NICE/ERG Clarification Questions

Single Technology Appraisal (STA)

Ipilimumab for previously untreated advanced malignant melanoma [ID74]

Received: 7th November 2013
Responded: 21st November 2013

- Please address **PRIORITY REQUESTS** first.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.
- Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Section A Clarification on Effectiveness Data

Question	Response
Further study reports required	
A1. Please provide any additional efficacy, safety and survival data from the two on-going, retrospective, observational studies (CA184-332 and CA184-338) that may be available.	For Studies CA184-332 and CA184-338 yearly follow-up on the full cohort of patients from each study is planned up to and including 2016. The next scheduled analysis is expected to be available end of December 2013/ January 2014 and will include results on overall survival (OS), adverse events, treatment patterns, patterns of care and resource utilisation based on 1 year follow-up on both cohorts.

Question	Response
Ipilimumab trial data	
A2. **PRIORITY REQUEST:** Please provide a comparison of ipilimumab 3mg/kg and ipilimumab 10mg/kg in both the treatment-naïve subgroup population and the whole population (both previously treated and untreated) in all trials. For example, please provide the Kaplan-Meier curve for overall survival (OS) and progression-free survival (PFS) comparing ipilimumab 3mg/kg with 10mg/kg in the CA184-004 and CA184-022 trials for the whole population as presented for TA268. Please refer to Figures 2 and 3 of 'Updated analysis with revised patient access scheme for ipilimumab for previously treated unresectable malignant melanoma', submitted by Bristol Myers Squibb on 17th August 2012 (accessed at http://guidance.nice.org.uk/TAG/208/FAD/RevisedPASBMS/pdf/English).	The hallmark of ipilimumab benefit is long term overall survival (OS) and not progression-free survival (PFS) as reflected in the decision problem. Therefore, comparability of OS profiles of ipilimumab 3mg/kg and 10mg/kg are considered: There are currently only two trials with data available for patients treated with ipilimumab 3mg/kg and 10mg/kg within the same trial: CA184-004 and CA184-022.[1,2] However, as part of the submission file for "ipilimumab in previously treated unresectable malignant melanoma" [TA268], pooled data analysis comparing OS profiles of ipilimumab 3mg/kg (MDX010-20; CA184-022) and 10mg/kg (CA184-007; CA184-008;CA184-022) was presented for a mixed (both previously treated and untreated) patient population. The Kaplan Meier (KM) curve for this pooled data analysis is presented again here as **Figure 1**. Data from CA184-004 was not included in this pooled analysis, therefore the KM curve for OS in the whole population of CA184-004 is presented separately as **Figure 2**. No significant difference in survival was observed between the ipilimumab 3mg/kg and 10mg/kg treatment arms in the whole population analyses. Within the two trials including an ipilimumab 3mg/kg and 10mg/kg treatment arm, CA184-004 had 40 patients that were chemotherapy-naïve (i.e. had not received prior chemotherapy before study entry) and CA184-022 had 13 chemotherapy-naïve patients treated with ipilimumab at either dose. Given the patient numbers available, the data is insufficient to generate meaningful KM curves for the chemotherapy-naïve patient group in either study as discussed in section 6.2.6 of the main submission. However, the individual patient listing with details of PFS and OS, sorted first by prior chemotherapy status (No/Yes) and then by OS time in ascending order are provided as Appendices to this document (Appendix I for CA184-004 and Appendix II for CA184-022). An appropriately powered Phase III study, CA184-169, is ongoing to compare the risk/benefit between 3mg/kg and 10mg/kg. Accrual to the study has completed and outcome reporting is planned for 2016. Please note that there was a discrepancy in patient numbers reported in Table 8 of the main submission where four patients and one patient treated with ipilimumab 10mg/kg in CA184-004 and CA184-022 respectively were excluded from the chemotherapy-naïve population in error. They did in fact receive chemotherapy post discontinuation from the studies due to disease progression.

Question	Response
A3. **PRIORITY REQUEST:** Please provide justification for the assumption that concomitant DTIC therapy with ipilimumab 10mg/kg in the CA184-024 trial has no influence on the clinical efficacy of ipilimumab 10mg/kg monotherapy. Please justify this assumption in light of the evidence presented in Table 16 from the MDX010-08 trial, which shows that ipilimumab 3mg/kg + DTIC has a lower hazard of death than ipilimumab 3mg/kg monotherapy, and in conjunction with the assumption that ipilimumab 3mg/kg is clinically equivalent to ipilimumab 10mg/kg.	Hersh et al. (2011)[3] showed there was no influence of dacarbazine (DTIC) on ipilimumab pharmacokinetics or pharmacodynamics as evidenced by similar plasma concentrations and increase in lymphocyte counts in each treatment arm in study MDX010-08. The phase III study CA184-024[4] was designed to study the combination of ipilimumab 10mg/kg to DTIC (DTIC vs. DTIC + ipilimumab) but did not compare ipilimumab alone vs. DTIC + ipilimumab. Therefore the direct influence of DTIC on the clinical efficacy of ipilimumab cannot be deduced from this study. Although the phase II study MDX010-08[5] did demonstrate that 3mg/kg ipilimumab plus DTIC had a numerically better OS than 3mg/kg ipilimumab alone, this difference was not statistically significant (p=0.32) and the study was not powered for this comparison. In addition, no significant difference in objective response rate or disease control rate between 3mg/kg ipilimumab + DTIC and 3mg/kg ipilimumab monotherapy treatment arms was determined. Furthermore, as noted in the submission document, the median OS observed with ipilimumab 3mg/kg monotherapy from MDX010-08 was directly comparable with that observed with ipilimumab 10mg/kg + DTIC therapy in CA184-024 at 11.4 vs. 11.2 months respectively; suggesting higher dose and combination with DTIC does not influence response. An ongoing phase III study, CA184-169, compares the risk/benefit between 3mg/kg and 10mg/kg ipilimumab. Accrual to the study has completed and outcome reporting is planned for 2016.
A4. **PRIORITY REQUEST:** Please provide justification for the assumption that a fixed induction dose of ipilimumab 3mg/kg every three weeks for 12 weeks is clinically equivalent in terms of OS and PFS to maintenance therapy of ipilimumab given to responders every 12 weeks in the CA184-024 trial.	The hallmark of ipilimumab benefit is long term OS and not PFS. The contribution of maintenance dosing (i.e. every 12 weeks) to OS has not been officially investigated in a clinical trial setting. However, evidence from the OS Kaplan-Meier curve in chemotherapy-naïve and pre-treated patients from MDX010-20 (**Figure 3**) demonstrated a continuing OS plateau beginning at year 3 although no subject received maintenance dosing. The overall efficacy of ipilimumab in the MDX010-20 (OS at 1 year, ipilimumab alone: 46%) is comparable to that seen in the CA184-024 (OS at 1 year, ipilimumab + DTIC: 48%) where maintenance therapy is offered to responding patients. A subset analysis of 1,314 subjects from the pooled analysis of 1,861 ipilimumab-treated patients in 12 studies (across different doses and treatment regimens)[6] similarly showed a continuing plateau in OS from year 3. This subset analysis was based on subjects who received no more than four doses (i.e. only induction therapy) due to protocol design, toxicity, disease progression or investigator's decision.

Question	Response
A5. **PRIORITY REQUEST:** If available, please provide data on the BRAF V600 status of participants in the CA184-024 trial.	In the CA184-024 trial tumours were not assessed for the presence of the BRAF V600 mutation, hence the data are not available. Further, as highlighted in response to A12, ipilimumab's survival benefit is independent of BRAF mutation status.
A6. **PRIORITY REQUEST:** Please provide a breakdown of the reasons for non-completion of the EORTC QLQ-C30 questionnaire by treatment and at each time point (Table 17, page 70).	These data are not captured in the case report form and are therefore not available.
A7. Please provide further information about treatment discontinuations due to study-drug toxicity. How many patients received one dose, two doses, three doses and all four doses of ipilimumab 10mg/kg induction therapy? Were there any dosage adjustments/breaks in treatment due to toxicity?	Table 6.1.1.1 in the CA184-024 Clinical Study Report (CSR)[4] shows the number (%) of patients who received one, two, three and four doses of ipilimumab 10mg/kg. It also shows the number of patients who had breaks in their treatment. This table is presented here as **Table 1**. There were no dose adjustments for any patients in the induction phase. The reasons for omitted doses of ipilimumab in the induction phase of CA184-024 are shown in table 8.4.11 in the CA184-024 CSR.[4] This table is presented here as **Table 2**. Progressive disease was the most common reason for drug discontinuation in each arm of study CA184-024 (60.5% and 77.4% in the ipilimumab + DTIC and DTIC monotherapy arms respectively).
A8. Table 26 on page 94 states that 18.2% ipilimumab plus DTIC patients and 25.5% DTIC patients had an adverse event (AE) with outcome of death (although not related to the study drug). Please provide further details.	The types of adverse event with the outcome of death can be found in Appendix III to this document (Appendix III presents the tables of Appendix 6.3 of Study CA184-024).

Question	Response
A9. **PRIORITY REQUEST:** On page 96 the text states that "Subjects who survived more than 2 years from study entry and who had discontinued ipilimumab experienced few new onset immune-related AEs (or repeat occurrence if the same toxicity was also reported on study) more than 70 days after last dose, most of which were low grade in severity". Please provide more specific data; i.e. how many patients who survived more than 2 years from study entry experienced new onset immune-related AEs more than 70 days after the last dose, what were those adverse effects and what was the grade.	Of the 68 ipilimumab treated patients in study CA184-024 who survived more than 2 years, 10 (14.7%) experienced a new onset irAE more than 70 days after the last dose of study drug was administered.[4] New onset irAEs were low grade (Grade 1-2) in severity in 8 out of the 10 patients. Only two patients experienced Grade 3 or 4 new onset irAEs as detailed below: • Subject CA184024-12-24124 experienced non-serious Grade 3 pruritus (improved to Grade 1) and an SAE of Grade 3 hypophysitis (resolved) ~ 3 months after the second maintenance dose. • Subject CA184024-190-24435 experienced Grades 3 and 4 GGT enzyme increased and Grade 3 ALT and AST, liver enzymes increased ~ 4 months after the third induction dose (AST/ALT increase resolved; GGT increase was continuing at time of reporting [lab values were unavailable]). Full details on these 2 subjects can be found in the Appendix IV to this document (Appendix IV presents the tables of Appendix 6.8 of Study CA184-024).
A10. **PRIORITY REQUEST:** Please provide further data on all adverse effects occurring after the on-study period (rather than just immune-related AEs). Please provide this data for patients who did not survive more than 2 years from study entry, as well as for those who did.	We are unclear as to the question posed but provide in the Appendix to this document a summary of AEs in study CA184-024 occurring after 70 days of last dose for both patients who were alive at 2 years (Appendix V) and patients who were not alive at 2 years (Appendix VI).[4] If this data does not provide information you have requested, please do not hesitate to contact us for further clarification.
BRIM-3 Trial	
A11. Please provide confidence intervals for the median overall survival figures presented in column 3, Table 16, page 69, for the BRIM-3 trial.	**Median OS, months (95% CI)**[7] Vemurafenib: 13.2 (12.0 - 15.0) DTIC: 9.6 (7.9 - 11.8)

Question	Response
Network meta-analysis	
A12. **PRIORITY REQUEST:** The CA184-024 trial included patients irrespective of BRAF V600 mutation status, whilst the BREAK-3 and BRIM-3 trials only included patients that tested positive for the BRAF V600 mutation. Please give your reasoning for including these trials in the same meta-analysis despite this difference in the inclusion criteria.	Given that no quantitative synthesis of comparative efficacy is possible without combining BRAF V600 mutation-positive and BRAF V600 mutation-negative populations, it was considered whether the two populations are comparable and could therefore be included in the same mixed-treatment comparison (MTC). Tumour mutation status does not appear to be a treatment-effect modifier: in CA184-338 (for which comparative survival data of BRAF V600 mutation-positive and -negative were available), no differences in survival function (p=0.23) were observed between BRAF V600 mutation-positive and BRAF V600 mutation-negative patients treated with ipilimumab.[8] (Data on the BRAF V600 status of participants in the CA184-024 trial are not available; see question A5.) This difference in the inclusion criteria of trials included in the MTC is discussed as part of its limitations (page 94 in the main submission).
Search strategy	
A13. The search strategies reported for the clinical evidence searches show that the results have been limited to randomised controlled trials and systematic reviews. It would be helpful to know which study design search filters for RCTs and systematic reviews have been used for MEDLINE, EMBASE and CINAHL? (10.2 Appendix 2, pages 243-248).	The search filters (RCTs, systematic reviews and economic studies) applied in the searches were obtained and adapted from the SIGN search filter resource and translated across the database searches.[9]
A14. **PRIORITY QUESTION:** Given the search strategy study design limits, how was the non-RCT evidence (listed in Table 9, page 43) identified? Did you specifically search for non-RCT evidence? If so, please provide details of the relevant search strategies.	Non-RCT evidence was not searched for systematically because direct RCT evidence was identified for comparator therapies. Therefore, non-RCT evidence was only required for ipilimumab 3mg/kg monotherapy. Non-RCT evidence for ipilimumab 3mg/kg monotherapy is derived 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 are not currently available in full, in the public domain.

Question	Response
A15. In section 10.2.5, page 248, under details of additional searches, it states that additional searches were conducted in clinicaltrials.gov. Is the search strategy used for clinicaltrials.gov available?	In clinicaltrials.gov the following numbers of studies were found using the below search strategy: 135 studies found for: ipilimumab or Yervoy 135 studies found for: MDX-010 5 studies found for: MDX-101 129 studies found for: biocarbazine | melanoma 129 studies found for: DTIC or deticene | melanoma No studies found for: dtie or dtic | melanoma No studies found for: icdmt or icdt | melanoma 129 studies found for: wr-139007 | melanoma 4 studies found for: imidazole carboxamide | melanoma 14 studies found for: dabrafenib | melanoma 45 studies found for: vemurafenib or zelboraf | melanoma 83 studies found for: b-raf of braf | melanoma
A16. In section 10.2.5, page 248, under details of additional searches, only 3 conference proceedings are listed as being searched, however under the description of the searches for clinical evidence on page 35, there are 5 sources listed. Please could the sources searched be clarified?	Abstracts from 5 conference proceedings were searched. However, for the conference proceedings of the European Association of Dermato-Oncologists (EADO Congress) and Perspectives in Melanoma (PiM), abstracts are only made available to meeting delegates. Therefore, these could not be accessed or subsequently searched.
A17. Please justify the inclusion of dabrafenib in the eligibility criteria used in the clinical search strategy (Table 5, page 37), when it is not one of the comparators listed in the NICE scope and decision problem (Table 4, page 32).	Dabrafenib was not listed in the NICE scope and decision problem. However, dabrafenib was included in the list of comparator therapies alongside currently approved therapies (DTIC and vemurafenib) because NICE guidance for its use in BRAF V600 mutation positive, unresectable, advanced or metastatic melanoma is currently in development [ID605]. Therefore, it was considered relevant in context of the potentially evolving decision problem.

Section B Clarification on Cost-effectiveness Data

Question	Response
Economic model	
B1. **PRIORITY REQUEST:** Please explain the rationale for modelling the cost-effectiveness of ipilimumab for previously untreated melanoma using a treatment sequencing approach.	It is recognised that cancer modelling is often limited to three-state Markov models (progression-free, post-progression and death). It has to be noted that this simple model structure assumes that changes in drug treatment, medical management and utilities are causally linked to progression of the disease. The associated costs and utilities are further assumed to be constant within each health state (PFS or progressive disease). When modelling the cost-effectiveness of ipilimumab, many of these key assumptions do not apply: • The cost of ipilimumab is not directly linked to the progression status of melanoma because ipilimumab is not a continuously-dosed treatment (section 7.5.5 in main submission). • Drug costs in progressive disease are highly dependent upon the type and line of treatment being received. Patient time on each line of treatment is the most meaningful outcome for determining the costs of treatment (which are noted to represent between 56% and 71% of total costs in the model base case) (section 7.7.5 in main submission). • When data from the trial were analysed, utilities were shown not to depend on progression status and instead were best quantified using time to death and treatment received (section 7.4.3 in main submission). Consequently, a model structure dependent on line of treatment (i.e. treatment sequences), rather than solely on progression status, was considered most appropriate.
Additionally: a) Please clarify whether the five-year survival curves for ipilimumab and DTIC in the CA184-024 trial already take account of progression to next line therapies.	The OS data of patients in the CA184-024 trial who are still alive include progression to subsequent lines of therapy. However, as no patients (on either study arm) received either ipilimumab or vemurafenib as a subsequent therapy, the survival data from CA184-024 do not include these two active therapies involved in the submission. Given that all treatments (other than ipilimumab and vemurafenib) have been shown to have equal efficacy (i.e. best supportive care [BSC] efficacy) within the Korn meta-analysis, the efficacy of BSC only is taken into account in the OS curves derived from the CA184-024 clinical trial.

Question	Response
b) Please present a graphical comparison of the five-year survival curves for ipilimumab and DTIC from the CA184-024 trial and the five-year survival estimates for ipilimumab derived from the economic model.	The five-year survival curves for ipilimumab and DTIC from the CA184-024 and the economic model are presented in **Figure 4**. Given the modelled curve consisted of Kaplan-Meier data up to 2 years, and a fitted parametric curve up to 5 years (section 7.3.2 in the main submission), the Kaplan-Meier and modelled curves are identical for the first 2 years.
c) Please provide the rationale for not using a three-stage model structure for progression-free survival, post-progression survival and death as used in the previous appraisal of ipilimumab for second line treatment of advanced stage melanoma.	The model structure adopted is consistent with the previous model of second-line ipilimumab. The only difference in the first-line model is that progressive disease i.e. post progression survival is split into two health states (second and third line treatment). As the current decision problem is for first-line treatment of melanoma (not second line), the model required to assess this decision problem needed the ability to look at more than one treatment in sequence. This is because there is now more than one active treatment within this area (i.e. ipilimumab and vemurafenib) and current NICE recommendations allow these treatments to be used in sequence (please also see response to B1).
d) To help support internal/external validation of the current approach, please consider presenting the cost-effectiveness results for ipilimumab using a three-stage model without including sequencing of treatment, that is, the model previously used in Technology Appraisal 268, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'.	As explained for B1c, the model used in the appraisal of second-line ipilimumab adopted a similar structure and this first-line submission is consistent with that structure, which had been scrutinised and accepted by the ERG before. In the submission, an analysis was provided that shows only the impacts of ipilimumab versus the relevant comparators at first line (i.e. second line is modelled as BSC). In the economic model this analysis can be replicated by setting cells N44, N46 and N48 in the "Controls" sheet to "BSC". Results of this analysis can be found in Table 79 in the main submission and are presented in **Table 3**. Ipilimumab remained cost-effective compared to both DTIC and vemurafenib. Note: The above described analysis is not identical to that in TA268. Quality of life is still modelled using a 'time to death' approach; this analysis was also presented in TA268. However, the evidence (which was consistent for both first- and second-line trials) now overwhelmingly supports an absence of link between progression status and quality of life. Replicating the full TA268 analysis in this respect would therefore not reflect the current knowledge base.

Question	Response
B2. Please provide justification for the choice of modelled treatment pathways of care as presented in Figure 26. Please explain why all possible treatment permutations were not considered. For example, DTIC first line followed by vemurafenib second line is not considered as an option in the model but it is presented as an option in the current clinical care pathway shown in Figure 2.	As illustrated in Figure 26 in the submission, DTIC is considered as a first-line comparator only before second-line ipilimumab. Prior to the recommendation of vemurafenib in TA269, BRAF mutation-positive patients may have received first-line DTIC. With the recent availability of vemurafenib, these same patients could have received vemurafenib as a second line option. In the current environment however, DTIC followed by second-line vemurafenib was not considered a relevant comparator as expert opinion determined that this does not reflect clinical practice for treatment-naïve BRAF mutant-positive patients. There is the option of first-line DTIC before second-line ipilimumab (in line with TA268) but with access to first-line ipilimumab, treatment naive patients would be unlikely to receive DTIC first-line. Patients treated with ipilimumab first-line might still be expected to receive second-line vemurafenib, if they were eligible.
B3. **PRIORITY QUESTION:** For the comparison of ipilimumab with vemurafenib in BRAF V600 mutation-positive patients, please explain why the hazard ratio for OS determined using the MTC analysis (Figure 18) was not used in the modelling. The HR of 1.16 suggests that ipilimumab + DTIC therapy is less effective than vemurafenib but the extrapolation using independent arms of the CA184-024 (ipilimumab + DTIC) and BRIM-3 (vemurafenib) trials in the modelling shows higher QALYs with ipilimumab compared with vemurafenib.	The MTC data were not used in the economic model as the inspection of the Nelson-Aalen plots revealed that the hazards are not constant (section 7.3.2 in the main submission). This means that a single hazard ratio cannot be applied accurately to the entire life expectancy of patients. The composite 3-part curves constructed for each treatment attempted to represent the OS profiles for the interventions and comparators, adopting the hazards from registry data (from 5 years onwards) where the long-term outcomes were uncertain. The approach adopted is consistent with the selection methods recommended by the NICE DSU guidance.[10] The approach is also consistent with the previous appraisals of second-line ipilimumab and vemurafenib, both of which received positive recommendations from NICE (TA268, TA269).

Question	Response
Additionally: a) Please provide an explanation for this difference and the rationale for using independent arms of two different clinical trials.	The MTC results highlight the inappropriateness of assuming a similar treatment effect for ipilimumab and vemurafenib. The mechanism of action of ipilimumab is fundamentally different to those of vemurafenib and DTIC, and differences in treatment effects are observed. • Patients receiving ipilimumab take longer to respond to therapy (therefore taking longer for OS benefit to become clear) as ipilimumab stimulates the body's own immune system to fight cancer cells. • Vemurafenib has a faster mechanism of action compared with ipilimumab leading to early gains in OS. However, responses to vemurafenib may not be durable and the majority of people who receive it develop resistance and tumour relapse leading to lower OS in the long-term.[11] • This is not the case for ipilimumab where the majority of patients who demonstrate long-term survival in the clinical trials at 2 years have continued to survive until the end of follow-up (5-11 years over the entire data package). The patient populations in the two trials do not appear to differ radically in baseline characteristics, with two notable exceptions: • BRAF status – which has been shown not to affect efficacy of treatment with ipilimumab.[8, 12] • Treatment history – which has also been shown not to affect efficacy of treatment with ipilimumab.[13] Additionally the outcomes of patients receiving the comparator therapy in each trial are similar. A comparison of the DTIC arms concluded that outcomes were sufficiently similar to use the raw data without adjustment (Figure 35 in the main submission, which presents the survival of patients receiving DTIC for the earliest analysis presented in TA269 i.e. not including crossover patients). Given the limitations of the MTC, no preferable alternative was available.

Question	Response
b) Please estimate the implied HR for OS for the comparison of ipilimumab versus vemurafenib in the modelled extrapolation that uses independent arms by assuming no difference in efficacy for DTIC in the CA184-024 and BRIM-3 trials.	This is not possible as there is no common HR applied within the model over all time periods (due to the issues discussed in B3a, the survival profile of patients receiving ipilimumab is fundamentally different to that of patients receiving vemurafenib or DTIC). The following implied hazard ratios (ipilimumab versus vemurafenib) measured yearly for 5 years are therefore presented: • 1 year 1.256 i.e. in favour of vemurafenib. Note: This HR is higher than the MTC result (1.16). • 2 years 0.938 i.e. in favour of ipilimumab as patients show response to treatment and patients previously responding to vemurafenib develop resistance. • 3 years 0.883 • 4 years 0.877 • 5 years 0.874 – after which point equal efficacy is assumed as both treatments use information from registry data.
B4. Please clarify how progression on ipilimumab before the end of the 3 month treatment induction phase is modelled. Is the PFS curve for ipilimumab only used after the first 12 weeks?	Patients on ipilimumab were allowed to progress to second-line treatment during the induction period within the model. In clinical practice, however, many patients would not start another therapy until after the induction period; meaning that the model may overestimate the number of patients moving on to second-line treatment after ipilimumab. The proportion of patients receiving each dose of ipilimumab was calculated based upon the number of patients within the trial who received each dose out of those who were eligible to receive the dose at the time it was due (i.e. progression-free and alive). The model is relatively insensitive to assumptions regarding the first 12 weeks of treatment. For example if the alternative assumption is made i.e. no progression in the first 12 weeks (by setting 100% of patients who have not died and are not receiving palliative care to remain on ipilimumab for 12 cycles in the patient flow sheet) the ICER rises slightly to £35,040 compared to DTIC using CA184-024 data (£31,559 base case), £32,332 using pooled chemotherapy-naïve data (£28,465 base case) and remains dominant compared to vemurafenib using both datasets.
Survival analysis	
B5. Please provide the Kaplan-Meier curve for PFS of patients enrolled in the MDX010-08 trial for ipilimumab 3mg/kg and ipilimumab 3mg/kg + DTIC as presented in Figure 12 for overall survival.	The Kaplan-Meier curve for PFS of patients enrolled in the MDX010-08 trial for ipilimumab 3mg/kg and ipilimumab 3mg/kg + DTIC is provided as **Figure 5**.[5]

Question	Response
B6. Please provide the hazard ratio with 95% confidence interval for PFS in the CA184-024, MDX010-08, and BRIM-3 trials as presented in Table 16 for overall survival.	**Comparison (trial): HR (CI 95%)** • Ipilimumab 10mg/kg + DTIC vs. DTIC (CA184-024): 0.76 (0.63 - 0.93)[4] • Vemurafenib vs. DTIC (BRIM-3): 0.26 (0.20 - 0.33)[14] • Ipilimumab 3mg/kg + DTIC vs. Ipilimumab 3mg/kg (MDX010-08): 0.642 (0.383 - 1.075) Note: Study MDX010-08 was not designed for any formal testing/comparison between treatment arms and therefore must be interpreted with caution.
B7. **PRIORITY QUESTION:** Please provide justification for the method used to estimate OS and PFS on second-line treatment.	The approach was selected as there was information on the duration of PFS and OS for ipilimumab available from the second-line submission. The hazards for OS and PFS in the previous submission were time dependent, so the hazards experienced by patients would differ based on when the patient progressed to second-line treatment. This is very difficult to implement in a cohort model; 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 of first-line curves. This approach is considered appropriate given proportional hazards are observed between ipilimumab at first and second line. Furthermore, no published information is available for vemurafenib efficacy used as second line therapy. Without the hazard ratio of OS calculated between ipilimumab at first- and second-line, there would be no information base upon which to make assumptions regarding the estimates of the efficacy of vemurafenib at second-line. The assumption of equal loss of efficacy between first- and second-line for vemurafenib compared to ipilimumab appears reasonable given the lack of alternative data **Figure 6** shows the ipilimumab Kaplan–Meier curves for first- and second-line.
Additionally: a) Please explain the rationale for estimating second line survival curves by adjusting the first line survival curves downwards by an apparently arbitrary hazard ratio.	The hazard ratio was produced (as shown in worksheet “2nd Line OS HRs” in the model) by calculating the hazard ratio required to set the first-line mean survival duration equal to the mean survival presented for ipilimumab at second-line in TA268. This was done using the WhatIf analysis optimiser in MS Excel®. Given that proportional hazards exist between first- and second-line ipilimumab, the application of a hazard ratio (based upon the accepted second-line model) is considered appropriate. This was necessary to avoid the additional complexity of modelling patients individually based on their time of progression to second-line treatment.

Question	Response
b) Please provide the justification for not using the OS and PFS curves from TA268 to directly model second line therapy rather than indirectly by applying an adjustment to first line curves based on second line life years.	The OS and PFS curves from the second-line submission cannot be directly applied to cohort of patients receiving first-line treatment. The baseline of the second-line curves is the time at which patients start second-line treatment. In the first-line model, this is distributed across the model, as patient's progress from first-line treatment on to second-line. Therefore, at any given time in the model, patients on second-line should experience different risks of death and progression, depending on when they progressed. This was accounted for by estimating second-line outcomes based on the duration of second-line OS and PFS while allowing the hazards of death and progression to vary over time. Given that proportional hazards exist between first- and second-line ipilimumab for OS and PFS, the application of a hazard ratio (based upon the accepted 2nd line model) is considered appropriate.
B8. Please provide the hazard ratios (with 95% confidence intervals) and the Kaplan-Meier curves of OS and PFS for the metastasis stage M1c subgroup population of the CA184-024, MDX010-08, and BRIM-3 trials.	Kaplan-Meier curves of OS and PFS for the metastasis stage M1c subgroup population of the CA184-024 trial are presented below in **Figure 7** and **Figure 8**.[4] Kaplan-Meier curves of OS and PFS for M1c subgroup population are not available for the MDX010-08 or the BRIM-3 trial.
B9. Please provide additional justification for the choice of cut-off point of two years for Kaplan-Meier data from the CA184-024 trial before fitting a parametric curve to the trial data up to five years.	The cut-off time of 2 years for OS curves was determined by visual inspection of Nelson–Aalen plots, which present the change in hazards over time. These are presented in Figures 30 and 31 of the submission (page 124).
Additionally: a) Please explain the choice of cut-off point from a clinical point of view. Why would the hazard be expected to change at two years?	In addition to the rationale regarding statistical fit (above), the data accumulated from several ipilimumab trials shows that patients surviving up to 2 years represent a population of individuals that are likely to maintain response and experience long-term benefit. Survival analysis up to 2 years shows a steady decrease in patient numbers and although patients on ipilimumab still derive benefit as evidenced by the separation of the Kaplan-Meier curves at an early stage and the continuation of this separation, a plateau in the curve is achieved at 2 years. The Maio data shows the survival rates out to 5 years and the values are relatively stable from 2 years onwards.[15] The Haanen poster looks specifically at a survivor population and shows that the actual number surviving beyond 2 and 3 years.[16]

Question	Response
b) Please present cost-effectiveness results using alternative cut-off points to show the sensitivity of the results to changes in the switch point.	Results for alternative cut-off points at 1.5 and 2.5 years can be found in Appendix VII. The ICER is relatively insensitive to the choice of cut-off point: ICER vs. DTIC in the mutation positive population of £32,240, £31,559, £31,240 for cut-off points of 1.5 years, 2 years and 2.5 years and dominant vs. vemurafenib for all cut-off points using CA184-024 data and ICER vs. DTIC in the mutation positive population of £29,993, £28,465, £29,201 for cut-off points of 1.5 years, 2 years and 2.5 years and dominant vs. vemurafenib for all cut-off points using the pooled chemotherapy-naïve data.
B10. Please clarify that there are no relevant UK sources of registry data for long-term survival of advanced melanoma.	The lack of UK registry data was acknowledged in the committee meetings for TA268. For the appraisal of vemurafenib (TA269), the ERG recommended the use of the AJCC registry data, giving the following justification: "*In considering the long-term prognosis of patients with malignant melanoma, it is important to use the most complete and detailed registry analysis available.*"
Quality of life	
B11. Please clarify the reasons for assuming that health-related quality of life with vemurafenib is identical to ipilimumab at each time point before death (Table 44).	Given the comparability of the number of serious adverse events (SAEs) for patients treated with ipilimumab and vemurafenib, it was assumed that the quality of life of ipilimumab- and vemurafenib-treated patients were not significantly different. Making an assumption was further necessary as no data were available for vemurafenib. This assumption is considered as conservative for two reasons: • Vemurafenib is continuously dosed whereas ipilimumab is not. Utility decrements are applied continuously in the model meaning that the reduction in quality of life due to AEs with ipilimumab is likely to be overestimated. • The long-term impact of AEs is likely to be greater with vemurafenib, as the treatment is continuously dosed for responding patients and adverse events will continue to develop (e.g. long-term skin disorders (photosensitivity)) whereas ipilimumab is given short-term (average length of induction ~12 weeks) and the majority of ipilimumab AEs occur during the induction period.

Question	Response
Adverse events	
B12. Please confirm that the adverse event risk associated with ipilimumab for endocrine disorders is 0.4% (Table 39). The clinical study report for the CA184-024 trial suggests that this value is 2.8%.	The 0.4% figure used is the drug-related AE incidence from table S.6.11 (page 531) of the CA184-024 trial CSR. The 2.8% figure reported in table 8.5.2A (page 156) is referenced to the immune-related AE incidence reported in table S.6.41 (page 596).[4] These two measures use different criteria, and the figure most relevant to the intervention was used in the economic evaluation.
Search strategy	
B13. In section 10.10.4, page 259, an economics filter from the CRD website is mentioned. CRD has developed a search strategy for identifying economic studies however this does not appear to be the one that is used in the strategies presented. Please could the source of the economics filter used in the search strategies for MEDLINE, EMBASE and CINAHL be identified?	The search filters (RCTs, systematic reviews and economic studies) applied in the searches were obtained and adapted from the SIGN search filter resource (http://www.sign.ac.uk/methodology/filters.html) and translated across the database searches.[9]
B14. The search strategies listed in section 10.13, pages 268-273, appear to be those relating to HRQL rather than strategies designed to capture cost studies or resource use studies. Have the correct search strategies been reported for this section?	No, the HRQL strategies were duplicated in error. Cost and Resource use search strategies provided in Appendix VIII.
B15. NHS HEED is reported as a database that was searched on pages 110, 151, and 161. Should this be NHSEED or HEED, or both, that were searched?	NHS EED was searched.

Section C Textual Clarifications and Additional Points

Question	Response
C1. On page 22, the number of patients in England and Wales who are expected to be diagnosed with advanced melanoma (stage IIIc-IV) and potentially eligible for treatment in 2014 does not take into account the 3.5% increase per year and is inconsistent with Table 81 on page 210; please clarify that the figure 1,190 reported on page 22 should read 1,319, consistent with Table 81.	The figure on page 22 for the number of patients diagnosed in England and Wales should read 1,319 as suggested.
C2. **PRIORITY QUESTION:** The NICE remit was "To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for previously untreated unresectable stage III or IV malignant melanoma". However, the estimated number of patients eligible for treatment with ipilimumab described in section 8.1 (page 210) is calculated using the proportion of patients with stage IIIC or IV disease. Please clarify whether ipilimumab is also intended for use in patients with stage IIIA and IIIB disease, and, if so, estimate the number of patients eligible for treatment including these patients.	Ipilimumab is licensed for the treatment of advanced (unresectable or metastatic) melanoma in adults and therefore is intended for use in patients with stage IIIC and IV disease. Patients with resectable stage IIIA and IIIB disease are assumed to be treated with surgery and associated radiotherapy rather than systemic therapy. I.e. patients with stage IIIA and IIIB disease are not expected to be treated with ipilimumab.
C3. In Figure 22, page 91, the number of subjects at risk is missing from the figure for the pooled dataset. Please provide these data.	The number of subjects at risk is provided in **Figure 9** below.
C4. **PRIORITY QUESTION:** Please define "duration of melanoma" in Table 12, page 50; does this relate to the time since diagnosis of the primary melanoma, or time since diagnosis of metastatic disease? In addition, on page 86, it states that "Duration of melanoma was higher in the pooled chemotherapy-naïve data set, presumably due to the fact that these patients may not be newly diagnosed." Please define what is meant by "newly diagnosed".	Duration of melanoma is defined as the time from initial pathological diagnosis of malignant melanoma to first dose of study therapy. In this context "newly diagnosed" represents patients that have not received any prior therapy for malignant melanoma. In the case of the pooled chemotherapy-naïve data set, patients may have received immunotherapy, melanoma vaccine or anti-CTLA-4 antibody therapy for melanoma ≥5 years prior to study enrolment.
C5. The text at the bottom of page 95 appears to contradict that presented in Table 28, page 96. For example, in the text it states that the median time to resolution across all classes of immune-related AEs ranged from 1.4 to 4.7 weeks, however, in Table 28, the median time to resolution ranges from 2.0 to 4.7 weeks.	Table 28 corrupted in formatting: correct details of duration and resolution of all immune-related AEs presented in **Table 4**.[4]

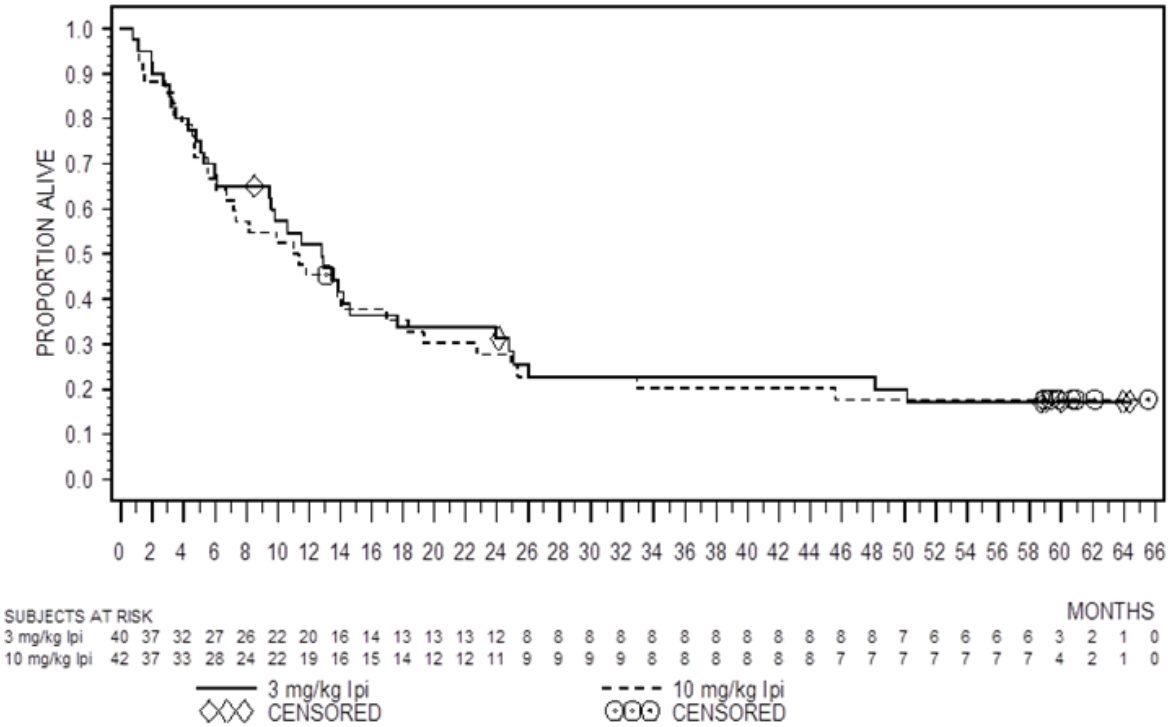
Question	Response
C6. The fourth paragraph of page 101 states that “Secondary analyses of 5-year data show an extended improvement in median OS of 24.5 weeks for ipilimumab 10mg/kg + DTIC therapy vs. DTIC monotherapy”. Should this read “Secondary analyses of 5-year data show an extended improvement in MEAN OS of 24.5 weeks for ipilimumab 10mg/kg + DTIC therapy vs. DTIC monotherapy”, consistent with the summary on page 100, and the fourth paragraph on page 65 (mean survival of 91.1 weeks compared with 66.6 weeks)?	The sentence highlighted should read “mean” (not median) as suggested.

Tables and Figures

Figure 1: Overall survival profiles for ipilimumab 3mg/kg and 10 mg/kg; pooled dataset (CA184-022; MDX010-20; CA184-007; CA184-008) Kaplan Meier curve*

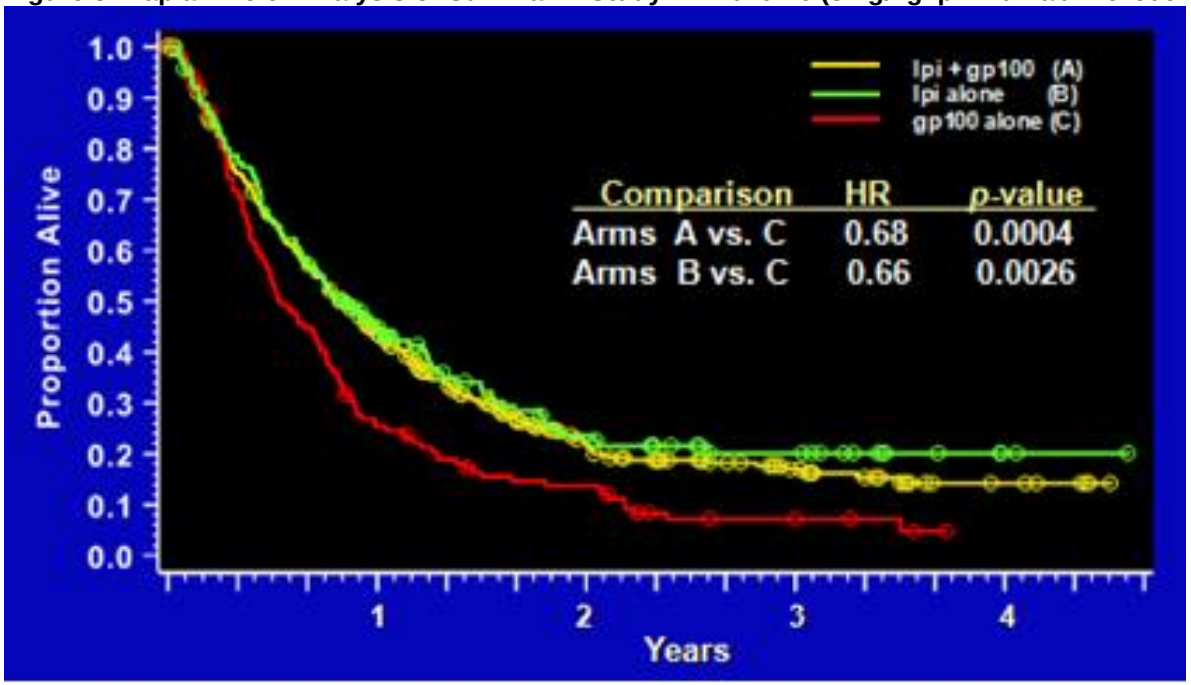
*95% confidence intervals denoted by dashed lines

Figure 2: Overall survival Kaplan Meier curve from CA184-004; total population analysis



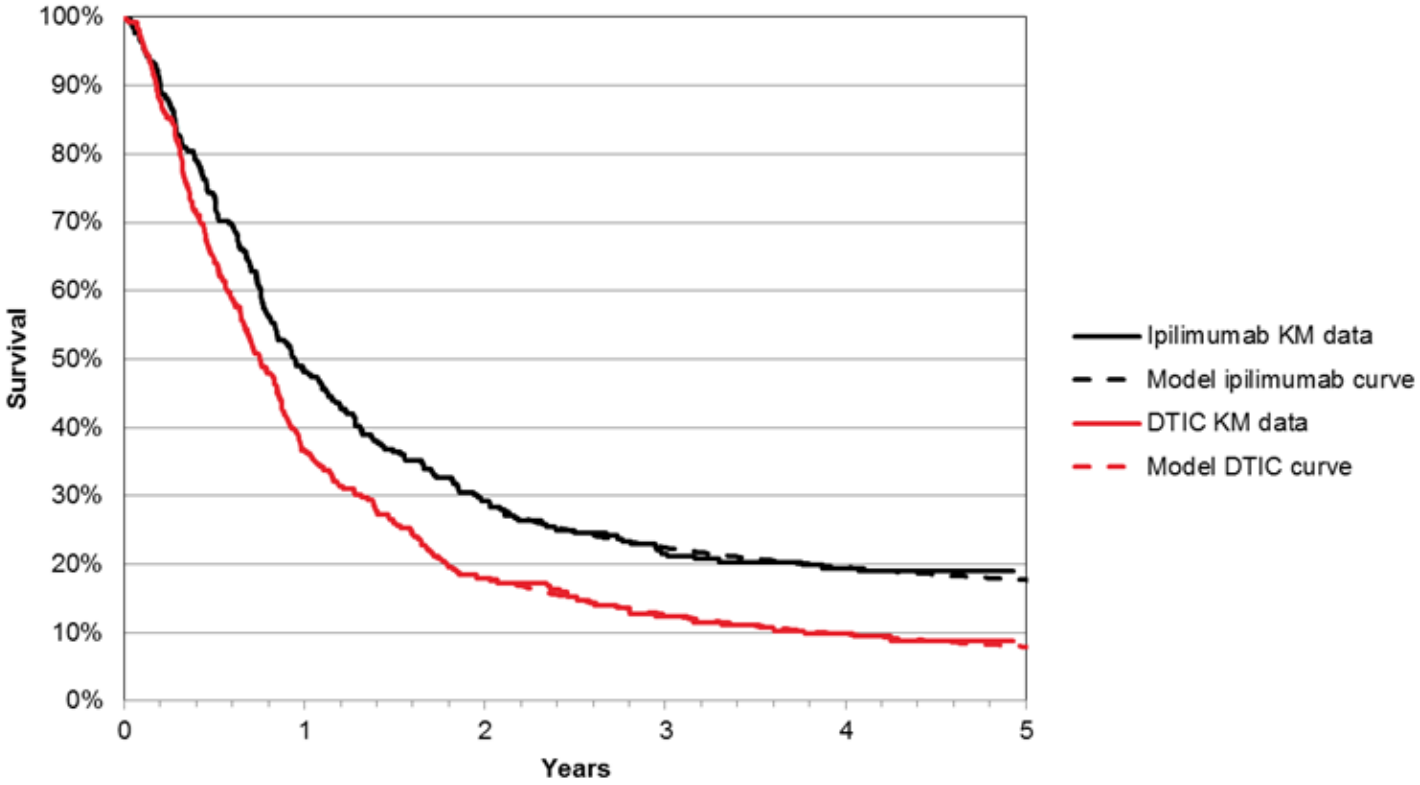
GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
3 mg/kg Ipi	32/40	12.8 (9.49 - 17.6)
10 mg/kg Ipi	34/42	11.2 (6.08 - 16.9)

Figure 3: Kaplan Meier Analysis of Survival in Study MDX010-20 (3mg/kg ipilimumab without maintenance therapy)



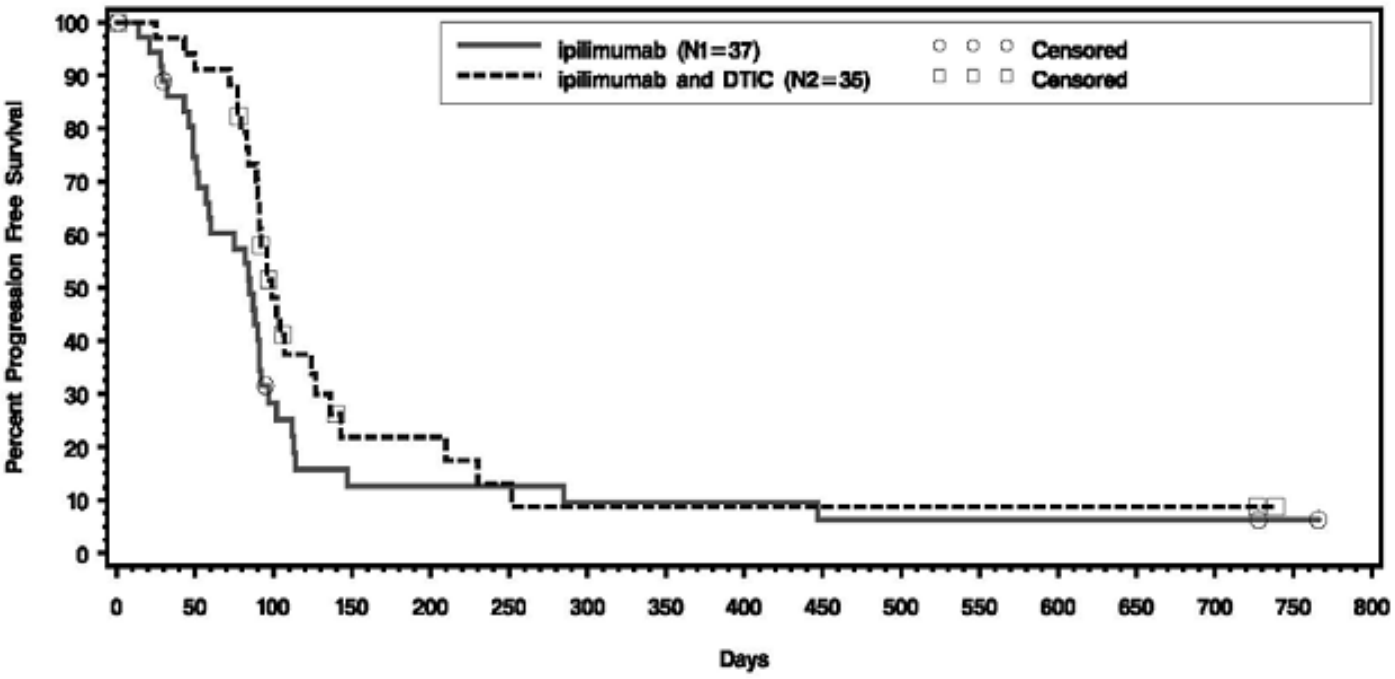
HR, Hazard ratio; Ipi, Ipilimumab 3mg/kg.

Figure 4: Kaplan–Meier plot vs. fitted curves of 5-year time horizon



DTIC, Dacarbazine; KM, Kaplan–Meier.

Figure 5: Kaplan-Meier curve for PFS of patients enrolled in the MDX010-08 trial for ipilimumab 3mg/kg and ipilimumab 3mg/kg + DTIC[5]



DTIC, Dacarbazine; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 6: Kaplan-Meier curves for first and second line

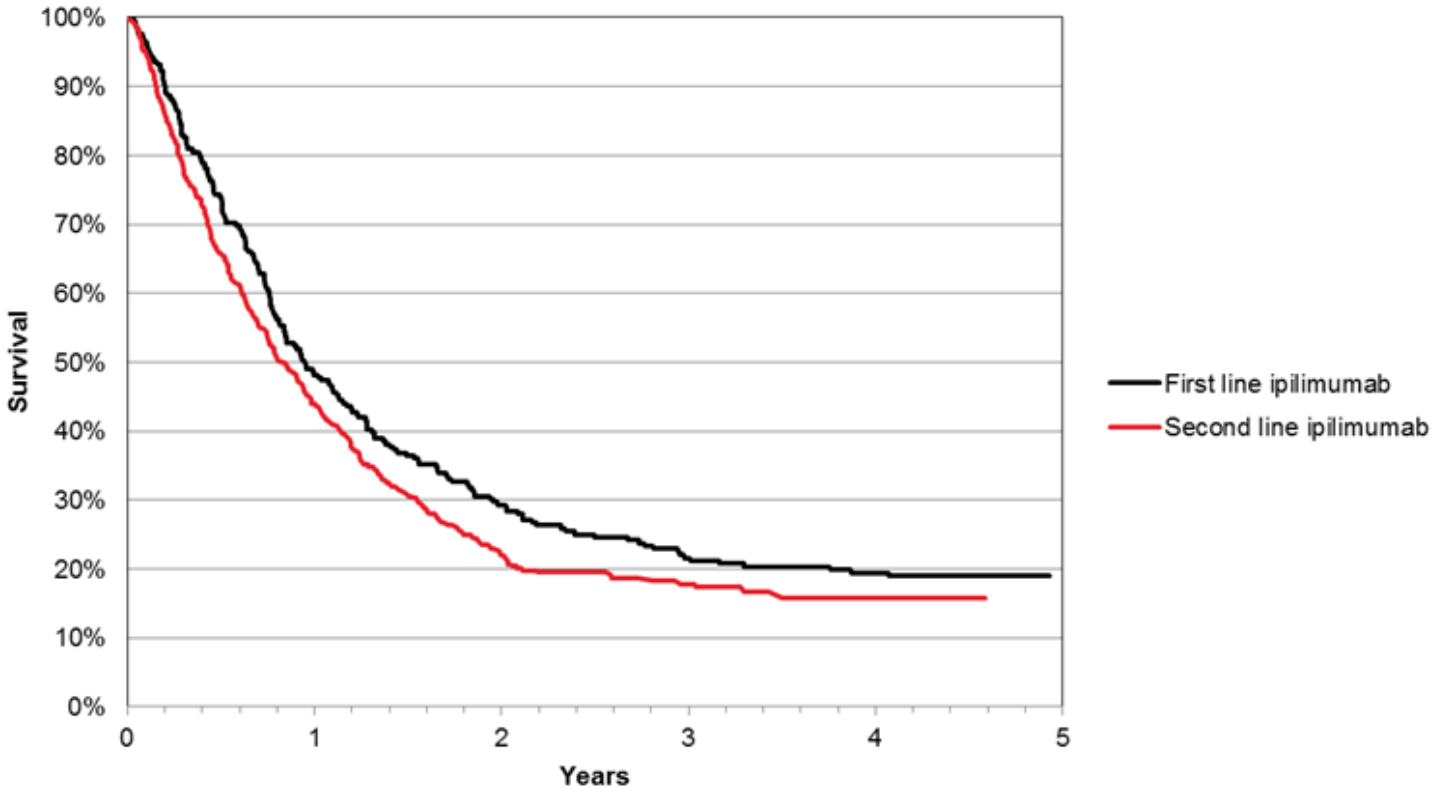
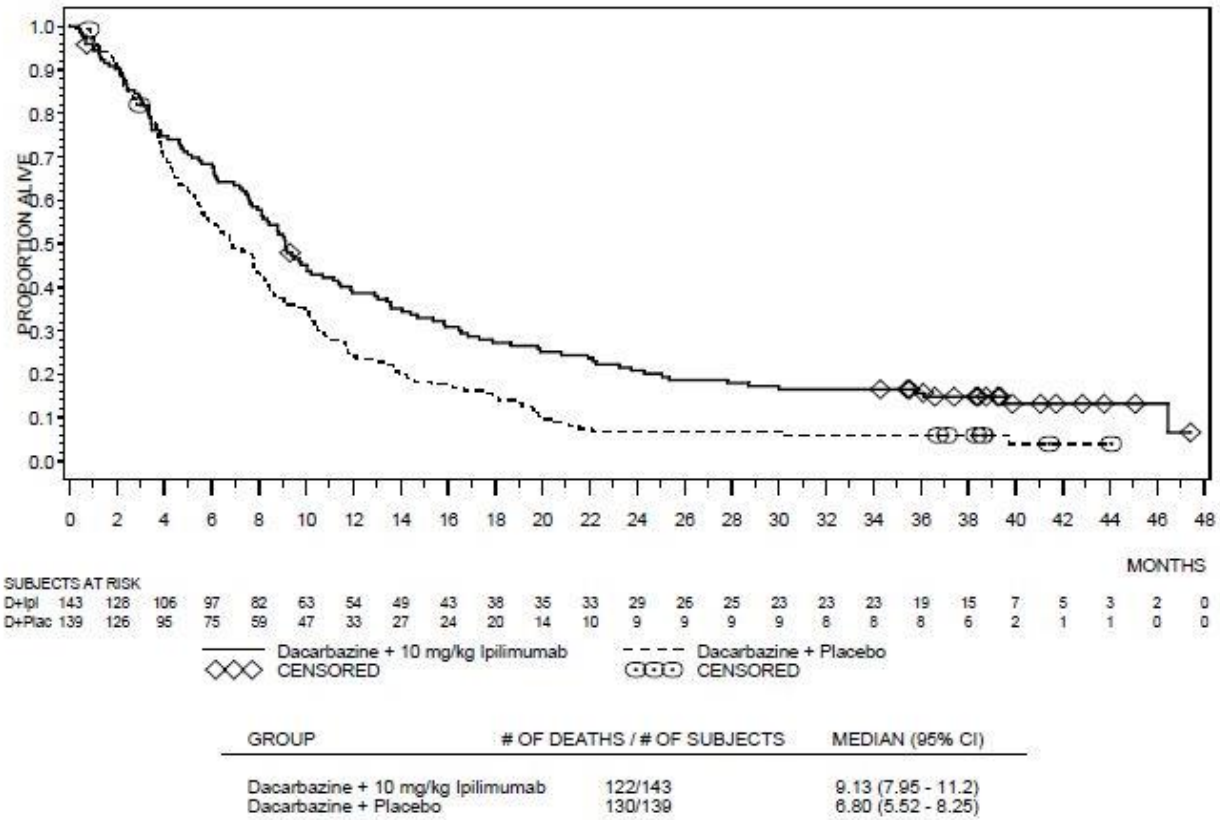


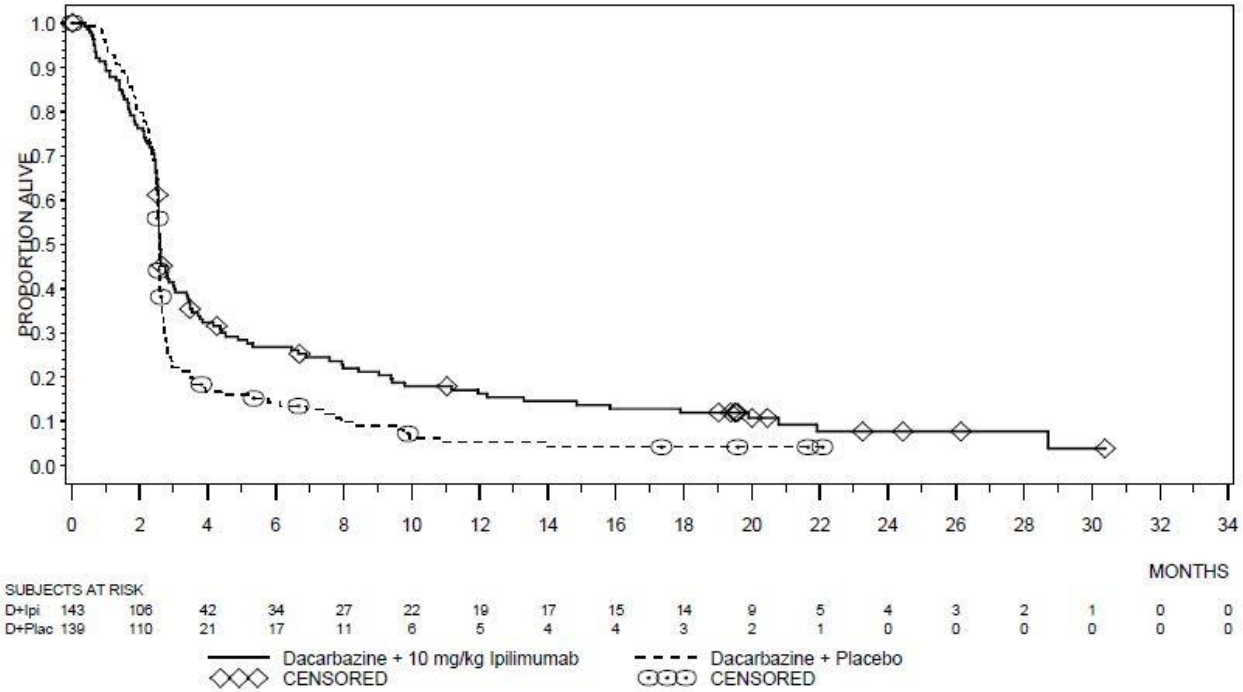
Figure 7: Kaplan-Meier plot of OS for baseline M-stage = M1c patients enrolled in CA184-024[4]



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Dacarbazine + 10 mg/kg Ipilimumab	122/143	9.13 (7.95 - 11.2)
Dacarbazine + Placebo	130/139	6.80 (5.52 - 8.25)

OS, overall survival.

Figure 8: Kaplan-Meier plot of PFS for baseline M-stage = M1c patients enrolled in CA184-024[4]



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Dacarbazine + 10 mg/kg Ipilimumab	122/143	2.60 (2.56 - 2.86)
Dacarbazine + Placebo	127/139	2.56 (2.53 - 2.60)

PFS, progression-free survival.

Figure 9: Predicted improved survival with ipilimumab 3mg/kg monotherapy in untreated patients: pooled dataset[17]

[redacted]

Table 1: Number of doses of ipilimumab or placebo in the induction phase of CA184-024[4]

		NUMBER OF SUBJECTS (%)	
		10 MG/KG IPILIMUMAB + DACARBAZINE N = 247	PLACEBO + DACARBAZINE N = 251
Number of Doses of Ipilimumab per Subject in the Induction Phase			
	Number of Subjects	247	1
	Mean (SD)	2.9 (1.04)	1.0 (0.0)
	Median	3.0	1.0
	Min - Max	1 - 4	1 - 1
	1	32 (13.0)	1 (0.4)
	2	45 (18.2)	0
	3	78 (31.6)	0
	4	92 (37.2)	0
Number of Doses of Placebo per Subject in the Induction Phase			
	Number of Subjects	0	250
	Mean (SD)	0	3.4 (0.92)
	Median	0	4.0
	Min - Max	0	1 - 5
	1	0	13 (5.2)
	2	0	35 (14.0)
	3	0	36 (14.4)
	4	0	165 (66.0)
	5	0	1 (0.4)

Table 2: Omitted doses of ipilimumab or placebo in the induction phase of CA184-024[4]

	NUMBER OF SUBJECTS (%)	
	10 MG/KG IPILIMUMAB + DACARBAZINE N = 247	PLACEBO + DACARBAZINE N = 251
Subjects Treated in the Induction Phase	247 (100.0)	250 (99.6)
Subjects with at Least One Omitted Dose in the Induction Phase (a)	101 (40.9)	40 (16.0)
Reason for Omitted Dose (b,c)		
DIARRHEA	6 (5.9)	0
NON-DIARRHEA TOXICITY	83 (82.2)	28 (70.0)
OTHER	15 (14.9)	13 (32.5)
Number of Omitted Doses in the Induction Phase (a)		
0	146 (59.1)	210 (84.0)
1	91 (36.8)	37 (14.8)
2	10 (4.0)	3 (1.2)

Table 3: Cost-effectiveness results for ipilimumab using a three-stage model without including sequencing of treatment i.e. no active treatments at 2nd line but BSC only

CA184-024 clinical trial data for ipilimumab				Pooled chemotherapy-naïve data for ipilimumab			
DTIC		Vemurafenib		DTIC		Vemurafenib	
ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*	ICER	Inc. Net Benefit*
£42,449	£6,732	£28,980	£191	£38,364	£12,109	£22,305	£2,585

DTIC, Dacarbazine; ICER, incremental cost-effectiveness ratio. * at a willingness to pay threshold of £30,000 per QALY for vemurafenib and £50,000 per QALY for DTIC

Table 4: Duration and resolution of irAEs reported in CA184-024[4]

irAE category	Subjects with event, n (%)	Median duration, weeks	Median time to resolution, weeks
GI			
Grade 2-4	39 (15.8)	NA	2.0
Grade 3-4	14 (10.0)	2.0	2.1
Diarrhoea			
Grade 2-4	31 (12.6)	NA	1.4
Grade 3-4	10 (4.0)	1.6	2.0
Liver			
Grade 2-4	89 (36.0)	NA	3.4
Grade 3-4	69 (27.9)	3.1	3.4
Endocrine			
Grade 2-4	5 (2.0)	NA	NE
Grade 3-4	0	-	-
Skin			
Grade 2-4	46 (18.6)	NA	4.1
Grade 3-4	8 (3.2)	1.7	4.7

GI, gastrointestinal; irAEs, immune-related adverse events; NA, not analysed; NE, not estimable

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