NCPE Assessment

Technical Summary

Pembrolizumab (Keytruda®)

22027

December 2023

Applicant: MSD Ireland

Pembrolizumab in combination with chemotherapy as neo-adjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®) for this indication. Following assessment of the Applicant's submission, the NCPE recommends that pembrolizumab plus chemotherapy, followed by pembrolizumab monotherapy (Keytruda®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (MSD Ireland) Health Technology Assessment of pembrolizumab plus chemotherapy, followed by pembrolizumab monotherapy. 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 March 2023, MSD Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost effectiveness and potential budget impact of pembrolizumab plus chemotherapy (neo-adjuvant), followed by adjuvant pembrolizumab monotherapy, compared to neo-adjuvant chemotherapy. Pembrolizumab plus chemotherapy is licensed as neo-adjuvant treatment, and then pembrolizumab is continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early stage triple negative breast cancer (TNBC) at high risk of recurrence. Reimbursement is sought under the Oncology Drugs Management System. Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity, involved in the control of T-cell responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses.

The recommended dose for pembrolizumab is 200mg once every three weeks (or 400mg once every six weeks) administered via intravenous (IV) infusion. Treatment with pembrolizumab plus chemotherapy is recommended for eight cycles if pembrolizumab is given at 200mg once every three weeks (or four cycles if pembrolizumab is given at 400mg once every six weeks) in the neo-adjuvant setting, or until disease progression that precludes definitive surgery or unacceptable toxicity. Adjuvant treatment with pembrolizumab as monotherapy is recommended for nine cycles of 200mg once every three weeks (or five cycles of 400mg once every six weeks), or until disease recurrence or unacceptable toxicity. The Applicant's submission considered the pembrolizumab 200mg once every three weeks regimen.

The current standard of care (SOC) in the neo-adjuvant setting, in Ireland, is paclitaxel and carboplatin (cycles one to four), followed by doxorubicin or epirubicin and cyclophosphamide (cycles five to eight). The Applicant reported that no active pharmacological treatment is currently offered in the adjuvant setting (where neo-adjuvant chemotherapy has been delivered). Based on clinical opinion to the Review Group, the Review Group considers that there are other potential comparators. These include neo-

adjuvant chemotherapy (excluding carboplatin) and adjuvant chemotherapy (in those who have not received neo-adjuvant treatment). Also, up to 66% of patients who do not achieve a pathological complete response (pCR) to neo-adjuvant treatment are expected to receive adjuvant capecitabine.

1. Comparative effectiveness of pembrolizumab plus chemotherapy

The efficacy and safety of pembrolizumab plus chemotherapy (followed by pembrolizumab monotherapy) was assessed in KEYNOTE-522. This is an ongoing, phase III, double-blind, randomised controlled trial of pembrolizumab plus chemotherapy (neo-adjuvant), followed by adjuvant pembrolizumab monotherapy (herein 'the pembrolizumab arm' [n=784]), compared to neo-adjuvant chemotherapy, followed by no active adjuvant treatment (herein 'the chemotherapy arm' [n=390]), in patients with locally-advanced or early stage TNBC with a high risk of recurrence. During the neo-adjuvant treatment phase, participants in the pembrolizumab arm received pembrolizumab, 200mg IV once on Day 1 of each three-week cycle, plus chemotherapy. Chemotherapy consisted of carboplatin, area under the curve (AUC) 5, once every three weeks (or AUC 1.5 once every week) and paclitaxel 80mg/m^2 once every week [for cycles 1-4], followed by doxorubicin 60mg/m^2 or epirubicin 90mg/m^2 and cyclophosphamide 600mg/m^2 once every three weeks [for cycles 5-8]. Subsequent adjuvant treatment was pembrolizumab 200mg IV once on Day 1 of each three-week cycle. Participants in the chemotherapy arm received placebo plus chemotherapy (chemotherapy as described in the pembrolizumab arm) as neo-adjuvant treatment, followed by placebo in the adjuvant stage.

The co-primary endpoints of KEYNOTE-522 were pCR (defined as pathological stage ypT0/Tis ypN0, i.e., no invasive residual in breast or nodes; non-invasive breast residuals allowed at the time of definitive surgery) and event free survival (EFS) as assessed by the investigator. Key secondary endpoints included pCR (using alternative definitions), overall survival (OS) and EFS (in patients who were PD-L1 positive). Data from the fourth interim analysis (March 2021) with a median follow-up of 37.8 months were included in the submission. Statistically significant improvements in the co-primary endpoints of pCR (estimated difference 7.5% (95% confidence interval [CI] 1.6, 13.4)) and EFS (hazard ratio [HR] 0.63 (95% CI 0.48, 0.82)) were demonstrated in the pembrolizumab arm compared with the chemotherapy arm. A

statistically significant difference was not observed for OS between arms (HR 0.72 (95% CI 0.51, 1.02)). The addition of pembrolizumab to chemotherapy had no impact on participants' health-related quality of life (HRQoL).

The Review Group highlight a number of limitations when considering the evidence presented. The KEYNOTE-522 trial did not include adjuvant capecitabine as a comparator which is not fully reflective of SOC in Ireland. Thus, the efficacy observed in KEYNOTE-522 may be an overestimate of the benefit of pembrolizumab relative to current SOC in Ireland. Further the validity of pCR as a surrogate endpoint in the neo-adjuvant setting in early breast cancer is uncertain. It is unclear if the EFS benefit observed at the interim analysis will translate to a survival benefit in the long term. The OS data is immature; a longer follow-up would be needed to indicate whether there is a sustained benefit to OS. KEYNOTE-522 was designed to evaluate whether the addition of pembrolizumab as a neo-adjuvant and adjuvant treatment is beneficial compared to neo-adjuvant chemotherapy without adjuvant therapy. By this design, it is not possible to determine relative efficacy (on EFS and OS) in the distinct neo-adjuvant and adjuvant settings.

2. Safety of pembrolizumab plus chemotherapy

The safety of pembrolizumab has previously been evaluated in multiple studies; no new safety signals were identified in KEYNOTE-522. The safety of pembrolizumab in locally advanced or early stage TNBC was previously evaluated in an early-phase study (KEYNOTE-173). Special warnings and precautions associated with use of pembrolizumab include immune-related reactions (including pneumonitis, colitis, hepatitis, endocrinopathies and skin-related reactions). In KEYNOTE-522, the most frequently reported adverse events (AEs) [incidence ≥30%] in the pembrolizumab arm during both the neo-adjuvant and adjuvant phases were nausea, alopecia, anaemia, neutropenia, fatigue, constipation, diarrhoea, vomiting, and alanine transaminase (ALT) increase. Serious treatment-related AEs (TRAEs) occurred in 34.1% of patients in the pembrolizumab arm and in 20.1% of patients in the chemotherapy arm. Most TRAEs occurred during the neo-adjuvant phase rather than during the adjuvant phase. Immune-mediated AEs of grade 3 or higher occurred in 12.9% and 1.0% of patients, in the pembrolizumab arm and in the chemotherapy arm, respectively.

3. Cost effectiveness of pembrolizumab plus chemotherapy

Pembrolizumab plus chemotherapy (neo-adjuvant), followed by adjuvant pembrolizumab monotherapy, is compared to neo-adjuvant chemotherapy, followed by no active adjuvant treatment, in the cost-effectiveness model. This comparator does not reflect SOC in clinical practice in Ireland, which includes adjuvant capecitabine for patients who do not achieve pCR following neo-adjuvant therapy. The Applicant provided a scenario analysis including adjuvant capecitabine for a proportion of patients, however, this was not considered to generate reliable estimates of cost-effectiveness due to limitations of the model structure and available evidence base.

Methods

In a four-state Markov cohort state transition model, the treatment effects captured were delay of disease progression and death. Key efficacy inputs were EFS and OS. Modelled population characteristics were derived from KEYNOTE-522. Treatment duration for both arms was informed by time-on-treatment (ToT) data from KEYNOTE-522. Long-term survival estimates were obtained from fitting piecewise models at a particular cut-point (week 43 for the pembrolizumab arm, week 50 for the chemotherapy arm) to patient-level EFS and OS data collected in KEYNOTE-522. Utility values were derived from EQ-5D-5L data (from KEYNOTE-522), and mapped to EQ-5D-3L. The analysis was conducted from the perspective of the HSE.

The Review Group identified a number of limitations in the Applicant's model, some of which were addressed in the NCPE adjusted base case. These included alternative parametric model selection for EFS, and the removal of the Applicant's assumption of lifetime treatment effect. Structural changes which could not be addressed include: the absence of a post-locoregional recurrence (LR) 'remission' health state in the model, which is not aligned with clinical opinion. In addition, there is no differentiation of 'pre' and 'post' progression disease in the distant metastasis (DM) health state, when in reality it is possible that mortality, costs, and HRQoL could differ considerably. Other limitations of the model include: the modelled comparator is not reflective of SOC in Ireland; EFS data from KEYNOTE-522 (median follow-up of 42 months) are immature; data on post-DM OS are immature; the choice of piecewise approach used to extrapolate EFS data is subjective and the model is sensitive to the choice of cut-point.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1, and the NCPE-adjusted base case in Table 2. The probabilities of cost-effectiveness, for pembrolizumab plus chemotherapy (neo-adjuvant), followed by adjuvant pembrolizumab monotherapy, compared to neo-adjuvant chemotherapy, followed by no active adjuvant treatment, in the NCPE adjusted base case was 0% at the €20,000/QALY threshold and 14.9% at the €45,000/QALY threshold. Deterministic sensitivity analysis indicated that the most influential parameters in the model were the approach used to extrapolate EFS data.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Chemotherapy (neo-adjuvant)	51,389	9.55	-	-	-
Pembrolizumab plus chemotherapy (neo-adjuvant); Pembrolizumab monotherapy (adjuvant)	118,569	11.08	67,180	1.53	44,001

***ICER**: incremental cost-effectiveness ratio; **QALY**: quality adjusted life year;*
[a] Corresponding probabilistic ICER using 1,000 iterations = €44,012/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% is applied to costs and outcomes.
[b] A commercial in confidence (CIC) patient access scheme (PAS) applies to pembrolizumab, not included here.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Chemotherapy (neo-adjuvant)	43,001	10.91	-	-	-
Pembrolizumab plus chemotherapy (neo-adjuvant); Pembrolizumab monotherapy (adjuvant)	113,124	11.97	70,123	1.06	66,186

***ICER**: incremental cost-effectiveness ratio; **QALY**: quality adjusted life year;*
[a] Corresponding probabilistic ICER using 1,000 iterations = €64,682/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% is applied to costs and outcomes
[b] A CIC PAS applies to pembrolizumab, not included here.

4. Budget impact of pembrolizumab plus chemotherapy

The price to wholesaler for one 200mg vial of pembrolizumab is €3,153.86. The total cost of pembrolizumab plus chemotherapy, per patient, per treatment course is €58,452.31 (based on the assumption that all patients receive pembrolizumab 200mg once every 3 weeks for the maximum duration of 17 cycles and eight cycles of chemotherapy). The Applicant estimated 719 patients will be treated with neo-adjuvant pembrolizumab plus chemotherapy over five years. The Applicant estimated that 516 patients will be treated with adjuvant pembrolizumab over five years. The five-year cumulative gross drug budget

impact was an estimated €67 million (€53 million excluding VAT) and the net drug budget impact was an estimated €64 million (€51 million excluding VAT). Clinical opinion, obtained by the Review Group, anticipates higher patient numbers (circa 200 patients per year) for pembrolizumab (based on uptake seen in an early access programme). This resulted in an estimated five-year cumulative net drug budget impact of €93.1 million.

5. Patient submission

No Patient Organisation Submissions were received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®) plus chemotherapy, followed by pembrolizumab monotherapy, 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.