



**NCPE report on the cost effectiveness of Pembrolizumab (Keytruda®)
for the first line treatment of unresectable or advanced metastatic melanoma in adults.**

The NCPE has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®). Following NCPE assessment of the applicant's submission, pembrolizumab is considered cost effective for the first line treatment of unresectable or advanced metastatic melanoma in adults, relative to 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.

Background

In October 2015, MSD submitted a dossier examining the cost effectiveness of pembrolizumab for the first line treatment of adults with unresectable or advanced melanoma. Final data submitted by the Applicant was received on 5th 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 ipilimumab for BRAF negative patients, and ipilimumab, vemurafenib and dabrafenib for BRAF positive patients. This was considered appropriate by the NCPE, although it was noted that the BRAF/MEK inhibitor combination of dabrafenib and trametinib is now commonly used in Ireland for BRAF positive patients, which is associated with a greater relative efficacy than dabrafenib alone.

1. Comparative effectiveness of pembrolizumab

Relative efficacy outcomes for the comparison with ipilimumab were derived from the KEYNOTE-006 study. This study was an open-label, Phase III randomised control trial of 834 patients with advanced or unresectable metastatic melanoma who had received no previous systemic treatment. Patients were assigned to one of three arms, pembrolizumab 10mg/kg every 2 weeks, or pembrolizumab 10mg/kg every three weeks, or ipilimumab 3mg/kg every three weeks for a maximum of four doses. Patients received treatment until progressive disease or unacceptable toxicity. Efficacy analyses were performed in the intent-to-treat population.

The study was stopped prematurely, at the second interim analysis (IA2) in March 2015, as it was judged to have met its primary endpoints of PFS and OS. IA2 is considered the definitive OS analysis for this study, at a median follow up time of 13.85 months. Median OS was not reached in any arm by the time of IA2. Hazard ratio (HR) for OS was 0.69 (95% CI 0.52, 0.9, p=0.00358) for pembrolizumab 10mg/kg every three weeks versus ipilimumab, and OS rate at 12 months was 68.4% for pembrolizumab versus 58.2% for ipilimumab. PFS results were based on the first interim analysis, the HR was 0.58 (95% CI 0.47, 0.72, p<0.00001) for

pembrolizumab 10mg/kg every three weeks versus ipilimumab, and the PFS rate at 6 months was 46.4% for pembrolizumab versus 26.5% for ipilimumab.

While crossover was not permitted, patients could receive other drug therapies after discontinuing treatment. Significant numbers of patients in both the ipilimumab and pembrolizumab arms received subsequent treatment with agents known to have a positive survival benefit in metastatic melanoma. No adjustment for the treatment effects of subsequent treatments has been made in IA2, thus the treatment effects attributed to both ipilimumab and pembrolizumab in KEYNOTE-006 may not be the result of those interventions alone. Therefore there is considerable uncertainty associated with the survival benefit attributed to ipilimumab and pembrolizumab in this study.

There are no head to head trials comparing pembrolizumab to the BRAF inhibitors vemurafenib and dabrafenib for the treatment of BRAF positive patients. The company undertook a Bayesian network meta-analysis (NMA) to derive relative efficacy data for pembrolizumab, ipilimumab, vemurafenib and dabrafenib. There was considerable heterogeneity in patient populations between the trials included in the meta-analysis, and trial results for dabrafenib and vemurafenib were confounded by treatment crossover. The cost-effectiveness model results for BRAF positive patients are presented as a scenario analysis due to the uncertainty introduced by this NMA. This was considered appropriate by the NCPE, given that the treatment choices for BRAF positive patients will be driven by the presenting clinical characteristics more than the relative efficacy with pembrolizumab.

2. Safety of pembrolizumab

In KEYNOTE-006, adverse events (AEs) of any grade occurred in 95.3% pembrolizumab and 93.4% ipilimumab patients. Grade ≥ 3 AEs occurred in 33.2% pembrolizumab patients compared with 36.7% ipilimumab patients. Serious AEs occurred in 24.9% pembrolizumab patients compared with 30.1% ipilimumab patients. 5 pembrolizumab patients died on treatment compared to 3 ipilimumab; none of the pembrolizumab and one of the ipilimumab deaths was considered by the investigator to be related to the drug treatment. The most common drug related AEs with pembrolizumab are fatigue (19.1%), diarrhoea (14.4%), pruritus (14.1%), rash (13.4%), arthralgia (11.6%), asthenia, vitiligo, and nausea (11.2%). The most frequently observed immune related adverse events with pembrolizumab 10mg/kg

Q3W were hypothyroidism (8.7%) and hyperthyroidism (3.2%). Colitis (2.5%) and hepatitis (1.8%) of Grade 3-4 severity were also reported.

3. Cost effectiveness of pembrolizumab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were progression free survival and overall survival. Inputs for the comparison of pembrolizumab and ipilimumab in BRAF negative patients were derived from KEYNOTE-006. Inputs for the comparison of pembrolizumab with ipilimumab, vemurafenib and dabrafenib were derived from the network meta-analysis conducted for the submission, and are presented as a scenario analysis due to the significant methodological deficits in the NMA. Cost effectiveness 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 could 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-006. For the BRAF inhibitors, adverse event frequencies are taken from the pivotal registration trials and dose intensity is assumed to be 100%.

PFS and OS results from the interim analysis of KEYNOTE-006 are extrapolated to the full time horizon of the model, using parametric extrapolations and data from external sources. The NCPE had concerns over a number of the assumptions employed in these extrapolations, including the appropriateness of the external data, and the assumption that the treatment effects of pembrolizumab 10mg/kg every three weeks can be used as a proxy for the licensed dose of 2mg/kg every three weeks. The company provided the 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 for BRAF negative patients. This scenario utilises a mixed exponential model and a case mix adjusted analysis of American registry data. No attempts were made to adjust the results from the BRAF inhibitor pivotal trials for differences

in patient characteristics with KEYNOTE-006, which results in uncertainty in the results of the model for BRAF positive patients.

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; 23 different AEs were incorporated in the model including 6 with zero cost. These were mainly Grade ≥ 3 AEs that occurred in more than 3% patients and some immune related AEs are also captured in the model, including colitis, endocrine dysfunction, and respiratory dysfunction.

In the base case submitted by the company, utility was assigned based on 'time to death'. The NCPE did not agree with this approach, and implemented progression based utilities in their preferred set of amendments.

Many patients in KEYNOTE-006 received additional active systemic treatments such as anti-PD1 agents, ipilimumab, BRAF and MEK inhibitors and interferon after experiencing progression, and the treatment effects of these are included in the model, attributed to pembrolizumab and ipilimumab. The considerable costs of these subsequent treatments have not been included in the model. The effect of their omission is unknown, but casts doubt over the integrity of the ICER generated by the model.

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 (c) implemented updated monitoring, administration and terminal care costs. The implementation of these measures changed the costs and QALYs associated with pembrolizumab and ipilimumab compared to the company base case, but did not affect the dominant position of pembrolizumab (QALY gain 0.42, incremental costs €-3,093). The probability of pembrolizumab being cost effective relative to ipilimumab at a WTP threshold of €45,000/QALY is 82.5%.

The company presented a large variety of scenario analyses and performed detailed sensitivity analyses. In almost all scenarios, pembrolizumab remained dominant to ipilimumab. The model is particularly sensitive to the extrapolation methods employed. The

ICER is sensitive to the price of ipilimumab. A confidential discount is available to the HSE on the list price of ipilimumab, which when implemented in the model, generates a significant change in the ICER.

4. Budget impact of pembrolizumab

The budget impact models presume that there will be a 70% uptake of pembrolizumab in the first year, and thereafter it will displace ipilimumab as first line treatment for advanced metastatic melanoma, with 100% eligible patients receiving treatment. The applicant assumes 100% market share for pembrolizumab. The budget impact assumes the dose intensities of the model are replicated in real life (87.7% pembrolizumab and 81.3% ipilimumab), 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 €63million.

It is envisaged that first line use of pembrolizumab will displace ipilimumab to second line use. The net drug budget impact for pembrolizumab, assuming no ipilimumab treatment is required is -€6million.

5. Conclusion

Previously ipilimumab was found not to be cost-effective at the list price submitted. It was reimbursed after the negotiation of a confidential discount. Following review of the company submission, pembrolizumab is considered to be cost-effective relative to ipilimumab for the treatment of adult patients with unresectable or metastatic melanoma, at a threshold of €45,000/QALY.

Ipilimumab will continue to be used in the second line treatment setting. Therefore there will be considerable budget impact associated with the adoption of pembrolizumab, as reflected in the gross budget impact.

The NCPE performed a separate review of the cost-effectiveness of pembrolizumab in ipilimumab-refractory patients, and it was found not to be cost-effective in this setting.