NCPE Assessment

Technical Summary

Pembrolizumab (KEYTRUDA®)

23056

May 2025

Applicant: MSD Ireland

Pembrolizumab, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1.

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, for this indication, 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

MSD Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1. MSD Ireland is seeking reimbursement of pembrolizumab on the Oncology Drug Management Scheme.

Pembrolizumab is a monoclonal antibody designed to exert dual ligand blockade of the programmed death-1 (PD-1) pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. Pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity. Pembrolizumab is administered by intravenous infusion at a dose of 200mg once every three weeks or 400mg once every six weeks. For this indication, pembrolizumab is given in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy.

Standard of care (SoC) in Ireland, for this indication, is trastuzumab in combination with fluoropyrimidine and platinum-containing chemotherapy. Chemotherapy regimens used in clinical practice include FOLFOX-6 (fluorouracil (5-FU), oxaliplatin and leucovorin), CAPOX (capecitabine and oxaliplatin) and FP (5-FU and cisplatin). Clinical opinion suggests that these regimens have similar efficacy and choice of regimen depends on patient-specific factors. The comparator for this Health Technology Assessment is SoC alone.

1. Comparative effectiveness of **pembrolizumab**

KEYNOTE-811 was a phase III, global, double-blind, randomised placebo-controlled trial designed to evaluate the efficacy and safety of pembrolizumab in combination with trastuzumab and chemotherapy (pembrolizumab + SoC) versus placebo plus trastuzumab

and chemotherapy (SoC alone) for the first-line treatment of adults with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma. Pembrolizumab was given at a dose of 200mg once every three weeks.

The intention-to-treat population included two distinct cohorts; a Global Cohort and an additional Japan-specific Cohort. The Japan-specific cohort is not considered further in this evaluation. Randomisation was stratified by PD-L1 expression status (CPS ≥ 1 or < 1), chemotherapy regimen (FP or CAPOX) and geographic region (Western Europe/Israel/North America/Australia, Asia or Rest of World). The licence relates to those participants enrolled in the Global Cohort who had tumours which expressed PD-L1 with a CPS ≥ 1 (594 out of 698 participants, 85.1%). Results presented below pertain to this cohort unless otherwise stated. Treatment in KEYNOTE-811 continued until disease progression, unacceptable toxicity or a maximum of 35 three-week cycles (approximately two years). The primary endpoints were progression-free survival (PFS) as determined by blinded independent central review and overall survival (OS).

Baseline demographics between treatment arms were generally well balanced. The median age was 63 years, 80% were male, 63% were White and 33% were Asian. Eighty-five percent of participants received CAPOX with the remainder receiving FP. At the final analysis (data cut 20 March 2024) the median duration of follow-up was 18.2 months. Overall, 24.2% of participants in the pembrolizumab + SoC arm and 16.9% of participants in the SoC alone arm remained in the study. Treatment was ongoing for 2.3% of participants in the pembrolizumab + SoC arm versus 1.4% of participants in the SoC alone arm. Pembrolizumab + SoC was associated with statistically significant improvements in OS (hazard ratio (HR) 0.79; 95% confidence interval (CI) 0.66 to 0.95) and PFS (HR 0.72; 95% CI 0.60 to 0.87) compared with SoC alone. Median OS in the pembrolizumab + SoC and SOC alone arm was 20.1 months (95% CI 17.9 to 22.9 months) and 15.7 months (95% CI 13.5 to 18.5 months), respectively. Median PFS in the pembrolizumab + SoC arm and SoC alone arm was 10.9 months (95% CI 8.5 to 12.5 months) and 7.3 months (95% CI 6.8 to 8.4 months), respectively.

Patient reported outcomes for health-related quality of life in for the Global Cohort (irrespective of PD-L1 status) showed similar results between treatment arms.

The Applicant suggests that results from a post-hoc analysis of participants with tumour PD-L1 expression CPS ≥ 1 enrolled in the non-Asia region better represent the effectiveness of pembrolizumab + SoC in Irish clinical practice. This Non-Asia Region Cohort comprised two of the three pre-specified region subgroups, namely Western Europe/Israel/North America/Australia and Rest of World (Brazil, Chile, Guatemala, Russian Federation, Turkey and Ukraine). In the Non-Asia Region Cohort pembrolizumab + SoC was associated with statistically significant improvements in OS (HR 0.68; 95% CI 0.55 to 0.84) and PFS (HR 0.65; 95% CI 0.52 to 0.81) compared with SoC alone. Median OS in the pembrolizumab + SoC and SOC alone arm was 18.6 months (95% CI 15.5 to 21.2 months) and 12.6 months (95% CI 11.1 to 14.7 months), respectively. Median PFS in the pembrolizumab + SoC arm and SoC alone arm was 9.9 months (95% CI 8.3 to 11.4 months) and 6.4 months (95% CI 5.6 to 7.4 months), respectively. Although a greater treatment benefit was observed in the Non-Asia Region Cohort, outcomes for OS (HR 0.77; 95% CI 0.56 to 1.04) and PFS (HR 0.70; 95% CI 0.51 to 0.97) in the Western Europe/Israel/North America/Australia subgroup (n=193) remained in line with the outcomes reported for the Global Cohort with tumour PD-L1 expression CPS ≥ 1. Thus, the greater treatment benefit observed in the Non-Asia Region Cohort is driven by the Rest of World subgroup. The Review Group consider that the clinical effectiveness data from the post-hoc analysis of the Non-Asia Region Cohort is subject to bias and overestimates the treatment benefit in the patient population in Irish clinical practice.

2. Safety of **pembrolizumab**

Safety of pembrolizumab, in the KEYNOTE-811 trial, was generally consistent with the established safety profile of pembrolizumab, and no new safety concerns were identified. At interim analysis 2 (data cut 25 May 2022) the proportion of patients in the Global Cohort with Grade 3-5 adverse events (AEs) was 70.9% in the pembrolizumab + SoC arm versus 65.0% in the SoC alone arm. The most common Grade 3 and 4 AEs reported were anaemia (12.6% of patients receiving pembrolizumab + SoC versus 10.1% of patients receiving SoC alone), diarrhoea (9.7% versus 8.4%) and decreased neutrophil count (8.3% versus 8.7%). Serious AEs occurred in 44.9% of patients receiving pembrolizumab + SoC versus 45.4% receiving SoC alone. The Summary of Product Characteristics carries special warnings for immune-mediated AEs and infusion-related reactions. Safety data from the final analysis were consistent with these data.

3. Cost effectiveness of **pembrolizumab**

The cost-effectiveness analysis is based on the Non-Asia Region Cohort of the KEYNOTE-811 trial. As discussed in section 1, this choice of population is likely to overestimate the treatment benefit in the Irish healthcare setting.

Methods

The cost-effectiveness model is a cohort level partitioned-survival model, which includes three mutually exclusive health states; progression-free (PF), progressed disease (PD) and death. These states capture PFS and OS which were the two primary endpoints of the KEYNOTE-811 trial. In each cycle, patients accrue quality-adjusted life years (QALYs) and incur costs specific to the treatment arm and the health state occupied. A time horizon of 40 years reflecting a lifetime horizon was used.

The key treatment effects captured by the cost-effectiveness model were the delay of disease progression and death. Treatment effects for OS and PFS were modelled by fitting either standard parametric or spline models to the Kaplan Meier curves of each KEYNOTE-811 treatment arm separately, and extrapolating over time. The Applicant chose the 3-knot odds spline model and the Generalised Gamma distribution to model OS in the pembrolizumab + SoC arm and SoC alone arm, respectively. The Review Group had concerns with this approach due to over-reliance on visual fit, poor statistical fit, selective use of clinical opinion, and an implausible increasing long-term relative treatment effect. To address these concerns the log-logistic distribution was used to model OS, in both arms, in the NCPE adjusted base case.

Utility data were derived from KEYNOTE-811. The Applicant used a time-to-death utility approach. There was a substantially lower number of patients contributing to the utility for < 30 days to death category, which leads to additional uncertainty and may result in potential bias. Also, the choice regarding the cut-off to create categories in time-to-death utilities in general is arbitrary and subjective, which may also lead to bias. In the NCPE adjusted base case health state utility values were based on progression status.

The dose of pembrolizumab was assumed to be 200mg once every three weeks. Treatment duration was based on time-on-treatment Kaplan Meier data from the KEYNOTE-811 trial.

These data reflect a two-year stopping rule for pembrolizumab which is not in line with the licence and may not reflect its use in clinical practice. Therefore, the cost per treatment course of pembrolizumab may be underestimated in both the Applicant and NCPE adjusted base cases.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE adjusted base case base case assumptions are shown in Table 1 and Table 2, respectively

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC alone	66,096	1.19	-	-	-
Pembrolizumab + SoC	167,961	2.15	101,865	0.96	106,066

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care
[a] Corresponding probabilistic ICER using 1,000 iterations =€101,302/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC alone	66,326	1.33	-	-	-
Pembrolizumab + SoC	167,541	1.88	101,215	0.55	183,911

QALY: quality adjusted life years; ICER: incremental cost-effectiveness ratio; SoC: standard of care
[a] Corresponding probabilistic ICER using 1,000 iterations =€187,818/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

Sensitivity analysis

Under the Applicant's base case the probability of cost-effectiveness was 0% at the €20,000 per QALY threshold and 0.2% at the €45,000 per QALY threshold. Under the NCPE adjusted base case the probabilities of cost-effectiveness were 0% at both thresholds. Time-on-treatment was not included in the probabilistic or deterministic sensitivity analyses despite it being an influential and uncertain model input. The Review Group conducted a scenario analysis on the NCPE adjusted base case whereby time-on-treatment was assumed equivalent to PFS. In this scenario, the ICER was €361,099 per QALY.

Under the NCPE adjusted base case assumptions a total rebate of 84.5% on the price to wholesaler of pembrolizumab would be required for it to be considered cost effective at a

willingness-to-pay threshold of €45,000 per QALY.

4. Budget impact of **pembrolizumab**

The price to wholesaler for one vial of pembrolizumab 25mg/ml concentrate for solution for infusion (pack size 4ml) is €3,109.86. Using time-on-treatment data and relative dose intensities from the KEYNOTE-811 trial, the total cost, per patient, per treatment course of pembrolizumab + SoC is estimated to be €140,505 (including VAT and applying a Framework Agreement rebate of 9%). As discussed in section 3, the cost per treatment course of pembrolizumab in clinical practice may be underestimated because of the KEYNOTE-811 stopping rule.

The Applicant predicts that the market share of pembrolizumab + SoC in the eligible population will be 40% in Year 1 increasing to 80% in Year 5. Therefore, 19 patients will be treated in Year 1 increasing to 40 patients in Year 5. The estimated five-year cumulative gross and net drug budget impact of pembrolizumab + SoC is €21.54 million including VAT and €17.44 million including VAT, respectively. The Review Group consider that market share may be higher than predicted by the Applicant.

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that Pembrolizumab (Keytruda®) not be considered for reimbursement, for this indication, 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.*