NCPE Assessment

Technical Summary

Pembrolizumab (Keytruda®)

HTA ID 23070

August 2025

Applicant: MSD

Pembrolizumab (Keytruda®), in combination with fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced, unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative 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) 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 July 2024, MSD submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab (Keytruda®) in combination with fluoropyrimidine and platinum-containing chemotherapy (pembrolizumab + ChT) for the first-line treatment of locally advanced, unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1. MSD is seeking reimbursement of pembrolizumab on the Oncology Drug Management System.

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, given until disease progression or unacceptable toxicity. For this indication, pembrolizumab is given in combination with fluoropyrimidine and platinum-containing chemotherapy (pembrolizumab + ChT).

Standard of care in Ireland, for this indication, is fluoropyrimidine and platinum-containing chemotherapy regimens (ChT alone). The preferred chemotherapy regimen for this indication is FOLFOX (5-fluorouracil in combination with folinic acid and oxaliplatin). CAPOX (capecitabine in combination with oxaliplatin), FP (5-FU in combination with cisplatin), and 5-FU monotherapy are also used. Clinical opinion advises that fluoropyrimidine and platinum-containing chemotherapy regimens are considered to have equivalent effectiveness. This is supported by the broader literature relating to treatment of gastric and gastro-oesophageal adenocarcinomas In patients with carcinoma of the oesophagus or HER-2 negative GEJ

adenocarcinoma, pembrolizumab may be given in combination with these regimens where PD-L1 with CPS ≥ 10.

Nivolumab, in combination with fluoropyrimidine and platinum-based combination chemotherapy (nivolumab + ChT) is licensed for the first line treatment of adult patients with HER2 negative advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 5. It is not reimbursed in Ireland for this indication.

The comparator for the licensed population for this evaluation is ChT alone. A scenario analysis has been conducted where nivolumab + ChT might be a relevant future comparator in the sub-population with CPS ≥ 5.

1. Comparative effectiveness of pembrolizumab

KEYNOTE-859 was a phase three, randomised double-blind trial designed to evaluate the efficacy and safety of pembrolizumab in combination with either CAPOX or FP (pembrolizumab + ChT) versus placebo in combination with either CAPOX or FP (ChT alone) in adults with HER2-negative advanced gastric or GEJ adenocarcinoma with known PD-L1 expression. Randomisation (1:1) was stratified by geographic region, PD-L1 tumour expression status (CPS < 1 versus CPS ≥ 1) and doublet chemotherapy regimen. Treatment continued until disease progression or unacceptable toxicity. Additionally, a stopping rule was applied specifically for pembrolizumab, 5-FU (both capped at maximum 35*three-week cycles), and platinum containing compounds, oxaliplatin and cisplatin (capped at maximum 35*three-week cycles but may be capped at six*three-week cycles if specified by local guidelines).

The primary endpoint was overall survival (OS) with progression-free survival (PFS) by blinded independent central review (BICR). The licenced population, those with PD-L1 CPS ≥ 1, refers to a sub-population of the trial population (n=1,235; 78%). Efficacy results presented herein refer to the licensed population.

Baseline characteristics of the PD-L1 CPS ≥ 1 subpopulation were generally well balanced across treatment arms. The median age of participants was 62 years, 70% were male, 56% were White and 64% had an Eastern Cooperative Oncology Group (ECOG) performance score of one. The proportion of participants with PD-L1 tumour expression status of CPS ≥ 10 was 45%. The vast majority received CAPOX as opposed to FP (86% versus 14%) as the investigator's choice of chemotherapy.

At the first interim analysis (data cut-off date (DCOD) of October 2022), with a median follow-up of 12 months, pembrolizumab + ChT demonstrated a statistically significant improvement in OS of 1.6 months compared with ChT alone (hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.66 to 0.84). A statistically significant improvement in PFS by BICR of 1.3 months was also observed for pembrolizumab + ChT (HR 0.75, 95% CI 0.63 to 0.82). Clinically meaningful differences in health-related quality of life outcomes between treatment arms were not observed. Following Preliminary Review, the Applicant provided results from the final analysis (DCOD September 2024). Based on a median follow-up of 54 months, the modest OS and PFS benefit demonstrated by pembrolizumab + ChT remained consistent with results of the interim analysis. The Review Group noted that subgroup analyses by PD-L1 expression, conducted at the interim analysis (DCOD October 2022), indicated that higher PD-L1 expression is a potential driver of efficacy in this patient population.

Based on results from KEYNOTE-859, the addition of pembrolizumab to chemotherapy regimens provides a relatively modest OS and PFS benefit in the licensed population. Limitations of the KEYNOTE-859 trial include the implementation of a treatment stopping rule for pembrolizumab that is not reflective of the licensed indication; trial participants being younger than patients treated in Irish clinical practice and a difference in subsequent treatments received compared with Irish clinical practice.

An indirect treatment comparison was required to inform the scenario analysis in the sub-population with CPS ≥ 5. The Applicant conducted a time-varying fixed effects fractional polynomial network meta-analysis (FP-NMA) to compare the efficacy (OS and PFS) of pembrolizumab + ChT with the efficacy of nivolumab + ChT in the sub-population with CPS ≥

5. Data from the sub-population of the KEYNOTE-859 trial with CPS ≥ 5, using a DCOD August 2023, were used to inform inputs for the pembrolizumab + ChT arm while the CheckMate-659 trial was used to inform inputs for the nivolumab + ChT. Between study heterogeneity using random effects could not be assessed, as the evidence network was insufficient. As such, a major underlying assumption of this analysis is that between study heterogeneity is negligible. Additionally, the cut-off of CPS ≥ 5 was not prespecified for the KEYNOTE-859 trial, and as such the analysis may not be powered. The results of the NMA suggested no statistically significant difference between pembrolizumab + ChT and nivolumab + ChT. The Applicant declined to update the FP-NMA with the most recent datacut (DCOD September 2024) of the KEYNOTE-859 trial, which the Review Group considered to be a major limitation of the comparative effectiveness analysis. Furthermore, the Review Group preferred to apply a constant hazard to the control arm due to overfitting to the data and implausible increasing long-term relative efficacy from the FP-NMA results. The Review Group did not consider results from the FP-NMA to be reliable for decision-making.

2. Safety of pembrolizumab

The safety profile of pembrolizumab in the KEYNOTE-859 trial is generally consistent with the established safety profile of pembrolizumab. No new safety concerns were identified. No disease-specific precautions associated with gastric or GEJ cancer are listed in the Summary of Product Characteristics (SmPC). However, the Review Group highlighted that addition of pembrolizumab to chemotherapy regimens was associated with a higher incidence of grade three or four adverse events (59.4% versus 51.1% in the ChT alone arm) in KEYNOTE-859. Serious adverse events also occurred at a higher rate (45.2% versus 40.2 %). Additionally, pembrolizumab + ChT should be used with caution in patients aged 75 years and older after careful consideration of the potential benefit/risk balance on an individual basis

3. Cost effectiveness of pembrolizumab

Methods

The cost-effectiveness model (CEM) 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 endpoints in the KEYNOTE-859

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 CEM were the delay of disease progression and death.

Kaplan Meier (KM) data (DCOD September 2024) from the KEYNOTE-859 trial were used to estimate PFS and OS curves for the pembrolizumab + ChT and ChT alone treatment arms. In the Applicant base case spline curves were fitted to the KM data for PFS and OS. The Review Group considered that the long-term extrapolations for OS and PFS in the Applicant base case were overly optimistic and assumed a large increasing survival benefit in favour of pembrolizumab + ChT. The Review Group considered the log-logistic distribution to be more appropriate to model OS and PFS in both treatment arms, which assumed a constant relative benefit for pembrolizumab + ChT over time.

For the scenario analysis in the CPS ≥ 5 sub-population, the Applicant used time-varying HRs from the FP-NMA to model treatment effects for pembrolizumab + ChT and nivolumab + ChT. The Review Group considered extrapolations from OS and PFS in the Applicant's FP-NMA to lack face validity. The Review Group considered an alternative approach, whereby a constant HR was applied to the extrapolated ChT alone curve, to result in more clinically plausible estimates. This was based on the HRs observed for the comparison between nivolumab + ChT and ChT alone for PFS and OS in the CheckMate-649 trial (OS HR 0.70 95% CI (0.61 to 0.81); PFS HR 0.71 95% CI (0.61 to 0.82)).

Utility values in the CEM were derived from KEYNOTE-859. The Applicant chose a time-to-death utility approach. The Review Group considered that the time cut-offs used to create the time-to-death categories were subjective. The Review Group considered a health state approach, with utilities based on progression status to be more appropriate.

The Applicant modelled time-on treatment for pembrolizumab using KM data from the KEYNOTE-859 trial. The Review Group considered that using KM data from the trial, where a treatment stopping rule of 24 months or 35* three-week cycles, would likely underestimate the treatment duration of pembrolizumab in Irish clinical practice. The SmPC for

pembrolizumab states that treatment can continue until disease progression or unacceptable toxicity; no treatment stopping rule is specified. As such, the Review Group considered it more appropriate to model time-on-treatment with pembrolizumab using PFS data. The mean PFS, and therefore, mean time-on-treatment with pembrolizumab was estimated to be 77.18 weeks (1.48 years).

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. NCPE adjusted base case assumptions included alternative modelling assumptions of OS and PFS, the use of health-state utility values instead of time-to-death utility values and modelling time-on-treatment for pembrolizumab using PFS as a proxy.

Table 1: Applicant base case incremental cost-effectiveness results in population with CPS ≥ 1[a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ChT alone	73,417	1.15	-	-	-
Pembrolizumab + ChT	144,087	1.91	70,670	0.76	93,149

ChT: doublet chemotherapy; ICER: incremental cost effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.
[a] Corresponding probabilistic ICER using 2,000 iterations =€93,354/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] A PAS is applicable to pembrolizumab, not included in this Table.

Table 2: NCPE adjusted base case incremental cost-effectiveness results in population with CPS ≥ 1[a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ChT alone	76,859	1.10	-	-	-
Pembrolizumab + ChT	203,197	1.58	126,338	0.47	267,870

ChT: doublet chemotherapy; CPS: combined positive score; ICER: incremental cost effectiveness ratio; NCPE: National Centre for Pharmacoeconomics; PAS: patient access scheme; QALY: quality-adjusted life year.
[a] Corresponding probabilistic ICER using 2,000 iterations =€272,449/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] A PAS is applicable to pembrolizumab, not included in this Table.

The results of scenario analyses in the CPS ≥ 5 population, assuming nivolumab + ChT is a relevant future comparator, are presented in Table 3 (Applicant assumptions) and Table 4 (NCPE preferred assumptions).

Table 3: Applicant scenario incremental cost-effectiveness results in population with CPS ≥ 5[a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)

Nivolumab + ChT	138,485	2.74	-	-	-
Pembrolizumab + ChT	150,130	3.01	11,645	0.27	42,999

ChT: doublet chemotherapy; CPS: combined positive score; ICER: incremental cost effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.
[a] Corresponding probabilistic ICER using 5,000 iterations =€48,165/QALY. Corresponding probabilistic ICER using 2,000 iterations=52,669/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] A PAS is applicable to both nivolumab and pembrolizumab, not included in this Table.

Table 4: NCPE adjusted scenario incremental cost-effectiveness results in population with CPS ≥ 5[a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab + ChT	200,561	1.75	-	-	-
Pembrolizumab + ChT	232,393	1.81	31,832	0.06	576,089

ChT: doublet chemotherapy; CPS: combined positive score; ICER: incremental cost effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year
[a] Corresponding probabilistic ICER using 5,000 iterations = €591,826/QALY. Corresponding probabilistic ICER using 2,000 iterations is 2,000= €561,247/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] A PAS is applicable to both nivolumab and pembrolizumab, not included in this Table.

Sensitivity analysis

Using the Applicant base case assumptions, the probability of cost-effectiveness, in the population with CPS ≥ 1, at a willingness-to-pay threshold of €20,000 per QALY was 0.95% and 2.75% at a willingness to pay threshold of €45,000 per QALY. Under NCPE adjusted base case assumptions, the probability of cost-effectiveness of pembrolizumab was 0.15% at a willingness-to-pay threshold of €20,000 per QALY and 0.75% at a willingness to pay threshold of €45,000 per QALY. Using all other NCPE adjusted base case assumptions, the Review Group conducted a scenario where a treatment stopping rule of 24 months was applied to pembrolizumab, which resulted in an ICER of €173,150 per QALY.

Under the NCPE adjusted base case assumptions, in the CPS ≥ 1 population, an approximate rebate of 90% on the price to wholesaler of pembrolizumab would be required for it to be considered cost effective at the willingness-to-pay threshold of €45,000/QALY. The Review Group noted this does not account for any commercial in confidence Patient Access Scheme rebates.

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 €3,015.61. Using the NCPE base case assumption of time-on-treatment from the CEM and considering the relative dosing intensity from the pivotal trial,

patients are assumed to receive 12.28*six-weekly cycles of pembrolizumab at a dose of 400mg. The estimated mean treatment course cost of pembrolizumab + ChT in the budget impact analysis is €173,016 including VAT and €138,196 excluding VAT.

The Applicant predicted that 100 patients will be treated with pembrolizumab + ChT in year one, increasing to 148 patients in year five. Using the Review Group's preferred assumptions regarding treatment duration of pembrolizumab, the cumulative five-year gross drug budget impact of pembrolizumab was estimated to be €112.14 million including VAT. The cumulative five-year net drug budget impact was estimated to be €109.45 million including VAT.

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that pembrolizumab, in combination with fluoropyrimidine and platinum-containing chemotherapy, not be considered for reimbursement, for this indication. unless cost effectiveness can be improved relative to existing treatment*.

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