Ipilimumab – factual error check

Description of problem	Description of proposed amendment	Justification of amendment	ERG response
The ERG correct an error in the background mortality (page 60), however although the error is identified, the fix applied in not correct. Although the error relating to the switch time was corrected (changing >=5 to >=6 in columns P and N in both patient flow sheets the parameters ip_survat5 and comp_survat5 were not redesignated to reflect the end of five years With these parameters re-designated within the EXCEL model from row 1505 to row 1870 (15.73% to 15.33% in Ipilimumab arm and 3.65% to 2.01% in the BSC arm) The base case ICER is £60,737, with the ERGs correction this falls to £58,550, however with the fix applied to the ERG's estimate, the base case ICER falls to £54,966.	Amend the ICER change with the implementation of the ERG fix from £58,550 to £54,966.	A mistake has been made in the implementation of the ERG fix to the mortality logic	The manufacturer also provided two tables numbered 3 and 4. It is unclear to us where in the document these are and therefore what changes are requested. No changes have been made The adjustments outlined in column one have been integrated in the model and a revised Table 20 has been put in the report

Issue 3: PFS in the BSC arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57 it is stated that: "- in the absence of sufficient progression-free patients alive in the gp100 arm of the trial beyond 18 months, the model authors employed the same Log-logistic survival model to represent both PFS and OS for the comparator in the decision model. This has the effect of ensuring that there can be no patients in a post-progression condition for the comparator arm at any time after 18 months, thus introducing a notable bias into one arm of the model"	-in the absence of sufficient progression-free patients alive in the gp100 arm of the trial beyond 18 months, the model authors employed the same Log-logistic survival model to represent both PFS and OS for the comparator in the decision model.	The same curve parameters (shape of curve) are assumed for PFS and OS, however, there is a different starting point for the curves (at 18 months 16.3% of patients are still alive and only 1.8% of patients have not progressed). The curve from 18 months onwards is defined for OS and PFS using both the starting point at 18 months and the curve shape, and therefore the majority of alive patients on GP100 from this point onwards are in a post-progression condition. BMS believe that the statement by the ERG is not correct and that the last statement should be removed.	The ERG does not accept that the paragraph contains a factual error and has therefore not changed the wording in the report...

Issue 4: NICE End of Life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 71 the ERG state “The ERG does not believe the manufacturer’s estimate of life extension to be robust.”	The evidence of the trial strongly indicates that there is a genuine life extension, and that it is highly likely that the mean life extension exceeds 3 months, but the true size of the benefit remains unclear	BMS believe the statement should be clarified to be in line with the conclusion drawn by the ERG. While there is legitimate disagreement around the survival extrapolation, there is little uncertainty that the extension to life is substantial, and exceeds 3 months. This is underlined by the 4.5 year trial period - using the combined data for ipilimumab, survival increase was 4.6 months for the median life expectancy (303 days vs 196 days) and 5.5 months for the mean life expectancy (502 days vs 336 days).	The statement is related to the size of the manufacturer’s estimate of survival benefit which the ERG believes is not robust. The ERG has not changed the statement in the report.

Clinical Summary

Issue 5: Dosing of ipilimumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 9 it is stated that: "Recent marketing authorisation recommends that all four doses of ipilimumab be given to patients, as tolerated, regardless of disease progression. It is not known how this might affect the costs or OS benefit if ipilimumab was to be approved for use in clinical practice"	Recent marketing authorisation recommends that all four doses of ipilimumab be given to patients, as tolerated, regardless of disease progression.	The recent marketing authorisation that all four doses be given regardless of progression matches the MDX010-20 trial protocol where all four doses were to be given to all patients (except in the case of severe adverse events or death). Although some patients did discontinue due to disease progression this rate was higher in the GP100 arm (32.8% vs 24.4% in the Ipilimumab + Gp100 arm and 16% in the Ipilimumab only arm), and did not reflect a trial protocol of ceasing treatment at progression. We would therefore consider that the trial practices matches the practice described within the marketing authorisation and that therefore the affect of this on the costs and OS benefits are known using the trial information.	The Hodi (2010) paper submitted as evidence states that the majority of patients discontinued due to disease progression. If that is the case and a higher proportion of patients complete all four doses in clinical practice, this has the possibility of affecting both costs and OS – however, the magnitude of these effects is not known. No change has been made to the report.

Issue 6: Abbreviations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
irAE – immune-response adverse event (pg 5)	irAE – immune-related adverse event	This a typographical error, please amend	Corrected.

Issue 7: Trademark

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Yervoy® (pg 6)	Yervoy™	Yervoy does not have a registered trademark as yet.	Corrected.

Issue 8: The inclusion of study CA-184-022

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 6 the ERG stated that: " it is unclear why CA184-022 was included"	CA184-022 was included to provide clinical efficacy and safety evidence	The CA184-022 dose-ranging study was included to provide additional clinical efficacy and safety data as it includes data for 72 patients treated with the 3mg/kg dose which is the licensed dose of Ipilimumab, and was presented in both the clinical efficacy and safety sections of the submission. We accept the comment on page 21 that this may not have been made consistently clear in the submission	No correction required – as noted by the manufacturer this was not made consistently clear in their submission.

Issue 9: GP100 equivalent to BSC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page9the ERG queries the assumption that overall survival is equivalent between GP100 and BSC, quoting a median survival for BSC of approximately 7-8 months.	This should be amended as OS estimates when amended for the Korn (2008) population have been shown to be equivalent for GP100 and BSC	Based upon a mixed treatment comparison of relevant studies median overall survival was found to be 7 months for both GP100 and placebo (or BSC) after adjustments were made to reflect the Korn et al population (Kotapati, 2011) Median survival was slightly lower within the MDX010-20 trial, likely due to slight variations in population characteristics compared to the population within Korn et al. As there is no significant difference in the characteristics of patients between arms these differences will be present in all arms of the trial indicating that the use of the GP100 median OS of 6.4 provides a fair comparison to the Ipilimumab data for the trial population.	The ERG could not find these figures on page 9 but did find them on page 17 in a quote from published EMA documents. In addition, the Korn (2008) paper includes IPD for patients from all arms of the trials and so is a mix of patients treated with BSC and active drugs so the ERG has not changed its position.

Issue 10: Treatment related deaths

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 19 the ERG stated that: “In addition, grade 3/4 AEs occurred in 56.3% of patients treated with ipilimumab and dacarbazine, which was significantly higher (p<0.001) than in those treated with dacarbazine	Please add – ‘’ No drug-related deaths were reported in the ipilimumab-dacarbazine group; one fatal gastrointestinal haemorrhage was reported in the dacarbazine group.’’	We feel it is important to add information on treatment-related deaths about the study identified by the ERG for consistency as treatment related deaths are mentioned on page 18 in relation to submitted evidence.	This is already mentioned on page 34 but has been added to page 19.

and placebo (27.5%)"			

Issue 11: Study inclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 21 the ERG stated that: "Given that it is likely that for all clinical studies in this area the manufacturer will have sponsored the trial or at least supplied the drugs, it is somewhat surprising that the manufacturer did not include a search of their own internal database of studies" On page 22: "No other rationale for the use of this trial is provided." "The results of this study were found on line through the Bristol Myers Squibb website but no publication of the results was identified.	Manufacturer has submitted only the published clinical trial data	BMS submitted only the published clinical trial data Only phase 2 and 3 published data of ipilimumab at the licensed dose and setting (i.e. previously treated patients), with survival as an end-point, were considered for submission for the safety and clinical evidence (MDX010-20 and CA184-022 [72 patient data]). The CA184-004 study is not yet published thus not included. The CA184-007 study was included for additional safety data as it was exploring if the use of prophylactic steroids was useful in reducing the diarrhoea which can result with ipilimumab; we felt that it answered an important question on the safety management of ipilimumab thus included this published study even though it used a higher dose of ipilimumab.	As noted in the ERG report the MS does not make it clear how studies were selected. NICE often considers data from unpublished studies. The study mentioned includes patients who received the licensed dose of the drug and also reported OS. The ERG has not made a change to the report.

Issue 12: UK patients in study CA-184-022

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 24 it is stated that "The manufacturer points out that of the 72 patients assigned to the	Please remove sentence	There were no UK patients in the CA184-022 study. The study included 85 patients from five non-	Correction made.

licensed 3mg/kg arm, 28 were from the UK”		UK European countries.	

Issue 13: Combination of Ipilimumab Data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52 the ERG states that the method for combination of ipilimumab data from the 2 arms has not been provided	Ipilimumab data has been combined by simply amalgamating the datasets. No mixed treatment comparison or other method of weighting or altering either dataset has been used.	Clarification of method	This is not a factual error – this information was not provided in the MS. The ERG has not made a change to the text.

Issue 14: Combination of Ipilimumab Data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pg 73 it is stated: “Up to 60% of patients tolerated the full four courses of treatment”	Over 60% of ipilimumab patients tolerated the full four courses of treatment	65% of patients in both ipilimumab arms of the trial received the full four courses (67% in the ipilimumab only arm and 64% in the ipilimumab + GP100 arm)	Change made.