disregarded in this instance. • The survival of ipilimumab treated patients calculated by the ERG is considerably worse than that shown by the available 10 year data (Figure 6.7) and associated scenarios.	This is not a factual inaccuracy. The purpose of the additional scenarios presented by the ERG was to provide an exploratory analysis of the implications of the assumptions used in the manufacturer's modelling of the cost-effectiveness of ipilimumab. The manufacturer has acknowledged the arbitrary nature of the assumptions used in their analysis for the sequencing of treatments. The manufacturer has not provided an assessment of the clinical plausibility of the overall survival predicted from the sequence of treatments on three lines of therapy. This is because this information is not yet available. There are no completed clinical trials comparing the sequential use of treatments for previously untreated advanced melanoma. Therefore the ERG cannot provide a clinical validation of the overall survival predicted from the sequence of treatments. Instead, the ERG has provided an assessment of the

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		• Scenarios 7 to 16: The ERG implies that survival of ipilimumab 3mg/kg treated patients at first line is worse than the survival of ipilimumab 3mg/kg treated patients at second line.	implications of assuming different survival curves on the latter lines of treatment, where the key uncertainty lies.
The ERG suggests the use of tunnel states within the model for second-line ipilimumab (page 74) which is not technically feasible.	Remove this suggestion as it would not be technically feasible due to the computational limitations of carrying this out in Excel.	The ipilimumab model used in TA268 was based upon Kaplan-Meier data up to 18 months followed by a curve fit to the MDX-010-020 data up to 5 years and then registry data. Unfortunately the Kaplan-Meier data involves steep drops in OS and PFS over the first 18 months for a large number of time points (as would be expected for a severe disease such as melanoma) as such the number of tunnel states required to capture these drops would be exceptionally large and beyond the computational capacity of Excel.	This is not a factual inaccuracy. Longer computational time is not a reason for rejecting a more appropriate model structure. The main concern for the ERG is the fact that the manufacturer proceeded to adopt a modelling approach using sequential treatment when they were unable to fulfil the data requirements of this approach.
The ERG state that (page 17) "the main driver of cost-effectiveness for the comparison of ipilimumab with DTIC and vemurafenib is the assumptions around the sequencing of treatments."	Amend text on p.17 to: "the main driver of cost-effectiveness for the comparison of ipilimumab with DTIC ~~**and vemurafenib**~~ is the assumptions around the sequencing of treatments." I.e. remove "and vemurafenib" from the original sentence.	Comparing the ICERs produced using the simple three-state model i.e. without sequencing (Table 6.4 - £42,449 vs DTIC and Table 6.5 - £28,980 vs vemurafenib) to the base case (Table 6.1 - £16,958 vs DTIC Table 6.2 - £31,559 vs vemurafenib) shows that this statement is only true for the comparison vs DTIC (and sequencing has little effect vs. vemurafenib, as expected).	This is not a factual inaccuracy. The ERG holds the view that the main driver of cost-effectiveness for **both** comparisons (ipilimumab with DTIC and ipilimumab with vemurafenib) is the assumptions used to model the sequencing of treatments. This is clear from Tables 6.1, 6.2, 6.3, 6.4 and 6.5 of the ERG's report.
The ERG believe "that the only plausible model structure on which to base the estimates of cost-effectiveness of ipilimumab is to	No amendment required for ERG information only	The ERG conclusions are based on a misunderstanding of the model developed for the previous appraisal TA268, as the model structure we adopted is indeed consistent with	This is not a factual inaccuracy. The ERG is aware that the modelling approach used by

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consider first-line treatments only, which essentially uses a conventional three-state model based on pre-progression, post-progression, and death, with BSC being the only second-line treatment considered (p. 18)". Similar statements are provided on pages 18, 19, 66, 73 and 74.		the previous model of second-line ipilimumab (TA268), as we explained in the response to the ERG clarification questions. A sequential model is not only clinically plausible, but also better reflects current patterns of clinical practice in the NHS and the structure is largely consistent with previous models used to represent the treatment of advanced melanoma [TA268, TA269]. A simple three-state model, as preferred by the ERG, although preferable in terms of simplicity is less clinically plausible in this case as there is more than one line of active treatment given. If the model ignores the effect of one or more active treatments, its basis does not reflect actual clinical practice and therefore we perceive the ERG's model results are invalid. There is also no link between quality of life and progression status, which the ERG has assumed. In developing our economic model BMS took advice from a wide range of academic health economists and clinicians and considered both the previous ipilimumab NICE and SMC appraisals and the NICE vemurafenib appraisal. In addition, sequential models have been presented (and accepted) in previous appraisals (e.g. TA195).	the manufacturer is consistent with that used in TA268. However, in TA268 there are only two lines of therapy with the second line of therapy being best supportive care (BSC). The problem arises in this submission because there is an additional active line of therapy considered and the manufacturer has not appropriately modelled the sequential use of active treatments. The ERG agrees that modelling the sequential use of treatments is the most clinically plausible approach and better reflects current patterns of clinical practice. The ERG's concern lies in 'how' the manufacturer has modelled sequential treatments by using arbitrary assumptions, which are not supported by clinical evidence.

Issue 5 Modelled treatment pathways

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states "the pathway suggests that treatment with DTIC in first line can be followed by	Amend text on p. 66 to: "Whereas a sequence of DTIC in first line and vemurafenib in 2nd	DTIC followed by vemurafenib may technically be a possible sequence, but this would not be done in clinical practice, as both NICE guidelines and clinical opinion recommend that	This is not a factual inaccuracy. The wording used by the ERG

Vemurafenib in 2nd line." (page 66) Similar statements are present on pages 23 and 80.	line is possible, according to NICE recommendations DTIC is an inferior choice to vemurafenib in first line in BRAF mutation positive patients." Amend statements on pages 23 and 80 in line with this.	vemurafenib is given first line to BRAF mutation positive patients. In addition, DTIC has never been shown to prolong survival of melanoma patients (Korn *et al.* 2008) and therefore would be of no added clinical value. Clinical advice received when composing the submission indicated that BRAF mutation positive patients would usually receive vemurafenib first (i.e. first line), if eligible, following the recommendation of TA269. The clinicians stated that whereas such a sequence is permitted from an SPC perspective, it will not be employed in practice as DTIC was an inferior comparator in the BRIM-3 trial. If BRAF mutation positive patients were to receive an alternative first line treatment to vemurafenib, it would be ipilimumab based on the available literature (Jang and Atkins 2013).	on page 66 is much broader than indicated. The ERG simply referred to DTIC followed by vemurafenib as an option as it was presented in the manufacturer's submission as part of the current clinical care pathway (Figure 2, p25). The wording used by the ERG was broad in content "For example, DTIC first-line followed by vemurafenib second line was not considered as an option in the model but it was presented as an option in the current clinical care pathway in the MS (Figure 2, p 25). Although there are no concrete clinical guidelines to determine the exact sequence among the currently available therapies (i.e. DTIC, ipilimumab, vemurafenib and BSC), there are certain progressive trends with regard to the treatment of melanoma (e.g. vemurafenib being preferred in first line for patients with BRAF V600 mutation) and the treatment patterns are still largely subject to individual clinicians' discretion. As a result, there are a number of additional treatment permutations that could potentially be applied in clinical practice, which have not been captured in the manufacturer's analysis."

Issue 6 Utilities

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The ERG state that TA268 utilities were based on progression only (pages 82 and 94) and that the model presented is therefore not consistent.	Amend to reflect the utility analysis process carried out within TA268 and specify that the utilities presented within the manufacturer submission are, as stated, consistent with the utilities supplied by time to death within TA268.	Whilst the base case presented to NICE in TA268 was based upon progression-based utilities, additional analysis using time to death was carried out in response to committee concerns regarding the small impact of progression on utility using the MDX-010-020 trial data. This analysis can be found at http://www.nice.org.uk/nicemedia/live/12092/61324/61324.pdf. In TA268, ICERs were presented using the time to death utilities. As stated in the manufacturer submission, values are comparable between the CA184-024 and MDX-010-020 datasets.	The ERG has amended the text on pages 82 and 94 to state that the **base-case** utility values used in TA268 were based on progression**.**

Issue 7 Willingness to pay (WTP) threshold of £50,000 for end of life therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG did not understand why BMS used the willingness-to-pay (WTP) threshold of £30,000 per QALY for the comparison with vemurafenib and £50,000 per QALY for the comparison with DTIC – despite the rationale for using two different thresholds being stated in our submission in section 4 and 6.5.1. This is found on pages 95 and 96.	Remove respective statements or provide the explanation given in our submission in section 4 and 6.5.1 (p. 190).	Given BMS considers that treating with ipilimumab meets NICE's end of life criteria when compared with DTIC - this is described, in section 4 and 6.5.1 in the submission - the WTP threshold of £50,000 for end of life therapies is applied, (submission, p.190).	The ERG has amended the text on pages 91 and 92 by removing the respective statements that no explanation was provided by the manufacturer. (The manufacturer noted down the wrong page numbers, 95 and 96, for this query.)

Issue 8 Weekly acquisition cost of ipilimumab in first and second line

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG calculated that there is a "42% difference in the drug cost of ipilimumab per cycle between second-line and first-line treatment ([redacted] vs. [redacted]) (p. 92)". This is found on pages 17 to 20, 88 and 92	Remove respective sections and sensitivity analysis and present instead cost per patient receiving therapy with a discussion of the implications of lower dosing in CA184-024 with regards to efficacy.	The ERG calculated a cost per cycle for ipilimumab treatment. This type of analysis assumes that the ratio between costs and the number of cycles of therapy remains constant at first and second line. As ipilimumab is not dosed continuously this is not necessarily the case. The cost per patient receiving therapy should instead be calculated and compared. This is approximately [redacted] per patient at first line and [redacted] per patient at second line (calculated by dividing the total undiscounted drug costs at second line following DTIC by the number of new patients entering second line [column M in the patient flow sheet]). For ERG information, the cost per patient is higher at second line as more doses were received out of the 4 induction doses in MDX-010-020 compared to CA184-024 (i.e. 3.40 doses vs. 3.14 doses). It is not possible to calculate the impact of MDX-010-020 dosing on cost-effectiveness using the CA184-024 data as it is known that receiving all 4 doses impacts the outcome of patients receiving ipilimumab, i.e. increased OS is correlated with increased number of doses received.(Response to CHMP) This means that the analysis presented on pages 88 and 92 is biased against ipilimumab as the impact of increased costs with increased doses is taken into account but not the impact of increased efficacy with increased doses.	This is not a factual inaccuracy. The ERG calculated a cost per cycle to be consistent with the approach used by the manufacturer where they used a cost per cycle for second-line treatment on ipilimumab. In the scenario analysis presented in Section 6.3.4, the ERG was exploring the implications of the cost difference on the results of the cost-effectiveness analysis. To be consistent with the modelling approach used by the manufacturer, the ERG used a cost per cycle for second-line ipilimumab.

Issue 9 Search strategy - Conference proceedings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On p. 27 the ERG stated: "The manufacturer attempted to search the conference proceedings of the European Association of Dermato-Oncologists (EADO) and Perspectives in Melanoma (PiM), however the abstracts could not be accessed so were not searched." The language used suggests that BMS did not provide a reason for not searching the abstract - despite the reason being provided.	Amend text on p. 27 to: "The manufacturer attempted to search the conference proceedings of the European Association of Dermato-Oncologists (EADO) and Perspectives in Melanoma (PiM), however the abstracts could not be accessed **as abstracts are only made available to meeting delegates, so could not be** searched."	The reason that the abstracts could not be reviewed has been provided as a response to the ERG clarification questions, i.e. that abstracts are only made available to meeting delegates. Hence this reason should be included for clarity and transparency.	This is not a factual inaccuracy. However, we are happy to add the explanation.

Issue 10 Search strategy - Non-RCT evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On p. 28 the ERG stated: "The ERG asked the manufacturer to clarify how non-RCT evidence was identified; the manufacturer responded that non-RCT evidence was not searched for systematically." The language used suggests that BMS did not provide a reason for not searching the non-RCT evidence systematically - despite the reason being provided.	Amend text on p. 28 to: The ERG asked the manufacturer to clarify how non-RCT evidence was identified; the manufacturer responded that non-RCT evidence was not searched for systematically. **This was because direct RCT evidence was identified for comparator therapies through systematic searches. Only for ipilimumab 3mg/kg monotherapy was non-RCT data required and this was only available from BMS's internal data. Therefore a**	The reason why the search for non-RCT evidence has not been conducted systematically has been provided by BMS as response to the ERG clarification questions and should hence be included in the ERG report for clarity and transparency.	We have amended the wording in the report to include the reason why the manufacturer did not search for non-RCT evidence systematically.

	systematic search was not plausible."		
On p. 28 the ERG also stated: "Non-RCT evidence was not searched for systematically; therefore, other studies may have been missed."	In line with the above box, amend text on p.28 to: "Non-RCT evidence was not searched for systematically; **however the manufacturer clarified that a systematic search was not plausible as non-RCT evidence for ipilimumab 3mg/kg monotherapy was only available from BMS's internal data."**	BMS derived the available non-RCT evidence for ipilimumab 3mg/kg monotherapy from ongoing trials (CA184-332 and CA184-338) or pooled-data analysis (chemotherapy-naïve patients from MDX010-08, CA184-004, CA184-022 and MDX010-20) that were not available in the public domain in any form at the time the review was conducted – hence a systematic search would not be plausible.	We have deleted the words "therefore, other studies may have been missed" and included the reason why the manufacturer did not search for non-RCT evidence systematically. We have also amended page 29 similarly.
On p. 31 the ERG stated: "The review included data from observational studies, despite this study design being listed under 'exclusion criteria' for the review; in addition, there was no systematic search for the included non-RCT evidence."	Remove this statement on p. 31: "~~**The review included data from observational studies, despite this study design being listed under 'exclusion criteria' for the review; in addition, there was no systematic search for the included non-RCT evidence."**~~	Observational studies (as they are non-RCT evidence) were excluded as part of the review criteria from the systematic search for RCT evidence. No systematic search was conducted for the included non-RCT evidence as non-RCT evidence was only required for ipilimumab 3mg/kg monotherapy, derived from BMS's internal data. This point is made on page 28 in our submission (please also see explanations in boxes above).	This statement has been deleted from page 31, as suggested.

Issue 11 Inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On p. 28 the ERG stated: "No details of the study selection process were described in the MS; therefore, it is unclear whether appropriate methods were used to reduce the potential for reviewer bias and error."	Amend text on p.28 to: "**Details of the eligibility criteria applied as part of the study selection process were described** in the MS." We request consideration of removal or amendment of the statement regarding whether	To determine the final set of studies eligible for review, explicit inclusion/exclusion criteria were applied to the literature search results as outlined in our submission, section 6.2.1. Two reviewers independently inspected each reference identified by the literature search and applied study selection criteria. In the event of disagreement between the 2 reviewers, a third reviewer would have independently inspected	This is not a factual inaccuracy. The study selection process (i.e. two independent reviewers) was not reported in the MS.

	appropriate methods were used given the additional information provided here.	the paper and applicability of selection criteria attained by consensus. However, this was not necessary as no disagreements transpired.	

Issue 12 Clarification of significance and difference in patient populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52 the ERG stated: "The results of this pooled analysis suggested that a 10mg/kg dose is better than a 3mg/kg dose in terms of overall survival "	This statement on p.52 should be clarified and amended to: "The results of this pooled analysis suggested that a 10mg/kg dose is better than a 3mg/kg dose in terms of overall survival. **<u>However, the difference is not statistically significant and that the patient populations within the 10mg/kg trials are different to those in the 3mg/kg trials. Therefore these analyses should be viewed with extreme caution.</u>**" Please also amend the ERG scenarios in the cost-effectiveness section which use hazard ratios from the different sets of trial data to also reflect the above amendment.	The current ERG statement on the pooled analysis presented implies that the 3mg/kg and 10mg/kg treatment arms included are directly comparable. As presented in the original analysis for TA268, this is not the case. In general, patients in the ipilimumab 10mg/kg trials had more favourable prognoses. Additionally, as the ERG statement does not discuss the significance of any differences between ipilimumab 3mg/kg and 10mg/kg, it therefore implies that there is a significant difference in treatment effectiveness, which is misleading because the difference is in fact not statistically significant.	This is not a factual inaccuracy. It is clear from Figure 4.6, p 53, that the results of the pooled data analysis comparing OS profiles of ipilimumab 3mg/kg (MDX010-20; CA184-022) and 10mg/kg (CA184-077; CA184-008; CA184-022) for a mixed (both previously treated and untreated) patient population suggests than a 10mg/kg dose has better overall survival than a 3mg/kg dose. The manufacturer reported that there is no statistically significant difference in survival observed between the ipilimumab 3mg/kg and 10mg/kg treatment arms in the whole population analyses. However, the ERG notes that the difference is more prominent at different time points. Over the 70 month time period, the pooled analysis suggests that a 10 mg/kg dose is better than a 3 mg/kg dose in terms of overall survival. Furthermore, the 95% confidence intervals

			barely cross between 15 and 70 months suggesting a statistically significant difference. Therefore, in the ERG's view, there is currently no conclusive evidence that ipilimumab at a dose of 3 mg/kg is as clinically effective as a dose of 10 mg/kg.

Issue 13 Typographical error in summary

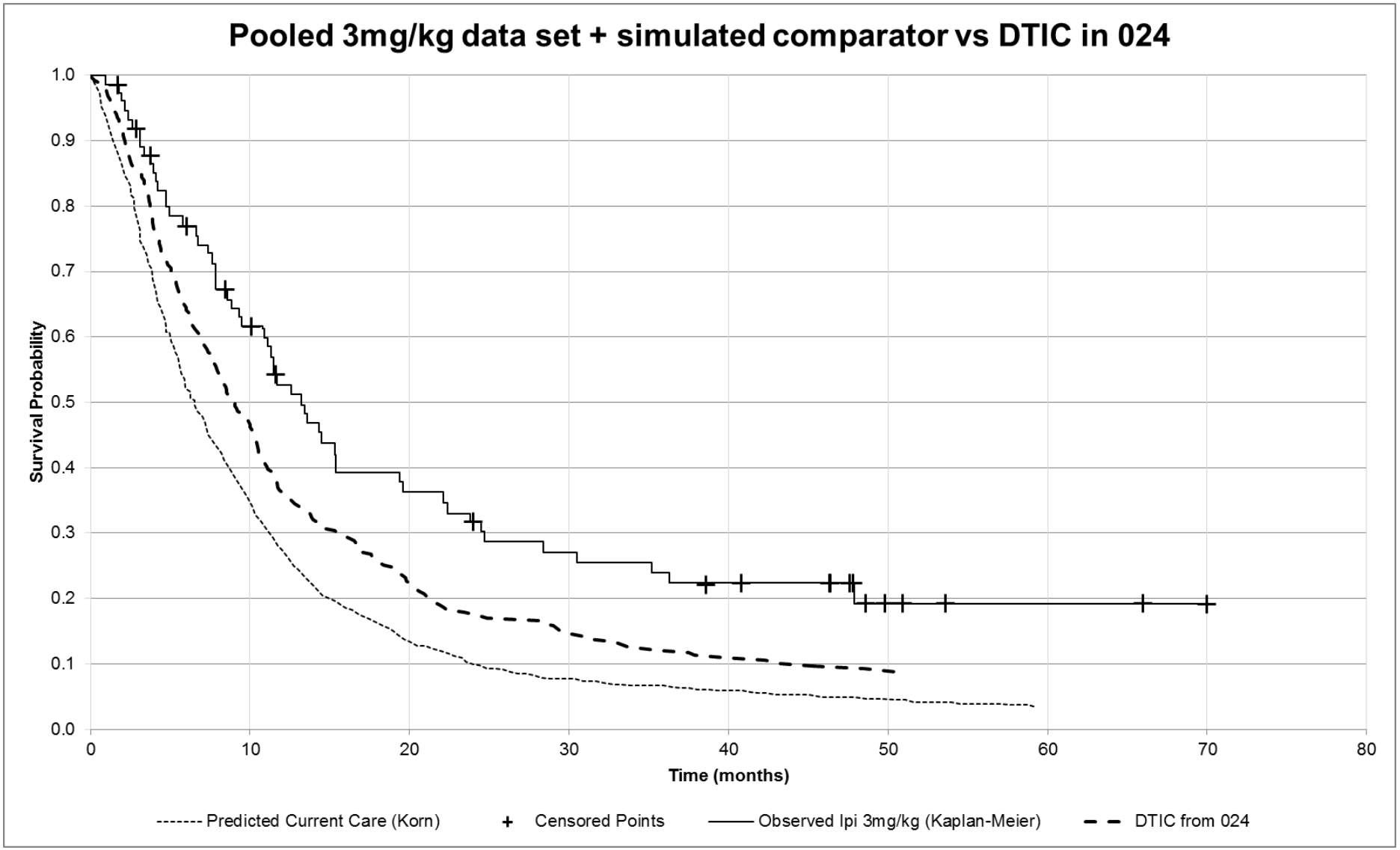
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographical error on page 20: "For the comparison of ipilimumab with DTIC in the mutation-positive or -negative population, the adjustment for 3mg/kg yielded considerably lower QALYs (2.35 QALYs compared with the base-case of 1.56 QALYs) and resulted in a multi-fold ICER of £331,091 per QALY. "	Amend text on p.20 to: "For the comparison of ipilimumab with DTIC in the mutation-positive or -negative population, the adjustment for 3mg/kg yielded considerably lower QALYs (**1.56** QALYs compared with the base-case of **2.35** QALYs) and resulted in a multi-fold ICER of £331,091 per QALY."	In the ERG report 1.56 and 2.35 are the wrong way round. This reduces the clarity of the statement.	The ERG has amended the text to reflect this typo.

Issue 14 Restricted means analysis described as not presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 125 the ERG stated: "The MS states that restricted mean analysis (carried out on patient level data from the 5 year cut of CA184-024) shows a survival gain of 5.7 months over the 5 year trial (MS page 65); however, these	Remove the statement on p.25: "The MS states that restricted mean analysis (carried out on patient level data from the 5 year cut of CA184-024) shows a survival gain of 5.7 months over the 5 year trial (MS page 65)**~~; however, these~~**	The Kaplan-Meier curves, from which we conducted our analysis, were provided to the ERG. Restricted means analysis is a standard statistical analysis (akin to calculating a median) based solely upon Kaplan-Meier data. This is the analysis that was presented. If the ERG require the provision of the code (in	This is not a factual inaccuracy. The data were not presented in the MS to enable us to verify this.

data are not presented elsewhere in the MS, so cannot be verified.”	~~**data are not presented elsewhere in the MS, so cannot be verified**~~.”	R) to calculate the restricted means this can be sent on request for validation that the correct statistical code was used.	

Figure 1: Pooled 3mg/kg data set and simulated comparator versus DTIC in study 024


Pooled 3mg/kg data set + simulated comparator vs DTIC in 024
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
80
Time (months)
Predicted Current Care (Korn)
Censored Points
Observed Ipi 3mg/kg (Kaplan-Meier)
DTIC from 024