NCPE report on the cost effectiveness of Pembrolizumab (Keytruda®) for the treatment of unresectable or advanced metastatic melanoma in adults refractory to ipilimumab.

The NCPE has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®). Following NCPE assessment of the applicant’s submission, pembrolizumab is not considered cost effective for the treatment of patients with advanced or unresectable metastatic melanoma who have progressed following treatment with ipilimumab.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant’s (MSD) economic dossier. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme Technology Review Group.

About the National Centre for Pharmacoeconomics
The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics February 2016
**Background**

In October 2015, MSD submitted a dossier examining the cost effectiveness of pembrolizumab for the treatment of adults with unresectable or advanced melanoma who have progressed following treatment with ipilimumab. Final data submitted by the Applicant was received on 5\textsuperscript{th} January 2016.

The recommended dose is 2mg/kg by IV infusion every three weeks. Treatment should continue until disease progression or no longer tolerated. No specific dose reductions are recommended.

In the submission, comparators investigated were paclitaxel and carboplatin, and a combination of both, taken to represent ‘Best Supportive Care’ (BSC). The optimal management of patients who have progressive disease following treatment with ipilimumab is undefined and largely dictated by clinical status and presentation. There is no clinical evidence to support the use of cytotoxic chemotherapy in advanced melanoma.

1. **Comparative effectiveness of pembrolizumab**

Relative efficacy outcomes for the comparison of pembrolizumab with best supportive care (BSC) were derived from the KEYNOTE-002 study. This study was an open-label, Phase II randomised control trial of 540 patients with advanced or unresectable metastatic melanoma who had experienced disease progression after treatment with ipilimumab. Patients were assigned to one of three arms, pembrolizumab 2mg/kg every 3 weeks (Q3W), or pembrolizumab 10mg/kg every three weeks (Q3W), or investigators choice of chemotherapy (dacarbazine, carboplatin and paclitaxel, paclitaxel monotherapy, temozolamide). Patients received treatment until progressive disease or unacceptable toxicity. Efficacy analyses were performed in the intent-to-treat population. A large proportion of patients (48%, n=86) crossed over to the pembrolizumab arms following progressive disease (PD) on ICC.

Only data from the second interim analysis (IA2) in May 2014 are currently available. Pembrolizumab 2mg/kg Q3W is associated with a statistically significant improvement in progression free survival (PFS) compared with chemotherapy, hazard ratio (HR) 0.57, (95% CI 0.45, 0.73), p<0.0001. After adjusting for crossover using the two-stage method, the HR for OS was 0.63 (95% CI 0.45, 0.88, p=0.007). The mean PFS for patients receiving
pembrolizumab was 25.43 weeks and the mean OS was 46.8 weeks at 73 weeks maximum follow up.

A systematic review was conducted to identify additional trials to contribute to the evidence base, but no relevant studies were identified.

2. Safety of pembrolizumab
In KEYNOTE-002, the incidence of adverse events (AEs) was similar in both arms of the study, 96.6% pembrolizumab patients experienced an AE compared to 97.7% ICC patients. The incidence of ≥Grade 3 AEs was lower in the pembrolizumab arm (46.6% vs 51.5%). Eleven deaths occurred in the pembrolizumab arm compared to 8 in the ICC arm; only one of the pembrolizumab and none of the ICC deaths were considered attributable to the drug treatment. Serious AEs occurred in 44.4% pembrolizumab patients compared to 33.3% in the ICC arm. The most common AEs in the pembrolizumab arm (occurring in ≥15%) were fatigue, pruritus, constipation, diarrhoea, nausea, anaemia, cough, decreased appetite and arthralgia. The most common AEs of ≥Grade 3 in the pembrolizumab arm, occurring in ≥2% of patients were anaemia, fatigue, hyponatremia, dehydration, and generalised oedema. 16.3% patients on pembrolizumab experienced an immune related AE, and 2.8% experienced a Grade 3-5 immune related AE. None of these caused death, but 1.1% led to treatment discontinuation. These immune related AEs include colitis, pneumonitis, rash, diarrhoea, and thyroid dysfunction.

3. Cost effectiveness of pembrolizumab
Cost effectiveness of pembrolizumab was investigated using a health state model with a 30 year time horizon.

The model simulates patients through three main health states: ‘pre-progression’, ‘post-progression’, and ‘death’. All health states are mutually exclusive, and death is the absorbing state. All patients start in the pre-progression state; transitions to the death state can occur from either the pre-progression or post-progression states. The model assumes patients continue to receive treatment until disease progression. It also assumes that once patients progress, no further subsequent active treatment is provided and patients receive only palliative care. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from KEYNOTE-002.
The key model inputs are PFS and OS. These treatment effects were derived from KEYSNOTE-002 and applied in the model. Because of the short duration of this study (treatment effects are derived from an interim analysis and have been confounded by crossover), it is necessary to extrapolate the treatment effects to the time horizon of the model. External data is employed for the extrapolation of these survival estimates.

The NCPE had concerns over a number of the assumptions employed in these extrapolations, especially regarding the appropriateness of the external data. The company provided an alternative OS scenario devised by the Liverpool Evidence Review Group on behalf of NICE and this forms the basis for the NCPE preferred set of assumptions. This scenario utilises a mixed exponential model and a case mix adjusted analysis of registry data.

Resource use in the model was based on the MELODY study, and captured costs associated with drug acquisition, adverse events, administration, monitoring, home care, palliative and terminal care. AEs considered to have significant healthcare resource use (HCRU) or HRQoL impact were incorporated into the model; 10 different AEs were incorporated in the model including 3 with zero cost. These were mainly Grade ≥3 AEs that occurred in more than 3% patients; endocrine dysfunction was the only immune related AE captured in the model. Since the ICC trial population did not actually receive the modelled treatment, it is uncertain if the frequency of AEs in this arm act as a proxy for BSC treatment in the model. The sensitivity of the model to this assumption was tested by zeroing AE costs in the BSC arm. This had a very small impact on the ICER.

In the base case submitted by the company, utility was assigned based on ‘time to death’. This method has the effect of disassociating changes in utility from disease status and treatment, and means the bulk of disutility is applied in the post-progression phase as the patient approaches death. It should be noted that there is no utility decrement associated with progressive disease in the model base case, when time to death utilities are employed. This is not considered a realistic scenario. The NCPE did not agree with this approach, and implemented progression based utilities in their preferred set of amendments.

The NCPE implemented a number of changes to the model, (a) implemented a revised OS extrapolation (b) used progression based utilities rather than time to death utilities and (c)
implemented updated drug acquisition and terminal care costs. The implementation of these measures changed the costs and QALYs associated with pembrolizumab compared to the company base case. The final ICER with the preferred set of NCPE assumptions was €85,766 (incremental costs €72,280, incremental QALY=0.84). The probability of pembrolizumab being cost effective at a WTP threshold of €45,000 per QALY is 2%.

The company presented a large variety of scenario analyses and performed detailed sensitivity analyses. The model is particularly sensitive to the extrapolation methods employed, and the HR employed for the crossover adjustment. The model is also sensitive to the duration of treatment with pembrolizumab.

4. **Budget impact of pembrolizumab**

The budget impact models presume that all eligible ipilimumab refractory patients will receive pembrolizumab in the first year, and thereafter there will be no eligible patients as pembrolizumab will replace ipilimumab as a first line treatment. The applicant assumes 100% market share for pembrolizumab. The budget impact assumes the dose intensities of the model are replicated in real life (87.5% pembrolizumab and 70.5% for BSC), and that a number of patients receive long-term treatment with pembrolizumab as per the model.

It is estimated that the gross cumulative 5 year impact will be about €1.8 million.

It is estimated that the net cumulative 5 year impact will be about €1.5 million.

5. **Conclusion**

Following review of the company submission, pembrolizumab is not considered to be cost-effective for the treatment of adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab, at a threshold of €45,000/QALY.

The NCPE performed a separate review of the cost-effectiveness of pembrolizumab in ipilimumab-untreated patients, and it was found to be cost-effective relative to ipilimumab in this setting.