Cost-effectiveness of pembrolizumab (Keytruda®) for previously untreated PD-L1 positive metastatic non-small cell lung cancer

The NCPE has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®). Following NCPE assessment of the applicant’s submission, pembrolizumab (Keytruda®) is not considered cost-effective for the treatment of previously untreated non-small cell lung cancer (NSCLC) and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant’s (Merck Sharpe and Dohme (MSD)) economic dossier on the cost effectiveness of pembrolizumab (Keytruda®). 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 (NCCP) 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 October 2017
Summary

In April 2017, MSD submitted a dossier examining the cost-effectiveness of pembrolizumab for the treatment of patients with previously untreated locally advanced or metastatic NSCLC with a tumour proportion score (TPS) ≥50%, and with no EGFR or ALK mutations. Final data submitted by the Applicant was received on 2nd August 2017.

The authorised dose is 200mg by IV infusion every three weeks. Treatment should be continued until disease progression or unacceptable toxicity. In clinically stable patients with initial evidence of disease progression, treatment should continue until disease progression is confirmed. Pembrolizumab is a humanised monoclonal antibody which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2, expressed on the surface of the tumour cells. Disruption of this PD-1 pathway by pembrolizumab allows the immune system to mount a response against the tumour cells by potentiating T cell immune responses, including anti-tumour responses.

In the submission, standard of care (SOC) chemotherapy, in the form of platinum doublet chemotherapy, was the comparator investigated. This was considered appropriate by the NCPE.

1. Comparative effectiveness of pembrolizumab

Relative efficacy outcomes for the comparison with SOC were derived from the Keynote-024 study. This study was an open-label, multi-national, Phase III randomised controlled trial of 305 patients with locally advanced or metastatic NSCLC, who had no previous treatment for advanced disease, had TPS≥50% as measured by the 22C3 pharmDx assay, and had no EGFR or ALK mutations. Patients were assigned to one of two arms, pembrolizumab 200mg every three weeks or SOC chemotherapy, the Investigators choice of one of the following 5 options:

- Gemcitabine 1250mg/m² Day (D) 1 and D8 and cisplatin 75mg/m² D1, every three weeks for 4-6 cycles
- Gemcitabine 1250mg/m² D1 and D8 and carboplatin AUC 5-6 D1, every three weeks for 4-6 cycles
• Paclitaxel 200mg/m\(^2\) D1 and carboplatin area under the curve (AUC) 5-6 D1, every three weeks for 4-6 cycles, followed by optional pemetrexed maintenance for patients with non-squamous histology

• Pemetrexed 500mg/m\(^2\) D1 and carboplatin AUC 5-6 D1, every three weeks for 4-6 cycles, followed by optional pemetrexed maintenance for patients with non-squamous histology

• Pemetrexed 500mg/m\(^2\) D1 and cisplatin 75mg/m\(^2\) D1, every three weeks for 4-6 cycles, followed by optional pemetrexed maintenance for patients with non-squamous histology

In the trial, treatment with pembrolizumab beyond progressive disease was permitted in the event of continuing clinical benefit and treatment duration was capped at a maximum of 35 cycles (2 years continuous treatment). Efficacy analyses were performed in the intent-to-treat population.

The trial met its primary endpoint of an increase in progression free survival (PFS), HR 0.5 (95% CI 0.37, 0.68). The median PFS with pembrolizumab was 10.3 months (95% CI 6.7, not reached) compared to 6 months (95% CI 4.2, 6.2) with SOC. Pembrolizumab was associated with a statistically significant increase in overall survival (OS) compared to SOC, HR 0.6 (95% CI 0.41, 0.89). Median OS was immature in both arms. Additional confidential data in relation to survival outcomes was provided by the company for consideration. There were not clinically meaningful differences in quality of life between the two treatment arms.

A scenario analysis using a network meta-analysis (NMA) to provide estimates of relative treatment efficacy versus individual SOC arms (e.g. carboplatin and gemcitabine, carboplatin and pemetrexed) was also presented.

2. Safety of pembrolizumab

Safety and tolerability was a secondary endpoint of the Keynote-024 trial. Similar numbers of AEs were reported in both treatment arms, in 96.1% pembrolizumab patients and 96.7% SOC patients. AEs considered by the investigator to be related to treatment were reported in 73.4% pembrolizumab patients and 90% SOC patients. There was a higher incidence of Grade 3-5 AEs in the SOC arm compared to pembrolizumab, 72.7% versus 53.2%. Similar
numbers of serious AEs were reported in both arms, approximately 44%. Treatment discontinuation due to AEs was higher in the SOC arm than the pembrolizumab arm, 14% versus 9.1%. There were 9 deaths due to an AE in the pembrolizumab arm, and 7 in the SOC arm. The most common AEs associated with pembrolizumab use were dyspnoea (22.1%), fatigue, constipation and diarrhoea (20.8%), decreased appetite (20.1%), nausea (19.5%), cough (16.9%), arthralgia and pyrexia (15.6%). The most common Grade 3-5 AEs were anaemia (4.5%), pleural effusion, diarrhoea and COPD (3.9%), hyponatraemia (3.2%) and pulmonary embolism, hyperglycaemia and pneumonitis (2.6%). Overall pembrolizumab was associated with a lower incidence of Grade 3-5 AEs and has an improved safety profile compared to SOC chemotherapy.

3. Cost effectiveness of pembrolizumab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were PFS and OS. Clinical efficacy inputs were derived from Keynote-024, and in a scenario analysis from the NMA. Cost effectiveness was investigated using a health state model with a 20 year time horizon. The model simulates patients through three health states: ‘Progression-free’, ‘Progressive disease’, and ‘Death’. All health states are mutually exclusive, and death is the absorbing state. All patients start in the progression-free state; transitions to the death state could occur from either the progression-free or progressive disease states. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from Keynote-024. Patients in the ‘Progressive disease’ state are assumed to receive one line of subsequent treatment.

Survival outcomes from Keynote-024 were extrapolated to the full time horizon of the model using parametric extrapolation. OS data was adjusted for treatment crossover. Resource use in the model was based on studies identified by a literature review and captured costs for drug acquisition and administration, hospital resource use, monitoring and follow up, management of AEs and terminal care costs. AEs which were of Grade≥3 severity and occurred in ≥5% in either arm of the trial population were included in the economic model, in addition to diarrhoea ≥Grade 2 and febrile neutropenia. In the base case utilities were modelled according to time to death; the NCPE changed this to utilities according to progression status in their preferred base case.
The NCPE implemented a number of changes to the model, resulting in a final ICER of €96,376/QALY (incremental costs €105,811, incremental QALYs 1.10) assuming a two year cap on treatment duration. Assuming treatment continues to progression in the NCPE adjusted model results in an ICER of €192,241/QALY (incremental costs €211,061, incremental QALYs 1.10).

The applicant presented a probabilistic sensitivity analysis. Assuming the 2-year cap on treatment duration, the probability of cost effectiveness at willingness-to-pay thresholds of €45,000 and €20,000/QALY was <1% and 0% respectively. The company presented a variety of scenario analyses and performed appropriate sensitivity analyses. The NCPE performed a number of additional sensitivity analyses to test assumptions made in the model.

4. **Budget impact of pembrolizumab**

The list price of pembrolizumab 100mg vial is €3,421.33. This price is further subject to VAT. The estimated annual cost of treatment per patient is €140,035 including VAT, assuming patients receive 17.38 cycles.

The applicant estimates that 77 to 79 new patients will be eligible for treatment annually, while the NCPE consider that this figure could be closer to 101-103 patients annually. The applicant estimates the gross budget impact to be approximately €50million over 5 years, while the NCPE estimates yielded a projected gross budget impact of €65.3 million. The applicant estimates the 5-year net budget impact to be approximately €47.4million over 5 years, while the NCPE estimates €61.7 million.

5. **Patient submissions**

No patient submissions were received during the course of this appraisal.

6. **Conclusion**

Following review of the applicant submission, pembrolizumab is not considered to be cost-effective relative to standard of care chemotherapy for the treatment of previously...
untreated advanced or metastatic non-small cell lung cancer with a TPS≥50% and no EGFR/ALK mutations, at a threshold of €20,000 or €45,000/QALY.