NCPE Assessment Summary

Pembrolizumab (Keytruda®)

25066

October 2026

Applicant: MSD Ireland

As monotherapy for the treatment of resectable, locally-advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a 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®) as monotherapy for the treatment of resectable, locally-advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1.

Following assessment of the Applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®) be considered for reimbursement 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 (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 June 2026, MSD Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab (Keytruda®) as monotherapy for the treatment of resectable, locally-advanced head and neck squamous cell carcinoma (LA-HNSCC) as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express programmed death ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1. MSD Ireland is seeking reimbursement of this pembrolizumab regimen (hereafter referred to as 'perioperative pembrolizumab') in hospitals, through the Oncology Drug Management Scheme (ODMS).

Pembrolizumab is administered by intravenous infusion at a dose of 200mg once every three weeks or 400mg once every six weeks. Standard of care (SoC) in Ireland for patients with resectable LA-HNSCC comprises surgery followed by radiotherapy, with the addition of cisplatin for patients with high-risk disease.

1. Comparative effectiveness of perioperative pembrolizumab

KEYNOTE-689 is an ongoing phase III, open-label, randomised controlled trial. The trial was designed to evaluate the safety and efficacy of perioperative pembrolizumab, in combination with standard adjuvant therapy, compared with standard adjuvant therapy alone, in patients with resectable LA-HNSCC. Standard adjuvant therapy comprised radiotherapy alone for patients without high-risk disease and radiotherapy with concomitant cisplatin for those with high-risk disease (hereafter termed SoC). Pembrolizumab was administered intravenously at a dose of 200mg once every three weeks for two cycles during the neoadjuvant phase. During the adjuvant phase, pembrolizumab was administered intravenously at a dose of 200mg once every three weeks for up to 15 cycles, in combination with radiotherapy (2Gy daily for 30 fractions). Patients with high-risk disease received concurrent chemoradiotherapy consisting of radiotherapy (2Gy daily for 33 fractions) and cisplatin 100 mg/m² once every three weeks for three cycles. The primary endpoint was event-free survival (EFS), while major pathological response (mPR) was a key secondary outcome.

The intention-to-treat (ITT) population of KEYNOTE-689 comprised 714 participants

randomised to either the perioperative pembrolizumab arm (n=363) or the control arm (n=351). Over 95% of participants had a PD-L1 CPS ≥ 1. In line with the product licence, the results presented here are for the population with a PD-L1 CPS ≥ 1 (perioperative pembrolizumab arm n=347; control arm n=335). Baseline characteristics were generally balanced between treatment arms. The median age was 60 years, most participants were male (78.7%), white (78.2%), current or former smokers (78.6%), and HPV-negative (96.2%). Most participants had stage IVA disease (74.0%). More participants in the control arm had an Eastern Cooperative Oncology Group (ECOG) score of zero than in the perioperative pembrolizumab arm (60.0% versus 53.9% respectively). More participants in the perioperative pembrolizumab arm were classified as low risk following surgery compared with the control arm (55.3% versus 41.5% respectively).

At the July 2024 interim analysis, treatment with perioperative pembrolizumab resulted in a statistically significant improvement in EFS versus the control arm (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.55 to 0.89). Median EFS was 59.7 months (95% CI 37.9, upper bound not reached) in participants that received perioperative pembrolizumab, compared with 29.6 months (95% CI 19.5 to 41.9) in the control arm. Statistically significant improvements in mPR were also observed in participants that received perioperative pembrolizumab versus the control arm (9.8% difference, 95% CI 7.0 to 13.3). An mPR was observed in 34 participants that received perioperative pembrolizumab, versus zero in the control arm. Thirty two of the 34 observed mPR events occurred in participants with a CPS ≥ 10. Overall survival (OS) was a secondary endpoint in the study, but results were not formally tested in the CPS ≥1 population, in line with the prespecified multiplicity strategy. Median OS was not reached in the perioperative pembrolizumab arm compared with a median OS of 61.8 months in the control arm (HR 0.72, 95% CI 0.56 to 0.94).

2. Safety of perioperative pembrolizumab

The adverse event (AE) profile of the treatment regimen of perioperative pembrolizumab was generally consistent with the known safety profile of pembrolizumab monotherapy and the known safety profile of radiotherapy and the individual chemotherapy components. At the July 2024 interim analysis, the overall incidence of participants experiencing at least one AE during the combined treatment phases was similar between the perioperative

pembrolizumab and control arms (96.4% versus 96.8%, respectively). The most frequently reported AEs were stomatitis (41.6% versus 54.6%), radiation skin injury (39.9% versus 47.9%), decreased weight (35.7% versus 27.3%), and anaemia (34.1% versus 33.3%).

The proportion of participants experiencing a Grade 3 to 5 AE was comparable between treatment arms (76.2% in the perioperative pembrolizumab arm and 74.0% in the control arm). Serious AEs (of any cause) were reported in 49.6% of participants in the perioperative pembrolizumab arm and 36.8% of participants in the control arm. Pneumonia was the most commonly reported serious AE in both treatment arms. Treatment-related adverse events resulting in death occurred in four participants receiving perioperative pembrolizumab and one participant in the control arm.

3. Cost effectiveness of perioperative pembrolizumab

Methods

The Applicant compared perioperative pembrolizumab in combination with SoC, with SoC alone, using a Markov cohort model. The cost-effectiveness model (CEM) included four mutually-exclusive health states based on three disease stages (event-free (EF), local or salvageable recurrence (L/SR), incurable recurrence/progression (IRP)) and death. The IRP state consisted of two sub-states, pre-progression IRP and post-progression IRP, which enable the model to capture costs and HRQoL that reflect both first- and second-line metastatic treatments.

The treatment effects captured by the CEM include delay in disease progression or recurrence and death. The key efficacy input in the CEM was EFS, based on data from KETNOTE-689. The effect of the intervention on OS is modelled indirectly as a result of the increased length of time in the EF health state. In each cycle, patients accrued quality-adjusted life years (QALYs) and costs based on the utilities and costs specified for the health state occupied, the relevant treatment arm, and the time on treatment.

Transition possibilities between health states were primarily based on data from the KEYNOTE-689 trial. The proportion of time spent in the pre- and post-progression IRP substates were derived from the ratio of mean progression free survival (PFS) time and mean OS time estimated by a network meta-analysis (NMA) of first-line treatments for patients with recurrent/metastatic HNSCC.

Health state utility values for the EF, L/SR and IRP health states were derived by mapping the EQ-5D-5L utilities to EQ-5D-3L using the Hernandez et al. algorithm and valued using UK tariffs. Utilities for the EF, L/SR and pre-progression IRP substate were sourced from the KEYNOTE-689 trial. For the post-progression IRP substate, utilities were sourced from the EXTREME trial due to limited follow-up post-progression for patients with IRP in the KEYNOTE-689 study. The CEM included a one-off utility decrement for Grade 3 to 5 AEs that occurred in ≥ 5% in either arm of the KEYNOTE-689 trial.

The model included costs for drug acquisition and administration, surgery, radiotherapy, PD-L1 testing, subsequent treatments, disease management, and AEs. A once-off end-of-life cost was applied to all patients entering the death state.

The Review Group addresses a number of limitations in the Applicant's CEM . In the NCPE adjusted base case: a gradual waning of treatment-effect after the period of observed follow-up was assumed; background mortality was adjusted to account for higher mortality in patients with HNSCC compared with the general population; administration costs more reflective of immunotherapy administration were used; a regression model accounting for repeated measures was used for utility measurement.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE adjusted 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	57,573	4.91	-	-	-
Pembrolizumab	102,279	6.11	44,706	1.20	37,211

***QALY**: Quality adjusted life year; **ICER**: Incremental cost effectiveness ratio; **SoC**: Standard of care*

[a] Corresponding probabilistic ICER using 1,000 iterations =€36,119/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	58,929	4.30	-	-	-
Pembrolizumab	105,910	5.28	46,982	0.97	48,336

***QALY:** Quality adjusted life year; **ICER**: Incremental cost effectiveness ratio; **SoC**: Standard of care*

[a] Corresponding probabilistic ICER using 1,000 iterations =€49,228/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

Sensitivity analysis indicated that the most influential parameters were those adjusted in the NCPE adjusted base case, excluding the change made to immunotherapy administration costs. A price-ICER analysis, conducted using the NCPE adjusted base case indicated that a 15.0% and 59.8% reduction in the price to wholesaler of pembrolizumab was required to meet the €45,000 per QALY and €20,000 per QALY threshold, respectively.

4. Budget impact of perioperative pembrolizumab

The price to wholesaler for two vials of pembrolizumab 25mg/ml concentrate for solution for infusion (pack size 4ml) is €5,970.05. The mean cost per patient per treatment course, including pembrolizumab and cisplatin and inclusive of VAT, is estimated at €90,700. This is based on the mean number of treatment cycles observed in the PD-L1 CPS ≥1 population of KEYNOTE-689 (1.9 neoadjuvant pembrolizumab cycles, 11.4 adjuvant pembrolizumab cycles, 2.5 adjuvant cisplatin cycles).

The annual eligible population was estimated at 119 patients in year one, increasing to 125 patients by year five. Limited information on the proportion of patients in the population who undergo surgical resection in Ireland, and the proportion of patients with resectable LA-HNSCC who have a PD-L1 CPS ≥1, contribute to uncertainty in the population estimates.

The estimated five-year cumulative gross drug budget impact for perioperative pembrolizumab as an adjunct to SoC is €25.8 million (including VAT). Minimal cost-offsets are anticipated, due to the displacement of low-cost cisplatin. Additional healthcare costs associated with PD-L1 testing and pembrolizumab administration are also expected, estimated by the Applicant to be approximately €560,000 over the five-year time horizon.

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that pembrolizumab (Keytruda®), for the indication under assessment, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*Next steps: The NCPE Assessment Report (and) recommendation (and Patient Organisation submission), will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

Further information on this process may be found here.