NCPE Assessment

Technical Summary

Pembrolizumab (Keytruda®)

22006

18 December 2023

Applicant: MSD Ireland

Pembrolizumab in combination with lenvatinib for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

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®) not be considered for reimbursement unless 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 February 2023, MSD Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab (Keytruda®) in combination with lenvatinib (Lenvima®) for the treatment of advanced or recurrent endometrial carcinoma. MSD Ireland is seeking reimbursement of pembrolizumab for this indication on the Oncology Drugs Management System. Pembrolizumab is a programmed death-1 (PD-1) receptor inhibitor that is currently reimbursed for a number of cancer indications on the ODMS. Current standard-of-care for this indication comprises chemotherapy such as platinum-based chemotherapy (PBC), doxorubicin or paclitaxel. Pembrolizumab is administered as an intravenous infusion at a dose of 200mg once every three weeks. Lenvatinib is administered orally at a dose of 20mg once daily continuously. Lenvatinib is currently reimbursed for thyroid carcinoma and hepatocellular carcinoma on the High Tech Drug Arrangement.

1. Comparative effectiveness of pembrolizumab (Keytruda®)

The efficacy and safety of pembrolizumab was investigated in the KEYNOTE-775 trial, a phase III, open-label randomised active controlled trial in participants with advanced, recurrent or metastatic endometrial carcinoma. Pembrolizumab in combination with lenvatinib (PEM + LEN) (n=411) was compared with treatment of physician's choice (TPC; n=416) which comprised doxorubicin or paclitaxel. Participants had demonstrated radiographic progression on prior PBC. Pembrolizumab was administered for a maximum of 24 months (35 x 21-day treatment cycles). The dual primary endpoints in the KEYNOTE-775 trial were progression-free survival (PFS), based on blinded independent central review, and overall survival (OS). Results for the intention-to-treat (ITT) population based on the final analysis (data cut-off date 1 March 2022) were presented by the Applicant.

The median duration of follow-up in the final analysis was 14.7 months for all patients. The mean PFS for patients in the PEM+LEN arm was 11.5 months compared with 6.5 months in the TPC arm (hazard ratio (HR) for PFS 0.56 (95% confidence interval (CI) 0.48 to 0.66). The

mean overall survival was 20.3 months for patients in the PEM+LEN arm compared with 15.1 months in the TPC arm (HR for OS 0.65 (95% CI 0.55 to 0.77)). There was no significant difference between treatment arms in mean change from baseline at 12 weeks in health-related quality of life measured using the EQ-5D-5L.

The Review Group noted that the control arm in KEYNOTE-775 did not comprise all relevant comparators in Irish clinical practice, specifically PBC. Clinical opinion, to the Review Group, indicated that patients with advanced or recurrent endometrial carcinoma would be likely to receive PBC re-challenge if progression occurred over a year since receipt of PBC or if PBC had been received in the adjuvant or neo-adjuvant setting. The Review Group highlight additional limitations of the clinical evidence including the open-label nature of the trial, uncertainty regarding the generalisability of results to Irish clinical practice and the optimal treatment duration of pembrolizumab.

2. Safety of pembrolizumab

The safety data for PEM+LEN is informed by the All Participants as Treated population of KEYNOTE-775, which comprises all patients who received at least one dose of study treatment (n=794). A higher proportion of patients in the PEM+LEN arm experienced grade three or higher adverse events compared with the TPC arm (88.9% compared with 72.7%). A third of patients in the PEM+LEN arm discontinued treatment (33%) due to adverse events, compared with 8% of participants in the TPC arm. The safety profile of PEM+LEN was generally consistent with the known safety profile of pembrolizumab monotherapy and lenvatinib monotherapy, respectively.

3. Cost effectiveness of pembrolizumab

Methods

A de novo partitioned survival model, developed in Microsoft Excel®, was used to evaluate the cost effectiveness of PEM+LEN compared with TPC (doxorubicin or paclitaxel). The model included three mutually exclusive health states; progression-free; post-progression and death. These states capture PFS and OS. Direct evidence from the final analysis of the KEYNOTE-775 trial was used to inform treatment effectiveness inputs in the cost-

effectiveness model. The Applicant considered that OS in the TPC arm should be adjusted for treatment switching, as 30.8% of patients in the TPC arm who experienced disease progression (n=80; 19.2% of the overall TPC arm) received subsequent therapies that are not reimbursed in Irish clinical practice. The Applicant considered the two-stage estimation (TSE) approach, without re-censoring, to be the most appropriate treatment switching method. Alternative treatment switching adjustment approaches were explored by the Applicant. Flexible spline models were used to extrapolate OS data for both the PEM+LEN arm and the adjusted data for the TPC arm, respectively. The Review Group note that standard parametric extrapolation distributions for each of the treatment switching methods explored, including the unadjusted (ITT analysis), were not available within the cost-effectiveness model. For PFS, the Applicant used the same flexible spline approach to extrapolate PFS data from KEYNOTE-775.

Utility data were derived from EQ-5D-5L data collected in the KEYNOTE-775 trial and mapped to the EQ-5D-3L using the van Hout et al algorithm. The Applicant base case analysis for estimating health-state utility values incorporated time-to-death, resulting in mean utility values across 12 health states. The Review Group noted very few observations for health states towards end of life. As such, the Review Group considered health state utility values based on progression status only to be more robust for inclusion.

The Applicant used the extrapolated time-on-treatment curve from the KEYNOTE-775 trial, capped by PFS, to estimate treatment course costs for both PEM+LEN and TPC. The Review Group considered that this approach underestimates the treatment course costs of pembrolizumab given the 24-month stopping rule that was included in the trial. There is no stopping rule specified in the Summary of Product Characteristics (SmPC) for this indication. In the NCPE adjusted base case time-to-disease progression is used to inform treatment course duration of pembrolizumab, in line with the SmPC. The Applicant assumed that dosing reductions for lenvatinib would occur on a weekly basis. The Review Group highlighted this is likely not reflective of Irish clinical practice; using the relative dosing intensity of lenvatinib from the trial had a moderate effect on the ICER.

The Review Group highlighted that, due to limitations of the cost-effectiveness analysis, the

Review Group could not validate whether the most appropriate OS modelling approach had been undertaken. There is potential for cost-effectiveness estimates to be biased in favour of PEM+LEN. Furthermore, the cost-effectiveness of PEM+LEN relative to PBC, which the Review Group consider to be a relevant comparator, is unknown.

Results

Results of the Applicant base case deterministic cost-effectiveness analysis, are presented in Table 1. The Review Group implemented alternative assumptions for estimating the treatment duration of pembrolizumab and health state utility values in the NCPE adjusted base case. Results of the NCPE adjusted base case analysis are presented in Table 2.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC	43,877	1.03	-	-	-
PEM+LEN[b]	158,639	1.98	114,762	0.94	121,749/QALY

***PEM**: pembrolizumab; **LEN**: lenvatinib; **TPC**: Treatment of physician's choice; **QALY**: quality-adjusted life year; **ICER**: incremental cost effectiveness analysis*

[a] Corresponding probabilistic ICER using 1,000 iterations =€122,674/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

[b] There are PAS' currently in place for pembrolizumab and lenvatinib, not included in this table.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC	43,877	1.03	-	-	-
PEM+LEN[b]	216,089	1.90	172,213	0.87	197,770/QALY

***PEM**: pembrolizumab; **LEN**: lenvatinib; **TPC**: Treatment of physician's choice; **QALY**: quality-adjusted life year; **ICER**: incremental cost effectiveness analysis*

[a] Corresponding probabilistic ICER using 1,000 iterations =€195,334/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

[b] There are PAS' currently in place for pembrolizumab and lenvatinib, not included in this table.

Sensitivity analysis

The probability of PEM+LEN being cost-effective was 0% at the willingness-to-pay thresholds of €20,000/QALY and €45,000/QALY, respectively, using NCPE adjusted base case assumptions. Parameters relating to OS and PFS curve fits for the TPC arm are the most influential parameters on results of the NCPE adjusted base case analysis. Using the unadjusted ITT analysis to inform OS for the TPC arm resulted in the ICER increasing to €221,571/QALY under the NCPE adjusted base case assumptions. Given an absence of long-term efficacy data for PEM+LEN, there is potential for the treatment efficacy of PEM+LEN to wane. A scenario assuming there will be a decline in the treatment efficacy of PEM+LEN

between years five and seven, such that by year seven there will be equivalence in the hazard for death between the PEM+LEN and TPC arm results in an ICER of €240,861/QALY.

Price-ICER analyses using the NCPE adjusted base case assumptions indicate that a 98.6% discount would be required on the price of pembrolizumab in order for pembrolizumab to be considered cost-effective at the willingness-to-pay threshold of €45,000/QALY. The associated cost of lenvatinib is an influence on the cost-effectiveness of pembrolizumab. There are commercial-in-confidence patient access schemes currently in place for pembrolizumab and lenvatinib; this is not considered in these estimates.

4. Budget impact of pembrolizumab

The price-to-wholesaler of a 100mg vial of pembrolizumab is €3,153.86. The Applicant anticipates that patients will receive 10.1 x 21-day treatment cycles of pembrolizumab and 11 x 21-day treatment cycles of lenvatinib. Using the NCPE adjusted base case assumptions from the cost effectiveness model, treatment with pembrolizumab is anticipated to continue for 78.67 weeks, equivalent to 26.22 x 21-day treatment cycles. Treatment with lenvatinib is estimated to continue for 55.23 weeks, equivalent to 18.41 x 21-day treatment cycles. In the NCPE adjusted base case, the per-patient cost of PEM+LEN in year one of treatment is estimated to be €164,093 (including value added tax (VAT)) and the cost in year two of treatment is estimated to be €66,633 (including VAT).

The Applicant assumes that 20 patients will be treated in year one rising to 29 patients in year five. The Review Group considered the treated patient population was underestimated. The Review Group estimated that a higher proportion of patients with advanced or recurrent endometrial carcinoma who have received PBC as first-line therapy will be eligible for second-line treatment (42.5% compared with 36% in the Applicant estimates). The Review Group estimate that 23 patients will be treated in year one rising to 34 patients in year five. The Review Group highlight that patients who receive PBC as adjuvant or neoadjuvant therapy only and are, thus, eligible for PEM+LEN as first-line treatment for advanced endometrial carcinoma, are not considered in budget impact estimates. In the KEYNOTE-775 trial, this cohort of patients comprised 36% of the KEYNOTE-775 trial population.

Using the Applicant assumptions, the five-year gross drug budget impact of PEM+LEN is estimated to be €13.08 million, including VAT. The cumulative five-year net drug budget impact is estimated to be €12.72 million, including VAT. The Review Group estimated the cumulative five-year gross drug budget to be €34.21 million, including VAT and the cumulative net drug budget impact to be €33.78 million including VAT.

5. Patient Organisation Submission

A patient organisation submission was received from The Irish Society of Gynaecological Oncology Patient and Public Involvement.

6. Conclusion

The NCPE recommends that pembrolizumab, in combination with lenvatinib, not be considered for reimbursement unless 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.*