NCPE Assessment

Technical Summary

Pembrolizumab (KEYTRUDA®)

22042

May 2024

Applicant: MSD Ireland

Pembrolizumab for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma and who have undergone complete resection.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (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, for this indication, if cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (MSD Ireland) Health Technology Assessment of pembrolizumab (Keytruda®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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 April 2023, MSD Ireland (the Applicant) submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab (Keytruda®) for the treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC and who have undergone complete resection. The Applicant is seeking reimbursement of pembrolizumab (Keytruda®) on the Oncology Drugs Management System. Pembrolizumab is an immunotherapy, which binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2. This potentiates T-cell responses, including anti-tumour responses, which restores the immune response.

1. Comparative effectiveness of pembrolizumab

The efficacy and safety of pembrolizumab was investigated in the KEYNOTE-716 trial, which is an ongoing Phase III study in participants with Stage IIB or IIC cutaneous melanoma. The study was conducted in two parts. In Part 1, participants were randomised 1:1 to receive double-blinded adjuvant therapy with pembrolizumab (adult dose: 200 mg intravenously [IV]; adolescent dose: 2 mg/kg IV) once every three weeks (Q3W), or saline placebo IV once Q3W. Both treatments were given for 17 cycles (approximately 1 year) or until disease recurrence or unacceptable toxicity. Both treatments were given alongside routine surveillance, which is considered to be the standard of care in Ireland. Eligible participants with disease recurrence, could then receive treatment with pembrolizumab (up to 17 cycles for resectable disease or up to 35 cycles for unresectable disease) in the crossover or re-challenge, open-label single-arm Part 2 of the trial.

Data from the January 2023 interim analysis 4 (IA4) informed the submission, in which the median duration of follow-up was 39.4 months (range: 26.0 to 51.4). The primary endpoint was recurrence-free survival (RFS). Overall survival (OS) and distant metastasis free survival (DMFS) were secondary endpoints. Part 1 of KEYNOTE-716 is complete; Part 2 was ongoing at the time of this Health Technology Assessment. The efficacy and safety results presented in the submission were from Part 1 only. The clinical efficacy population included 976 participants (pembrolizumab: 487; routine surveillance only: 489). The mean age was 59.3 years; 60.3% were male and 89.5% were white. Only two adolescents were enrolled;

generalisability of the KEYNOTE-716 trial to adolescents is thus uncertain. Across both arms, 64% and 35% of patients had Stage IIB and Stage IIC melanoma respectively.

As of IA4, median RFS was not estimable; the hazard ratio (HR) was 0.62, 95% CI 0.49 to 0.79. The Review Group highlights that the data are immature, as only 24% and 35.6% of patients in the pembrolizumab and routine surveillance only arms respectively had experienced a RFS event. The median DMFS was not reached in either arm, however fewer patients in the pembrolizumab arm had experienced an event (HR: 0.59, 95% CI 0.44 to 0.79). The OS data remains immature; longer follow-up is required to determine if pembrolizumab will be associated with an OS benefit for this indication. The impact of adjuvant pembrolizumab on the sequencing and efficacy of subsequent treatments in the advanced setting remains unknown.

2. Safety of pembrolizumab

The safety profile of pembrolizumab has previously been investigated in patients with various tumour types, including melanoma, across multiple studies. Safety data from Part 1 of the KEYNOTE-716 included 969 participants (n=483 receiving pembrolizumab) who received at least one dose of study treatment. At IA4, almost all participants in the pembrolizumab and routine surveillance only arms experienced an adverse event (AE) (95.4% versus 91.8%). The most common AEs (occurring in at least 5% of participants in one or more arms) were fatigue (29.6% versus 26.1%), diarrhoea (28.2% versus 20.6%), pruritis (27.7% versus 13.6%), and arthralgia (23.6% versus 17.5%). AEs (related to the study drug) leading to discontinuation were more common in the pembrolizumab arm (17.2% versus 4.7%). No new safety signals were observed in KEYNOTE-716, indicating that safety was consistent with the established safety profile of pembrolizumab.

3. Cost effectiveness of pembrolizumab

Methods

The analysis was conducted from the perspective of the health payer (HSE). The cost-effectiveness model consisted of four mutually exclusive health states designed to reflect the natural history of melanoma: recurrence-free, locoregional recurrence, distant

metastases, and death. The distant metastasis health state was divided into pre- and post-progression sub-states. Treatment effects, captured by the model, were the delay of disease recurrence and death. Direct evidence for pembrolizumab versus routine surveillance only were available from the KEYNOTE-716 trial (IA4) for the recurrence-free and locoregional recurrence health states and the distant metastasis pre-progression sub-state. Transitions from distant metastasis to death were informed by published literature. The Applicant assumed that the reduced risk of recurrence with pembrolizumab (observed in KEYNOTE-716) was maintained, after discontinuation of pembrolizumab, in the recurrence-free health state. The Review Group considers the trial data too immature to support this assumption. The NCPE-adjusted base case instead assumes a maintained benefit, after treatment discontinuation, up to year 5, followed by a gradual decrease until year 10, where there is no difference between treatments. The Applicant's approach to modelling the transition from recurrence-free to locoregional recurrence was considered to underestimate RFS, based on Clinical Opinion. Therefore, the Review Group selected an alternative model for both arms yielding more plausible estimates of RFS.

The KEYNOTE-716 trial was considered the most appropriate source of health-related quality of life evidence for the recurrence-free and locoregional recurrence health states. Utility for the distant metastasis health state was based on the time spent in the pre- and post-progression sub-states, as stratified by each treatment arm. The pre-progression sub-state utility was informed by KEYNOTE-716; the post-progression sub-state utility was informed by published literature.

The duration of treatment was informed by treatment-discontinuation data from KEYNOTE-716. The base case analyses assume that patients who receive pembrolizumab for this indication will not receive subsequent treatment with immunotherapies (i.e pembrolizumab, nivolumab or ipilimumab).

Results

Analyses presented here are based on the list prices. Results are presented for both the Applicant and NCPE-adjusted base case in Tables 1 and 2, respectively.

Table 1: Applicant base-case incremental cost-effectiveness results[a,b,c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Routine surveillance	137,721	8.62	-	-	-
Pembrolizumab	186,378	9.58	48,657	0.96	50,665

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality Adjusted Life Year.
a A commercial-in-confidence PAS is in place for pembrolizumab, but it is not included in this table. A discount rate of 4% applied to costs and outcomes.
b The corresponding probabilistic ICER is €49,818, based on 1,000 iterations.
c Figures in the table are rounded, and so calculations may not be directly replicable.

Table 2: NCPE-adjusted base-case incremental cost-effectiveness results[a,b,c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Routine surveillance	146,293	8.65	-	-	-
Pembrolizumab	199,479	9.58	53,186	0.93	57,496

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality Adjusted Life Year.
a A commercial-in-confidence PAS is in place for pembrolizumab, but it is not included in this table. A discount rate of 4% applied to costs and outcomes.
b The corresponding probabilistic ICER is €63,118, based on 1,000 iterations.
c Figures in the table are rounded, and so calculations may not be directly replicable.

The probabilities of cost effectiveness under the NCPE-adjusted base case assumptions, were 16% at the €20,000/QALY threshold and 40.8% at the €45,000/QALY threshold. Sensitivity analysis indicated that the most influential parameters in the NCPE-adjusted base case were the approach taken to model the transition from recurrence-free to locoregional recurrence and treatment costs in the first-line distant metastasis and locoregional recurrence health states.

A Price-ICER analysis, under the NCPE-adjusted base case assumptions, indicates that a reduction of about 23%, in the price-to-wholesaler of pembrolizumab, would be required to meet the €45,000/QALY threshold.

The Review Group conducted a scenario analysis whereby a proportion of patients in both arms are assumed to receive subsequent treatment with immunotherapies. The NCPE-adjusted deterministic ICER increased to €60,013/QALY.

4. Budget impact of pembrolizumab

The price to wholesaler for pembrolizumab (4ml vial of 25mg/ml) is €3,153.86. The cost of pembrolizumab per treatment course is €99,886 per adult and €64,925 per adolescent, assuming a mean treatment duration of 41.4 weeks from the KEYNOTE-716 trial. Many of the budget-impact model inputs are uncertain and this follows through to the outputs of the budget impact. The Applicant predicted that 48 patients will be treated in Year 1 rising to 50 patients in Year 5, resulting in a total of 244 patients receiving treatment over five years. The Review Group considered this to be an underestimate, based on Clinical Opinion obtained by the Review Group. The NCPE base-case assumed 276 patients would receive treatment over five years. The 5-year cumulative gross drug budget impact of pembrolizumab was estimated, by the Applicant, to be €24.4 million (€19.5 million excluding VAT). The Review Group estimate the gross drug budget impact to be €27.6 million (€22 million excluding VAT). Given that the comparator is routine surveillance, the net drug budget impacts are equivalent to the respective gross drug budget impacts.

5. Patient Organisation Submission

A patient organisation submission was received from Melanoma Support Ireland.

6. Conclusion

The NCPE recommends that pembrolizumab be considered for reimbursement, for this indication, 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.