STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab

This report was commissioned by the NIHR HTA Programme as project number 14/177/07

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The manufacturer identified five issues in relation to factual errors in the original ERG report. Four issues were considered to be by the ERG to require minor changes to the text, as suggested by the company. The pages of the report affected are presented here. Text that remains unaltered is greyed out.

Table 28 Comparator components, dose and dosing schedule

Chemotherapy (dose)	Proportion of patients (%) (KEYNOTE-002)	Administrations*			
		Days between	Period (days)	Length of breaks (days)	Frequency (cycles)
Dacarbazine (1000mg/m2)	26.3	21	Indefinite	-	Q3W
Paclitaxel (175mg/m2)	16.4	7	42	14	Q1W
Paclitaxel (in combination with carboplatin) (175mg/m2)	24.6	7	42	14	Q1W
Carboplatin (AUC=5)	7.6	21	Indefinite	-	Q3W
Temozolomide (1000mg/m2)	25.1	28	Indefinite	-	Q4W

AUC=area under the curve; Q1W=every week; Q3W=every three weeks; Q4W=every for weeks
*TA268[12]
Source: CS, adapted from tables 73, 74 and 75

5.4.6 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. The time horizon is set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[46] both costs and outcomes are discounted at 3.5%.

5.4.7 Treatment effectiveness

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.

The description contained within the CS as to how trial data have been incorporated into the model is considered by the ERG to be unclear. This summary, therefore, is based on an examination of the company's model.

Progression-free survival

Progression-free survival for patients receiving pembrolizumab 2mg/kg Q3W was modelled using data from the KEYNOTE-002 clinical trial up to 13 weeks, 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.

pembrolizumab 2mg/kg Q3W can have any meaningful effect on the estimated incremental cost per patient. The effective NHS price of a new product is determined by the company, either by its list price or through a PAS agreed with the Department of Health. The remit of the ERG only extends to checking that the dosing costs have been accurately calculated. In this appraisal all other cost elements included in the model have no real effect on the size of the ICER per QALY gained.

Therefore, the major aspect of the model to be considered relates to the patient benefit claimed by the company as a result of treating patients with pembrolizumab 2mg/kg Q3W rather than conventional therapies utilised in the control (chemotherapy/BSC) arm, expressed in terms of additional survival time (OS) and QALYs. In the company's base case analysis 72% of this estimated health gain occurs after RECIST assessed progression, mainly in the extended projection period (years 2 to 30), beyond the currently available follow-up data from the KEYNOTE-002 clinical trial. Thus, the most important element of the company's model is the long-term projection of interim clinical trial survival results to obtain an expected remaining lifetime for the trial population. Since 28% of the estimated health gain is attributed to the pre-progression phase of the KEYNOTE-002 trial, the analysis of these data constitutes the second key element of the submitted model worthy of close attention.

5.5.2 Progression-free survival

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.

The ERG has tested the use of simple exponential projective models from 90 days in both arms and obtained good results. In particular, the more parsimonious exponential approach (one less model parameter) achieves a slightly better fit to the pembrolizumab 2mg/kg Q3W data than the Gompertz function. Furthermore, the mean and maximum residuals are also smaller. The Gompertz model tends to over-estimate PFS in the long-term, whereas truncating the chemotherapy/BSC arm without any projection under-estimates PFS in the chemotherapy/BSC arm. Therefore, the incremental gain in PFS attributable to pembrolizumab 2mg/kg Q3W when projected in the long-term is exaggerated by about 30%.

This ERG model amendment has a substantial effect on treatment costs, especially for pembrolizumab 2mg/kg Q3W. Compared with the company's base case scenario, the incremental cost is reduced by more than £8,000 per patient, and the ICER is reduced by £7,181 per QALY gained.

Post-progression therapies

The company has assumed that post-progression therapies will only be used for palliative/BSC purposes (having no impact on OS), and will be balanced between the two arms of the trial. The ERG considers this to be a reasonable assumption since these patients have been heavily pre-treated with ipilimumab and various chemotherapy agents (77% of patients in the pembrolizumab 2mg/kg Q3W arm of the KEYNOTE-002 trial had two or more previous lines of therapy, and [redacted] had five or more lines of therapy). Following progression, it is very unlikely that further treatment for patients randomised to either the pembrolizumab 2mg/kg Q3W or the chemotherapy/BSC trial arms will differ.

5.5.5 Source of utility values

In the company base case the main utility parameters are drawn from EQ-5D responses in the KEYNOTE-002 trial scored according to the UK value set. However, in international trials it is often the case that patient responses to theEQ-5D questionnaire differ significantly. The ERG requested a breakdown of utility scores between US and non-US patients, which shows clearly that in the US subgroup EQ-5D responses are generally more optimistic. The company included a sensitivity analysis in their response to clarification questions. The ERG has made an appropriate amendment to the model which shows that using non-US utility data reduces incremental QALYs by 6.6% and increases the estimated ICER by £3,037 per QALY gained.

5.5.6 Life table mortality rates

The company's model uses published annual Life Table estimates[49] for England and Wales to represent other causes of death in long-term survival projections (10-30 years). Separate mortality rates for males and females are weighted for the gender balance in the KEYNOTE-002 trial for each year of age from 50 to 100. This approach is flawed because mortality is systematically lower for females than for males so that over time the gender balance shifts in favour of females. Without making allowance for this drift leads to an over-estimate of mortality in the cohort as a whole. The ERG has calculated representative mortality rates using dynamic weighting, which when applied in the model increases the incremental survival and QALYs by less than 1%, and reduces the estimated ICER by £25/QALY.