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

Pro-forma Response

ERG report

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab

You are asked to check the ERG report from **Liverpool reviews and implementation group (Lrig)** to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **14th July 2015** 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.

Issue 1 Understanding of tumour flare and its role

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 64 the ERG states "It is stated in the CS that the company's modelling approach relies on data from the KEYNOTE-002 trial and, as a consequence, the effect of 'tumour flare', which will lead to longer post-progression survival, has not been incorporated. The company states that this means that their approach to modelling is conservative." On page 75 "In the company's base case analysis 72% of this estimated health gain occurs after confirmed disease progression"	Provide further detail on the impact of tumour flare on RECIST assessed progression on page 64 or elsewhere as deemed relevant. Amend page 75 to state RECIST assessed progression rather than confirmed disease progression.	To provide the reader with a better understanding of the role of tumour flare. As this may have been unclear within the original submission we would like to provide further clarity on the role of tumour flare within the economic modelling. As stated within the clinical section of the original submission some patients with melanoma can have a transient tumour flare in the first few months after starting immunotherapy (i.e. pembrolizumab in this case) with subsequent disease response. This means that progression (as measured within the trial by RECIST) is not always a good proxy for true disease progression. Patients with tumour flare are classed as progressed by RECIST when they are in fact responding. Chemotherapy does not exhibit this type of response	We have incorporated the company's suggestions into our report (new text in red) On page 64, the relevant paragraph now reads: "It is stated in the CS that the company's modelling approach relies on data from the KEYNOTE-002 trial and, as a consequence, the effect of 'tumour flare' which may occur in the first few months after starting immunotherapy (such as pembrolizumab) and which will lead to longer post-progression survival, has not been incorporated. The company states that this means that their approach to modelling is conservative since patients with 'tumour flare' are classed as progressed by RECIST when they are in fact responding. Hence progression measured this way is not always a good proxy for true disease progression and may bias against pembrolizumab since 'tumour flare' does not occur with chemotherapy."

		therefore assessment according to RECIST will always bias against immunotherapy / there will always be patients exhibiting long-term survival post RECIST assessed progression.	On page 75, the relevant paragraph now reads: “In the company’s base case analysis 72% of this estimated health gain occurs after RECIST assessed progression …”

Issue 2 Minor text inaccuracy relating to PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64 "after which PFS was modelled by fitting a Gompertz model. In the chemotherapy/BSC arm KEYNOTE-002 K-M data were used without modification up to 62 weeks, after which all patients were assumed to have died."	"after which PFS was modelled by fitting a Gompertz model. In the chemotherapy/BSC arm KEYNOTE-002 K-M data were used without modification up to 62 weeks, after which all surviving patients were assumed to have progressed."	To correct the error in wording, not all patients are assumed to have died at this point.	We have amended the text (new text in red) to read: "after which PFS was modelled by fitting a Gompertz model. In the chemotherapy/BSC arm KEYNOTE-002 K-M data were used without modification up to 62 weeks, at which point less than 2% of patients remained progression free, after which all patients were assumed to have progressed or died"

Issue 3 PFS Kaplan Meier clarification for chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 64 and 75: it is noted that it is assumed all patients progress or die on the chemotherapy arm at 62 weeks. It would be worth pointing out that less than 2% of patients remain alive at this point.	Add the following to the statement regarding use of Kaplan-Meier data for PFS for the chemotherapy arm of the model: "at which point less than 2% of patients remained progression free"	Allows the reader to understand the impact of the simplifying assumption. Note that additional scenarios were provided using extrapolated curves rather than K-M data, which showed little impact on the ICER from this assumption.	We have amended the text accordingly on pages 64 and 75. For new text on page 64, see response to Issue 2. For page 75, we have added the following sentence (in red text) to the end of the relevant paragraph: "Figure 6 shows the KEYNOTE-

			002 PFS data used to populate the company's model. In the pembrolizumab 2mg/kg Q3W arm, K-M trial data are used directly until week 13 (91 days), and thereafter a Gompertz model is applied to project PFS indefinitely. In the chemotherapy/BSC arm, the trial K-M data are used directly until the final date when any patient was observed to be still progression-free (62 weeks), at which point all remaining patients are presumed to die or to suffer disease progression immediately. It should be noted that at this point (62 weeks), less than 2% of patients remained progression free."

Issue 4 Comment related to the use of the Schanderdorf data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Regarding the mid-term projection using Schadendorf data, in page 83 it is stated that: "this method of projecting survival is implausible."	The Schadendorf data was used since this was the most comprehensive long term data available for survival for immunotherapies. Additionally, it has been posited that once patients have survived a certain period of time, their chances of survival are similar to those of the general population. As the ERG recognised, there are low numbers of patients at risk between years 6 and 10 in the Schadendorf data used for modelling, and no deaths at this point in the published paper. It should be noted that there is no perfect method to estimate survival for this patient population given the limited data available. To address this, a large number of scenario analyses were provided around the modelling of survival. We recognize the ERG approach to obtaine survival estimates as an alternative, valid methodology that results in similar	To provide further clarification on this point.	We note the company's suggestion. However, it is the ERG's opinion that this method of projecting survival is implausible based on clearly stated logic. It is for the Appraisal Committee to consider whether they agree or disagree with the ERG and we do not believe any additional text is required in our report regarding this issue.

	estimates of mean survival as those presented in the CS.		

Issue 5 Minor text inaccuracy relating to utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 88 states that “The company has acknowledged that this is a relevant issue and included a sensitivity analysis in their response to clarification questions”	“The company included a sensitivity analysis in their response to clarification questions.”	To reflect more accurately MSD’s answer to the clarification question.	We have deleted the words “has acknowledged that this is a relevant issue and”