NCPE Assessment

Technical Summary

Pembrolizumab (Keytruda®)

HTA ID: 22026

April 2024

Applicant: Merck Sharp & Dohme

Pembrolizumab as monotherapy for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

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 (Merck Sharp & Dohme) Health Technology Assessment 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 March 2023, Merck Sharp & Dohme submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab (Keytruda®) as monotherapy for the adjuvant treatment of adults with renal cell carcinoma (RCC) at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. Merck Sharp & Dohme are seeking reimbursement of pembrolizumab on the Oncology Drug Management Scheme.

Pembrolizumab is a humanised monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity; thus, pembrolizumab potentiates T-cell immune responses, including anti-tumour responses. Pembrolizumab is administered as an intravenous (IV) infusion at a dose of 200mg once every three weeks or 400mg once every six weeks. This Health Technology Assessment and associated clinical trial evidence (KEYNOTE-564) are based on the 200mg dose. Treatment should be continued until disease recurrence, unacceptable toxicity, up to a maximum of one year.

The Applicant anticipates that pembrolizumab will be used according to its licensed indication (as stated above). In line with the current standard of care in Ireland, the proposed comparator is best supportive care in the form of routine surveillance.

1. Comparative effectiveness of pembrolizumab (Keytruda®)

The clinical evidence, supporting regulatory approval of pembrolizumab, comes from the ongoing KEYNOTE-564 trial. KEYNOTE-564 is a phase III, double-blind, randomised controlled trial (RCT) designed to evaluate the safety and efficacy of pembrolizumab (n=496) versus placebo (n=498). Eligible participants were adults with histologically confirmed RCC with clear cell component considered at intermediate-high risk, or high risk of recurrence following nephrectomy or with M1 NED (metastatic disease with no evaluable disease) status following nephrectomy and resection of metastatic lesions. Treatment was continued until confirmation of disease recurrence or unacceptable toxicity, up to a maximum of one-year. The primary endpoint was investigator-assessed disease-free survival (DFS), with overall survival (OS) measured as a key secondary endpoint.

Results from the December 2020 data-cut (median follow-up 23.9 months) include the first interim analysis, with updated results also available from a June 2021 data-cut (efficacy update analysis) (median follow-up 29.7 months). Both sets of results provided the clinical basis supporting regulatory approval. At the June 2021 data-cut, median DFS and OS were not reached in either treatment arm. The DFS hazard ratio (HR) was 0.63, 95% confidence interval (CI) 0.50 to 0.80, with an OS HR of 0.52, 95% CI 0.31 to 0.86. This data-cut was used to inform the cost-effectiveness analysis. The Review Group's main concern regarding the clinical evidence is the immaturity of the trial data. The 3rd pre-specified analysis with 57.2 months was recently published in the NEJM, with broadly consistent results to those observed in the earlier analyses. However this analysis was not available in time for inclusion in the current assessment. Final results are anticipated in December 2025.

2. Safety of pembrolizumab (Keytruda®)

Overall, the safety data from KEYNOTE-564 were consistent with the known safety profile of pembrolizumab, with no new safety concerns identified. Grade three or above adverse events (AEs) that occurred in greater than 5% of the KEYNOTE-564 population were considered in the cost-effectiveness analysis.

Any grade AEs were reported in 96.3% of individuals receiving pembrolizumab and 91.3% receiving placebo. Grade three or above AEs were more common with pembrolizumab (32.2%) compared to placebo (17.7%). The most commonly reported AEs, of any grade, experienced with pembrolizumab included fatigue, diarrhoea, pruritis, arthralgia, hypothyroidism, and rash. Fatigue and diarrhoea were also commonly reported with placebo. AEs with the greatest percentage difference between pembrolizumab and placebo were hypothyroidism, hyperthyroidism, pruritis, and rash, all of which are known AEs for pembrolizumab. The most commonly reported AEs of special interest, related to thyroid disorders and were experienced by a greater number of individuals receiving pembrolizumab.

A recent editorial in the NEJM highlighted the potential for overtreatment exposing approximately one in two patients to undue risks of short-term and long-term immune-mediated

adverse effects.

3. Cost effectiveness of pembrolizumab (Keytruda®)

Methods

The cost-effectiveness evaluation was informed by direct evidence from KEYNOTE-564; placebo was considered a proxy for routine surveillance. A cost-utility analysis was conducted using a four-state Markov cohort model developed in Microsoft Excel®. The model included four mutually exclusive health states; disease-free (DF), locoregional recurrence (LR), distant metastases (DM), and an absorbing death state.
Transition probabilities from the DF health state were based on extrapolated DFS and OS data from the KEYNOTE-564 trial. The Applicant selected jointly-fitted models with a time-varying effect for transitions from the DF health state. The Review Group had concerns regarding the validity of using a jointly fitted model. Independently fitted models were used in the NCPE-adjusted base case. Transitions from the DF to LR and DM health states are main drivers of the cost-effectiveness and are subject to a large amount of uncertainty due to the immaturity of the DFS data from KEYNOTE-564. OS data from KEYNOTE-564 informing the DF to death transition are also immature. Transitions from LR to DM were informed by data from a US based retrospective chart review study (n=32). Due to the small number of direct transitions from LR to death in this study, death from the LR state was assumed equivalent to transitions from DF to death. Transitions from the DM health state were based on the published literature and were dependent on first-line treatments received for advanced RCC.

Utility estimates for the DF and LR health states were informed by the KEYNOTE-564 trial. Due to a paucity of data in the DM setting in KEYNOTE-564, estimates were informed by the KEYNOTE-426 trial of pembrolizumab in combination with axitinib in advanced RCC. Health state utility values were adjusted for age and disutilities were included for AEs.

Direct medical costs were included for drug acquisition (including administration), disease management including salvage surgery for recurred disease, and subsequent treatments. A once-off end-of-life cost was applied. Irish costs were used where possible. The base case assumes that all individuals in the routine surveillance arm are eligible for nivolumab plus ipilimumab in the first-line advanced RCC setting. Individuals receiving adjuvant

pembrolizumab were assumed eligible for nivolumab plus ipilimumab if at least 24 months had elapsed between initiation of adjuvant pembrolizumab and development of DM.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group made several changes to the Applicant base case based on plausible alternative assumptions. These included using individually fitted survival curves in modelling transitions from the DF health state, together with the inclusion of serious AEs and grade 1 and 2 AEs relating to thyroid disorders. The results of the Applicant's base case, and NCPE-adjusted, deterministic cost-effectiveness analyses are presented in Table 1.

Table 1: Incremental cost -effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis					
Pembrolizumab	128,888	9.86	-	-	-
Routine surveillance	84,807	8.69	44,082	1.17	37,705[a]
NCPE-adjusted analysis					
Pembrolizumab	144,227	9.26	-	-	-
Routine surveillance	87,578	8.60	56,648	0.66	86,073[b]

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year
[a] Corresponding probabilistic ICER using 1,000 iterations = €40,146/QALY
[b] Corresponding probabilistic ICER using 1,000 iterations = €85,157/QALY
Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

Sensitivity analysis

Mean probabilistic ICERs were aligned with the deterministic ICERs. Sensitivity analyses indicated that the main driver of cost-effectiveness in both the Applicant and NCPE-adjusted base case was the approach to modelling transitions from the DF health state. The cost-effectiveness analysis was also sensitive to the rate of transition from the LR to DM health state, utility estimates, costs associated with drug administration and terminal care, and hazards of PFS and OS failure within the DM health state.

An analysis of the price-ICER relationship was conducted using the NCPE-adjusted base case. The price reductions required to achieve cost-effectiveness at the €20,000 and €45,000 per QALY thresholds were 60.2% and 40.6%, respectively.

4. Budget impact of pembrolizumab (Keytruda®)

The price-to-wholesaler of a 100mg vial of pembrolizumab is €3,153.86. VAT is applicable. The total cost per patient, per treatment course is about €97,502 (€77,916 excluding VAT), assuming a mean treatment duration of 13.5 treatment cycles, informed by the KEYNOTE-564 trial. This estimate included all relevant fees, mark ups and rebates.

The Applicant used several sources to inform eligible patient estimates. These included National Cancer Registry Ireland (NCRI) and Cancer Research UK data, data from the published literature and clinical opinion. Many of the inputs are very uncertain and there is therefore considerable uncertainty associated with budget impact estimates. The Applicant estimated an initial market share of 40% in year one increasing to 60% in year five. Overall, the Applicant estimated 49 individuals would be treated with pembrolizumab in year one, rising to 70 in year five. It is noted that the recent editorial in the NEJM highlighted that if the selection criteria of KEYNOTE-564 are implemented this will lead to overtreatment. As such, the budget impact figures will be underestimates. Based on the Applicant's assumptions, the five-year cumulative gross drug budget impact was estimated to be €31.45 million (€25.13 million excluding VAT). Reimbursement of pembrolizumab for this indication is not expected to result in the displacement of other drugs. Therefore, the net drug budget impact is the same as the gross drug budget impact.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

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.

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