Cost-effectiveness of pembrolizumab (Keytruda®), in combination with platinum chemotherapy and pemetrexed, for the first-line treatment of metastatic, non-squamous non-small cell lung cancer in adult patients whose tumours have no EGFR or ALK positive mutations.

The NCPE has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®). Following assessment of the applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®), be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

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 **August 2019**

Summary

In December 2018, MSD submitted a dossier which investigated the cost-effectiveness of pembrolizumab, prescribed in combination with platinum chemotherapy and pemetrexed (pembro+chemo), for the first-line treatment of metastatic, non-squamous non-small cell lung cancer (NSCLC) in adult patients whose tumours have no EGFR or ALK positive mutations. MSD are seeking reimbursement in the hospital setting.

Pembrolizumab is a humanised monoclonal antibody (mAb) 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. For this indication, pembrolizumab is administered at a dose of 200mg intravenously (IV) every three weeks. Treatment should be continued for as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Pembrolizumab is formulated as a 100 mg powder for concentrate for solution for infusion.

The main comparator is platinum based chemotherapy in combination with pemetrexed. Other relevant comparators include pembrolizumab monotherapy in patients with tumour proportion score (TPS) ≥50%, and various other chemotherapy regimens. These were considered appropriate by the Review Group and in line with current practice in the Irish setting.

1. Comparative effectiveness of pembrolizumab, prescribed in combination with platinum chemotherapy and pemetrexed.

Clinical evidence for pembro+chemo is predominantly derived from Keynote-189, an ongoing, global phase-III, double-blind, active-controlled trial in patients with metastatic, non-squamous NSCLC and no history of previous treatment for advanced disease. Eligible patients (n=616) randomised 2:1 to investigator's choice of platinum chemotherapy (either carboplatin AUC5 IV or cisplatin 75mg/m2 IV) and pemetrexed 500mg/m2 IV once every three weeks with either 200mg pembrolizumab IV (pembro+chemo arm) or placebo (placebo arm). All patients received a maximum of four cycles (3 months) of chemotherapy

and 35 cycles (2 years) of pembrolizumab. Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent. Primary efficacy endpoints were overall survival (OS) and progression-free survival (PFS). Efficacy analyses were performed on the intent-to treat population (ITT).

At the first interim analysis (September 2017) with a median follow-up of 10.5 months, pembro+chemo demonstrated improved OS compared to the placebo arm (hazard ratio (HR) 0.49 (95% CI 0.38 to 0.64; p<0.001). Median OS was not reached in the pembro+chemo group and the magnitude of long-term treatment benefit is difficult to quantify. Median PFS in the pembro+chemo group was 8.8 months (95% CI 7.6 to 9.2) compared with 4.9 months (95% CI 4.7 to 5.5), HR 0.52 (95% CI 0.43 to 0.64; p<0.001). As the proportional hazards assumption was found not to hold, reported HRs should be interpreted with caution.

Estimates of relative efficacy compared to pembrolizumab monotherapy in patients with TPS ≥50% were derived from an indirect treatment comparison using patient level data from Keynote-024 and Keynote-189. A network meta-analysis was presented to provide estimates of relative efficacy versus other chemotherapy regimens.

2. Safety of pembrolizumab, prescribed in combination with platinum chemotherapy and pemetrexed.

Safety and tolerability was a secondary endpoint of the Keynote-189 trial. Similar numbers of adverse events were reported in both treatment arms: 99.8% and 99% in the pembro+chemo and placebo-combination groups, respectively. Adverse events of grade ≥3 were reported in 67.2% patients in the pembro+chemo arm and 65.8% in the placebo-combination arm. Rates of adverse events were similar between patients receiving carboplatin and those receiving cisplatin. The proportion of patients that discontinued all trial drugs because of adverse events was greater in the pembro+chemo arm compared to placebo-combination (13.8% vs 7.9%). Almost twice as many patients discontinued pembrolizumab treatment compared to placebo (20.2% vs 10.4%).

Across both treatment arms the most common adverse events were nausea, anaemia and fatigue. Diarrhoea and rash were more commonly reported in the pembro+chemo

compared to the placebo-combination arm. Febrile neutropenia was the only grade ≥3 adverse event that was more frequent in the pembro+chemo arm. Adverse events of special interest reported in the pembro+chemo group included pneumonitis, hyperthyroidism, colitis, severe skin reactions, hepatitis and nephritis.

The European Medicines Agency (EMA) concluded that treatment with pembro+chemo was overall more toxic compared to treatment with platinum chemotherapy plus pemetrexed, or pembrolizumab monotherapy alone. They recommended that physicians consider this when deciding on the most appropriate course of treatment for their individual patient.

3. Cost effectiveness of pembrolizumab, prescribed in combination with platinum chemotherapy and pemetrexed.

A partitioned-survival economic model was developed to investigate the cost-effectiveness of pembro+chemo. Data from Keynote-189, Keynote-024 and the network meta-analysis were used to inform the model. A time horizon of 20 years was applied. The model comprised three mutually exclusive health states: pre-progression, post-progression and death. Patients entered the model in the pre-progression state and could move to either the progressed disease state or death. Patients in the progressed disease state could only move to the death state. The model was designed to investigate cost-effectiveness of pembro+chemo in the total population (all-comers) and three subpopulations: TPS <1%, TPS 1 – 49% and TPS ≥50%. Model outcomes included cost per quality adjusted life year (QALY). Comparators included platinum chemotherapy + pemetrexed, pembrolizumab monotherapy (in patients with TPS ≥50%) and other chemotherapy regimens commonly used in Irish clinical practice (including platinum + paclitaxel, platinum + gemcitabine). In the Applicant's base-case model, all costs were estimated based on Time on Treatment (TOT), which was not a pre-defined endpoint of the Keynote-189 trial. Utilities were estimated using data from Keynote-189 and 024. PFS was not used to derive any model outcomes. The Review Group had concerns regarding this as PFS was the only primary outcome from Keynote-189 for which data was mature.

Survival outcomes from Keynote-189 were extrapolated to the full time horizon of the model using parametric extrapolation. OS data for the Keynote-189 trial was immature and

long-term projections are subject to great uncertainty. Incremental cost-effectiveness ratios (ICERs) for all populations were highly sensitive to choice of parametric curve fitting. 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 adverse events and terminal care costs.

The Review Group applied changes to derive their preferred base case, modelling utility based on progression status rather than time to death, and presenting a weighted ICER for the TPS<50% population. The ICER was €85,364 per QALY (incremental costs €95,387; incremental QALYs 1.12) for pembro+chemo vs platinum chemotherapy + pemetrexed in the all-comers population, and €98,250 per QALY in the TPS<50% population. For the TPS ≥50% population, an ICER of €46,314 per QALY (incremental costs €49,375; incremental QALYs 1.07) was calculated for pembro+chemo vs pembrolizumab monotherapy. The Applicant's base-case ICERs are shown in Table 1.

Table 1Applicant base case ICERs

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
All-comers population (pembro+chemo vs chemo)					
Chemo	€53,463	1.23	-	-	-
Pembro+chemo	€148,850	2.53	€95,387	1.3	€73,627
TPS >50% population (pembro+chemo vs pembrolizumab monotherapy)					
Pembrolizumab	€130,693	2.39	-	-	-
Pembro+chemo	€180,067	3.65	€49,375	1.26	€39,042
TPS 1-49 % population (pembro+chemo vs chemo)					
Chemo	€58,287	1.21	-	-	-
Pembro+chemo	€152,575	2.60	€94,289	1.39	€67,607
TPS<1% population (pembro+chemo vs chemo)					
Chemo	€51,688	1.17	-	-	-
Pembro+chemo	€115,501	2.49	€63,813	0.63	€101,648

The Applicant presented a probabilistic sensitivity analysis suggesting that the probability of cost-effectiveness at the cost-effectiveness threshold of €45,000 per QALY in the all-comers population is 1.7%. No analysis was provided for the TPS ≥50% population. The Review Group conducted a probabilistic sensitivity analysis on the NCPE preferred base-case; the probability of cost-effectiveness in the all-comers population, at the cost-effectiveness

thresholds of €20,000 per QALY and €45,000 per QALY is 0%. The Review Group were unable to examine the probability of cost-effectiveness in the TPS ≥50% population.

4. Budget impact of pembrolizumab, prescribed in combination with platinum chemotherapy and pemetrexed.

The price to wholesaler of pembrolizumab 100mg vial is €3,286.81 excluding VAT. The cost per patient per year to the HSE (incorporating VAT and mandatory 5.5% rebate) is €134,320 assuming patients receive 17.39 cycles. For the purpose of the budget impact analysis, a cost per course of treatment with pembro+chemo of €118,439.32 (incl. VAT) is used.

The Applicant predicts that the number of patients eligible for treatment with pembro+chemo will increase annually, starting with 125 patients in year 1 and rising to 129 patients by year 5. However, the NCPE estimate that the figures could be closer to 196 patients in year 1 and 203 by year 5. The Applicant estimates the 5-year cumulative gross budget impact for pembro+chemo to be €75.47 million; the NCPE estimate a figure of €118.32 million. The Applicant estimates the 5-year cumulative net-budget impact to be approximately €33.32 million; the NCPE estimate a figure of €52.1 million.

5. Patient submissions

No patient submissions were received during the course of this appraisal

6. Conclusion

Following review of the Applicant submission, the NCPE recommends that pembrolizumab (Keytruda®), prescribed in combination with platinum chemotherapy plus pemetrexed for the first line treatment of non-squamous NSCLC, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.*

* This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medial Goods) Act 2013.