

# NCPE Assessment

## Summary

Pembrolizumab (Keytruda®)

HTA ID: 24013

10 March 2026

Applicant: MSD Ireland

Pembrolizumab, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®) in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment (this regimen is herein referred to as 'perioperative pembrolizumab') for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

Following assessment of the Applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®) be considered for reimbursement, for this indication, 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 perioperative 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 April 2025, MSD Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for resectable non-small cell lung carcinoma (NSCLC) at high risk of recurrence in adults. 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 NSCLC depends on patients' EGFR or ALK mutation status and PD-L1 tumour proportion score (TPS). Targeted therapies are used for patients with EGFR or ALK mutations. For patients with PD-L1 expression  $\geq 1\%$  neoadjuvant nivolumab in combination with chemotherapy is SoC. For patients with PD-L1 expression  $<1\%$ , the majority of patients are treated with surgery alone, with a minority also receiving neoadjuvant or adjuvant chemotherapy.

### **1. Comparative effectiveness of perioperative pembrolizumab**

#### *Perioperative pembrolizumab compared with neoadjuvant platinum-based chemotherapy*

KEYNOTE-671 was a phase III, double-blind, randomised controlled trial. The trial was designed to evaluate the safety and efficacy of perioperative pembrolizumab versus neoadjuvant platinum-containing chemotherapy, in patients with stage II, IIIA or IIIB NSCLC. Pembrolizumab was administered intravenously at a dose of 200mg once every three weeks for four cycles with either cisplatin and gemcitabine (squamous histologic features) or cisplatin and pemetrexed (non-squamous histologic features) in the neoadjuvant phase. Pembrolizumab was administered as 200mg once every three weeks for up to 13 cycles in the adjuvant phase. The dual primary endpoints were event-free survival (EFS) and overall survival (OS).

The intention-to-treat (ITT) population were randomly assigned to either perioperative pembrolizumab (n=397) or neoadjuvant chemotherapy alone(n=400). The ITT population was stratified by stage, PD-L1 expression (50% cut-off), histology and region. The mean age of participants was 63 years; the majority were male (70.6%) and white (61.4%). Approximately 57% of participants had a non-squamous histological subclassification. Most participants had stage III NSCLC (70%) and 55% had stage IIA NSCLC. At interim analysis 3 (IA3), treatment with perioperative pembrolizumab resulted in a statistically significant improvement in EFS compared to neoadjuvant chemotherapy (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.47 to 0.69). Median EFS was 57.1 months (95% CI 38.0 to 69.1) and 18.4 months (95% CI 14.8 to 22.1) for the perioperative pembrolizumab and neoadjuvant chemotherapy groups, respectively. A statistically significant improvement in OS was observed (HR 0.73, 95% CI 0.58 to 0.92). Median OS was not reached in the preoperative pembrolizumab arm at IA3.

*Perioperative pembrolizumab compared with surgery alone, or with neoadjuvant nivolumab in combination with chemotherapy*

Direct comparative trials of perioperative pembrolizumab versus neoadjuvant nivolumab plus platinum-containing chemotherapy, or versus surgery alone were not available. The Applicant conducted a network meta-analysis (NMA) informed by data from KEYNOTE-671, CheckMate 816 (the pivotal trial for neoadjuvant nivolumab and chemotherapy), and three trials for surgery alone (CHEST, NATCH and S9900). The analysis included just the EFS outcome, with separate analyses conducted for the PD-L1 TPS <1%, PD-L1 TPS 1-49% and PD-L1 TPS ≥50% subpopulations, as PD-L1 expression is likely to be an effect-modifier for immune checkpoint inhibitors (ICIs). The Review Group conducted an additional NMA of OS, stratified by PD-L1 category and using time-invariant HRs, based on the most up-to-date data from KEYNOTE-671 and CheckMate 861.

The results of the analysis indicate an improvement in EFS and OS for perioperative pembrolizumab over surgery alone, across subpopulations. For the comparison with neoadjuvant nivolumab, point estimates favoured nivolumab (for both EFS and OS) in the PD-L1≥50% subpopulation and pembrolizumab (for EFS only) in the PD-L1 1-49% subpopulation. However, 95% credible intervals were wide and contained the null in most cases. Therefore, it was not clear if there is a difference in effectiveness between the pembrolizumab and

nivolumab regimens.

## **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 the individual chemotherapy components. At the IA3 data-cut, the overall incidence of participants with AEs during the combined phases was similar in the pembrolizumab arm (99.5%) and the neoadjuvant chemotherapy alone arm (98.7%). A greater risk difference of AEs for the pembrolizumab arm during the combined phases were hypothyroidism, rash, fatigue, insomnia, dyspnoea, nausea, alanine aminotransferase increases, pruritis and pyrexia. These were mostly Grade 1 or 2.

The overall incidence of Grade 3 to 5 AEs during the combined phases was higher in the pembrolizumab arm (64.9%) than the neoadjuvant chemotherapy alone arm (53.4%). The types and frequencies of the most frequent Grade 3 to 5 AEs during the combined phases were similar between the two treatment arms. The overall incidence of participants with drug-related Grade 3 to 5 AEs during the combined phases was 45.2% in the pembrolizumab arm and 37.8% in the neoadjuvant chemotherapy alone arm.

## **3. Cost effectiveness of perioperative pembrolizumab**

The Applicant provided comparisons to (i) neoadjuvant nivolumab plus chemotherapy for the PD-L1 1-49% and PD-L1  $\geq 50\%$  subpopulations and (ii) surgery alone for the PD-L1  $< 1\%$  subpopulation.

### *Methods*

The Applicant compared perioperative pembrolizumab to the relevant comparators, using a cohort Markov model. The cost-effectiveness model (CEM) included four mutually exclusive health states based on three disease stages (event-free (EF), local-regional recurrence or progression (LRR), distant metastasis (DM)) and death. The treatment effects captured by the CEM included delay in disease progression or recurrence, and death. The key efficacy input in the CEM was EFS. The effect of the intervention on OS was 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 probabilities from the EF health state for perioperative pembrolizumab were based on the analysis of data from KEYNOTE-671 and the NMA (for EFS) to estimate transition probabilities. The Applicant used external data to inform transitions from LRR to DM or death and DM to death. For transitions from LRR to DM, the Applicant matched data from the United States' SEER-Medicare administrative claims and linked the database to KEYNOTE-671 participant characteristics. Transitions from DM to death were modelled using OS and PFS from KEYNOTE-189 and KEYNOTE-471 trials in metastatic NSCLC.

Health state utility values for the EF, LRR and DM (pre progression sub-state) were derived by mapping the EQ-5D-5L utilities, based on KEYNOTE-671 data, to EQ-5D-3L using the Hernandez et al. algorithm and valued using UK tariffs. Utilities for the 'post progression' DM sub-state were obtained from published literature. Utilities were age-adjusted and capped by the age- and sex-matched general population utility at the start of the model time horizon. The CEM included a one-off utility decrement for AEs  $\geq$  Grade 3 that occurred in  $\geq$  5% in either arm of the KEYNOTE-671 trial (ITT population) for perioperative pembrolizumab and CheckMate 816 for neoadjuvant nivolumab plus chemotherapy.

The model included drug acquisition, administration and AE costs for pembrolizumab, chemotherapy and nivolumab. Other healthcare resources were aggregated as health state-specific costs and included surgery and adjuvant radiotherapy, hospitalisations, outpatient appointments, primary care visits and subsequent treatments. Drug acquisition and administration costs were included for subsequent first- and second-line therapies in the DM health state. A once-off end-of-life cost was applied to all patients entering the death state.

The Review Group addressed some limitations in the Applicant's CEM by adjusting a number of parameters or assumptions. In the NCPE-adjusted base case, different models for the estimation of the relative treatment effect of nivolumab in the PD-L1 1-49% population, and of surgery-only in the PD-L1 <1% subpopulation were selected; an alternative source of evidence was used to inform the split of LRR and DM among EFS events; a mixed effect

regression model, including AEs, was used to estimate health-state utilities in preference to descriptive summary measures; duration of first-line metastatic treatments and DM health-state costs were changed. The distribution of PD-L1 subpopulations was also changed to align with the proportions observed in clinical trials in representative patient populations.

### 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. Analyses were conducted in subpopulations according to PD-L1 expression, as different comparators and different treatment effects apply to each subpopulation. A weighted analysis addressing the full population is also presented, based on varying proportions of each subpopulation within the target population. Under both the Applicant and NCPE base case assumptions, the gain in QALYs associated with pembrolizumab largely arises from the comparison with surgery alone in the PD-L1<1% subpopulation, with a considerably smaller QALY gain for PD-L1 1-49% and a loss of QALYs for PD-L1≥50% when compared with neoadjuvant nivolumab.

**Table 1 Applicant base case incremental cost-effectiveness results<sup>a,b</sup>**

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
<b>PD-L1 &lt; 1%</b>					
Surgery alone	127,963	3.20	-	-	-
Pembrolizumab	139,016	5.06	11,054	1.86	5,945
<b>PD-L1 1-49%</b>					
Nivolumab + ChT	110,896	5.85	-	-	-
Pembrolizumab	149,146	6.29	38,251	0.44	86,959
<b>PD-L1 ≥ 50%</b>					
Nivolumab + ChT	80,511	8.50	-	-	-
Pembrolizumab	138,727	7.54	58,216	-0.95	Dominated
<b>Full population<sup>b,c</sup></b>					
Weighted comparator (surgery alone + nivolumab)	115,512	4.79	-	-	-
Pembrolizumab	141,683	5.80	26,171	1.01	25,867

ChT: chemotherapy; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PD-L1: programmed death-ligand 1; QALY: quality-adjusted life years

<sup>a</sup> A commercial in confidence PAS is in place for pembrolizumab and nivolumab, not reflected in this table

<sup>b</sup> Corresponding probabilistic ICER using 1,000 iterations =€26,861/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and outcomes discounted at a rate of 4%.

<sup>c</sup> The Applicant's base-case weighted ICER is based on the proportions of PD-L1 expression categories (negative, low, high) reported in

**Table 2 NCPE-adjusted base case cost-effectiveness results<sup>a</sup>**

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
<b>PD-L1 &lt; 1%</b>					
Surgery alone	118,979	3.84	-	-	-
Pembrolizumab	131,026	5.02	12,048	1.18	10,227
<b>PD-L1 1-49%</b>					
Nivolumab + ChT	103,130	5.92	-	-	-
Pembrolizumab	142,299	6.24	39,168	0.33	120,034
<b>PD-L1 ≥ 50%</b>					
Nivolumab + ChT	78,370	8.44	-	-	-
Pembrolizumab	135,522	7.50	57,151	-0.95	Dominated
<b>Full population<sup>b, c</sup></b>					
Weighted comparator (surgery alone + nivolumab)	102,683	5.78	-	-	-
Pembrolizumab	136,000	6.10	33,317	0.32	104,866

ChT: chemotherapy; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PD-L1: programmed death-ligand 1; QALY: quality-adjusted life years

<sup>a</sup> A commercial in confidence PAS is in place for pembrolizumab and nivolumab, not reflected in this table

<sup>b</sup> Corresponding probabilistic ICER using 1,000 iterations =€95,965/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Cost and outcomes discounted at a rate of 4%.

<sup>c</sup> The NCPE-adjusted base case weighted ICER is based on proportions of PD-L1 expression categories (negative, low, high) derived from clinical trials in representative patient populations (PD-L1 <1%:36.3%, PD-L1 1-49%:30.4%, PD-L1 ≥ 50%: 33.4%)

### Sensitivity analysis

Sensitivity analysis indicated that the most influential drivers of the weighted analysis related to the distribution of PD-L1 subpopulations, the split of LRR and DM events among EFS events, and the model used for the estimation of the relative treatment effect of nivolumab in the PD-L1 1-49% population. A Price-ICER analysis, conducted using the NCPE-adjusted base case, in the full population using the weighted comparator, indicated that a 47% and 63% reduction in the price-to-wholesaler of pembrolizumab was required to meet the €45,000 per QALY and €20,000 per QALY threshold, respectively.

Due to the considerable uncertainty associated with the results of the NMA comparing perioperative pembrolizumab with neoadjuvant nivolumab plus chemotherapy, a key scenario assuming therapeutic equivalence between the two treatments was analysed by the Review Group. The ICER in the full population using the weighted comparator, in this scenario, under NCPE-adjusted base-case assumptions is €75,728 per QALY.

#### **4. Budget impact of perioperative pembrolizumab**

The price to wholesaler for one vial of pembrolizumab 25mg/ml concentrate for solution for infusion (pack size 4ml) is €3,015.61. The mean cost per treatment course per patient is estimated to be €78,494 (including VAT) (corresponding to 11.3 cycles, based on time-on-treatment data from KEYNOTE-671). In line with the NCPE-adjustment to the CEM, a corresponding adjustment to the BIM was made in relation to the distribution of PD-L1 subpopulations within the full population. Implausibly low estimates of the proportion of patients expected to receive neoadjuvant treatment were also updated by the NCPE. The cumulative five-year net drug-budget impact for the full population, estimated using the NCPE-adjusted BIM, is €40.7 million (including VAT).

#### **5. Patient Organisation Submission**

A patient organisation submission was received from the Irish Lung Cancer Community and has been shared with the HSE. This submission will form part of the information that the HSE considers when making their drug-funding decision

#### **6. Conclusion**

The NCPE recommends that pembrolizumab, for the indication under assessment, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments\*. The benefits of pembrolizumab, as part of a perioperative regimen, in improving OS and EFS, have been demonstrated compared with neoadjuvant chemotherapy. Indirect analysis indicates a benefit of perioperative pembrolizumab over surgery alone. However, it is not clear if there is a difference in effectiveness between the pembrolizumab and nivolumab regimens, as indirect comparisons of these regimens generated highly uncertain effect estimates that varied across subpopulations.

\*Next steps: The NCPE Assessment Report and recommendation, 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](#)