



Cost-effectiveness of pembrolizumab (Keytruda®) for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a TPS \geq 1% and who have received at least one prior treatment regimen

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 (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.

Summary

In July 2017, MSD submitted a dossier examining the cost-effectiveness of pembrolizumab for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 with a tumour proportion score (TPS) $\geq 1\%$ and who have received at least one prior treatment regimen. Final data submitted by the Applicant was received on 6th March 2018.

The authorised dose for this indication is 2mg/kg every three weeks by IV infusion. 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-L1 pathway by pembrolizumab allows the immune system to mount a response against the tumour cells by potentiating the T cell immune responses, including anti-tumour responses.

In the submission, standard of care chemotherapy (docetaxel) and nivolumab were the comparators investigated; this was considered appropriate by the NCPE.

1. Comparative effectiveness of pembrolizumab

Relative efficacy outcomes for the comparison with docetaxel were derived from the Keynote-010 study. This study was an open-label, multi-national, Phase III randomised controlled trial of 1033 patients with locally advanced or metastatic NSCLC, who had progressed after previous treatment, and had TPS $\geq 1\%$ as measured by the 22C3 pharmDx assay. Patients were assigned to one of three arms on a 1:1:1 basis, pembrolizumab every 3 weeks at a dose of 10mg/kg or 2mg/kg, or docetaxel 75mg/m² every three weeks. 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 presented in the pembrolizumab 2mg/kg and docetaxel arms. Data were presented from numerous data-cuts.

In the trial, pembrolizumab 2mg/kg was associated with an increase in overall survival (OS) compared to docetaxel in the patient population with TPS \geq 1%. The median OS with pembrolizumab was 10.4 months (95% CI 9.4, 11.9) compared to 8.5 months (95% CI 7.5, 9.8) with docetaxel. Pembrolizumab was not associated with a statistically significant increase in progression free survival (PFS). The overall response rate (ORR) was statistically significantly improved with pembrolizumab treatment, with an ORR of 18% seen in the pembrolizumab arm compared to 9.3% in the docetaxel arm. There were not clinically meaningful differences in quality of life between the two treatment arms.

A network meta-analysis (MMA) was conducted to provide estimates of relative treatment efficacy for nivolumab versus pembrolizumab. The applicant used a fractional polynomials approach and presented various scenarios involving different assumptions.

2. Safety of pembrolizumab

Safety and tolerability was a secondary endpoint of the Keynote-010 trial. Similar numbers of adverse events (AEs) were reported in both arms, in 97.6% pembrolizumab patients and 96.1% docetaxel patients. AEs considered by the investigator to be related to treatment were reported in 81.2% docetaxel patients compared to 63.4% pembrolizumab patients. There was a higher incidence of Grade 3-5 AEs in the docetaxel arm compared to pembrolizumab, 56% versus 46.6%. Similar numbers of serious AEs were reported in both arms, approximately 34%. Treatment discontinuation due to AEs was higher with docetaxel than pembrolizumab. There were 3 deaths attributed to study treatment in the pembrolizumab arm and 5 in the docetaxel arm. The most commonly reported treatment-related AEs with pembrolizumab were fatigue (13.6%), decreased appetite (13.6%), nausea (10.9%) and rash (8.6%). The most common Grade 3-5 AEs with pembrolizumab were pneumonia (4.1%), dyspnoea (3.8%) and fatigue (3.5%). Overall pembrolizumab was associated with a lower incidence of Grade 3-5 AEs and has an improved safety profile compared to docetaxel chemotherapy.

3. Cost effectiveness of pembrolizumab

For the cost-effectiveness analysis, the effectiveness inputs in the model were PFS and OS. Clinical efficacy inputs were derived from Keynote-010 and the NMA. Cost-effectiveness was

investigated using a three 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-010. Patients in the 'Progressive disease' state are assumed to receive one line of subsequent treatment.

Survival outcomes from Keynote-010 were extrapolated to the full time horizon of the model using parametric extrapolation. OS data was adjusted for treatment crossover. The applicant presented two separate sets of base case assumptions, which differed in the approach to survival extrapolation, but did not express a preference for which one should be used for decision making. Resource use in the model was based on studies identified by literature review and previous health technology assessments, 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 $\geq 5\%$ in either arm of Keynote-010 were included in the economic model, in addition to diarrhoea \geq Grade 2 and febrile neutropenia. In the base case utilities were modelled by a combination of time-to-death and progression based methods.

Analyses presented in this summary document are based on the list prices of the interventions. The NCPE implemented a number of changes to the model, resulting in a final ICER of €85,215/QALY (incremental costs €48,549, incremental QALYs 0.570) versus docetaxel. The NCPE consider that this ICER may be an underestimate as it does not incorporate the most recent treatment duration data, and assumes that treatment is discontinued at two years regardless of disease status. For the comparison with nivolumab, nivolumab was associated with lower costs and higher QALYs and so dominated pembrolizumab (incremental cost -€5,103, incremental QALYs 0.129).

In the applicant base case scenario considered most relevant by the NCPE, the ICER for pembrolizumab versus docetaxel was €81,518/QALY (incremental costs €50,037,

incremental QALYs 0.614), and for pembrolizumab versus nivolumab was €31,318/QALY (incremental costs €2,003, incremental QALYs 0.064).

The applicant presented a probabilistic sensitivity analysis. The probability of cost-effectiveness at a willingness to pay threshold of €20,000 and €45,000 was 0%. 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 50mg vial is €1,725.50. This price is further subject to VAT. The estimated annual cost of treatment per patient is €58,544.48 including VAT and rebate, assuming patients receive 9.73 cycles.

The estimates of budget impact assume that only patients with TPS 1-49% are eligible for treatment. The applicant estimates that 51 to 52 new patients will be eligible for treatment annually, while the NCPE consider that this figure could be closer to 70+ patients annually. The applicant estimates the 5-year gross budget impact to be approximately €14.76 million annually while the NCPE estimates yielded a projected gross budget impact of €21.68 million. The applicant estimates the 5-year net budget impact to be approximately €14.69 million, while the NCPE estimates €21.5 million.

5. State if any patient submissions were received, and name submitting organisations.

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

6. Conclusion

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.