NCPE Assessment

Technical Summary

Pembrolizumab (Keytruda®)

HTA ID: 23078

19 February 2026

Applicant: MSD Ireland

Pembrolizumab as monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma who are at a high risk of recurrence following complete resection and platinum-based chemotherapy

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®) for the adjuvant treatment of adults with non-small cell lung carcinoma who are at a high risk of recurrence following complete resection and platinum-based chemotherapy.

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 treatment.* Further, Clinical Opinion has advised that treatment, for this indication, would be individualised based on PDL1 TPS status. The NCPE recommends that pembrolizumab (Keytruda®) not be considered for use in patients with a PD-L1 TPS ≥ 50%.

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 (Keytruda®) as monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma (NSCLC) who are at a high risk of recurrence following complete resection and platinum-based chemotherapy. MSD Ireland is seeking reimbursement of pembrolizumab, for this indication, 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 following complete resection and platinum-based chemotherapy.

Standard of care in Ireland, following complete resection and platinum-based chemotherapy, is atezolizumab for patients with a programmed death ligand 1 (PD-L1) tumour proportion score (TPS) of ≥ 50% and active monitoring alone for patients with PD-L1 TPS < 50%. Clinical opinion suggests that adjuvant pembrolizumab will not be used for treatment of patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations. The relevant comparators are therefore (i) atezolizumab in patients with a PD-L1 TPS ≥ 50% (referred to, hereafter, as the PD-L1 TPS ≥ 50% subpopulation) and (ii) active monitoring in patients with a PD-L1 TPS < 50% (referred to, hereafter, as the PD-L1 TPS < 50% subpopulation).

The Applicant suggests that adjuvant pembrolizumab will only be used for treatment of the PD-L1 TPS < 50% subpopulation. This suggested place in therapy aligns with the opinion of a small number of clinicians but it is uncertain whether this opinion is generalisable to all

clinicians throughout Ireland. The Applicant has suggested this place in therapy, because there was no statistically significant benefit of adjuvant pembrolizumab over placebo in the PD-L1 TPS ≥ 50% subgroup of the pivotal KEYNOTE-091 trial and clinical opinion suggests that atezolizumab will remain the preferred treatment option for the PD-L1 TPS ≥ 50% subpopulation.

1. Comparative effectiveness of **pembrolizumab**

KEYNOTE-091 is a phase III, triple-blinded, randomised placebo-controlled trial designed to evaluate the efficacy and safety of pembrolizumab versus placebo in patients with stage IB, II, or IIIA NSCLC (as per American Joint Committee on Cancer, 7th edition) who have undergone complete resection. Pembrolizumab was given at a dose of 200mg once every three weeks. Treatment was administered for a maximum duration of 18 three-week cycles (approximately one year). The study was designed with dual-primary endpoints; disease-free survival (DFS) in the intention-to-treat (ITT) population and DFS in the PD-L1 TPS ≥ 50% subgroup of the ITT population. The ITT population is representative of all participants randomly assigned to a treatment arm.

Participants were stratified based on the following factors: stage (IB, II, IIIA); no adjuvant chemotherapy versus adjuvant chemotherapy; PD-L1 status (TPS < 1%, TPS = 1-49%, TPS ≥ 50%); and region (Western Europe, Eastern Europe, Rest of the world, Asia). Participants who received prior adjuvant chemotherapy represented 86% of the ITT population. During the regulatory assessment, the Applicant updated the sought indication by excluding patients who had not received prior adjuvant chemotherapy owing to lack of treatment effect in this subgroup. Therefore, unless otherwise specified, the clinical efficacy results from the prior adjuvant chemotherapy population are presented here, as this population is representative of the licensed indication.

In the prior adjuvant chemotherapy population (n=1,010), the mean age of participants was 63.4 years. Sixty-eight percent of participants were male. Participants were predominantly White (77.1%) or Asian (17.5%). The majority of participants had stage II disease at baseline (57.0%), 31.4% had stage IIIA, and 11.4% had stage IB. Almost one-third of participants had a PD-L1 TPS of 1-49%, with 28.1% having a PD-L1 TPS ≥ 50%, and 39.2% a PD-L1 TPS < 1%.

There was some imbalance in histology between treatment arms with 31% and 36.5% of participants having tumours with squamous histology, in the pembrolizumab and placebo arms, respectively. There was no mandatory testing of trial participants for either EGFR or ALK mutations, and for the majority of participants EGFR and ALK mutation status was unknown.

The median follow-up at the most recent data cut (Interim Analysis 3 (IA3); January 2023) was 46.7 months. In the prior adjuvant chemotherapy population, pembrolizumab was associated with a statistically significant improvement in DFS (hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.64 to 0.91). Median DFS in the pembrolizumab arm and placebo arm was 53.8 months (95% CI 46.2 to 70.4 months) and 40.5 months (95% CI 32.9 to 47.4 months), respectively. In a post-hoc analysis of the PD-L1 TPS < 50% subgroup of the prior adjuvant chemotherapy population, pembrolizumab was also associated with a statistically significant improvement in DFS (HR 0.72; 95% CI 0.59 to 0.89). Median DFS in the pembrolizumab arm and placebo arm was 51.7 months (95% CI 39 to 70.4 months) and 34.5 months (95% CI 23.3 to 46.4 months), respectively. One of the dual primary endpoints (DFS in the PD-L1 TPS ≥ 50% subgroup of the ITT population) was not met. Similarly, there was no statistically significant improvement in DFS in the pembrolizumab versus placebo arm of the PD-L1 TPS ≥ 50% subgroup of the prior adjuvant chemotherapy subpopulation (post-hoc analysis; HR 0.83; 95% CI 0.57 to 1.19). Median DFS in the pembrolizumab arm and placebo arm was 67.0 months (95% CI 44.3 months to Not Reached) and 57.8 months (95% CI 36.4 months to Not Reached). The Review Group notes that the PD-L1 TPS subgroups of the prior adjuvant chemotherapy population were not prespecified and so reported outcomes in these subgroups can be considered exploratory only. Much of the Applicant's submission is informed by these subgroups.

An overall survival benefit (OS) has not been demonstrated as OS data from KEYNOTE-091 remains immature. In relation to patient-reported outcomes, there were no clinically meaningful changes from baseline in either treatment arm of the prior adjuvant chemotherapy population.

There is no direct comparative evidence to inform the comparison of pembrolizumab to

atezolizumab in patients with PD-L1 TPS ≥ 50% following complete resection and adjuvant chemotherapy. As such, the KEYNOTE-091 and the IMpower010 trials were used to inform a Bucher indirect treatment comparison (ITC). The IMpower010 trial is a randomized, multicentre, open-label, phase III study of atezolizumab versus best supportive care after adjuvant cisplatin-based chemotherapy in participants with completely resected stage IB–IIIA NSCLC. Results from the ITC indicate that treatment with pembrolizumab is associated with worse DFS outcomes than treatment with atezolizumab (HR 1.87, 95% CI 1.08 to 3.25).

2. Safety of **pembrolizumab**

At the time of the most recent data cut-off (IA3; January 2023), a total of 580 participants had received at least one dose of pembrolizumab in KEYNOTE-091. The mean duration of treatment was 8.7 months. Overall, the safety profile of pembrolizumab was consistent with the known safety profile, which is mainly characterised by immune-related adverse reactions. The most frequently reported adverse events (AEs), with an incidence of greater than 15%, were increased weight, pruritus, hypothyroidism, arthralgia, diarrhoea, and fatigue. The number of participants experiencing at least one grade 3-5 AE was higher with adjuvant pembrolizumab compared with placebo but lower compared to an existing reference safety dataset (N=6,185). Discontinuations due to AEs and the frequency of AEs of special interest (including hypo- and hyperthyroidism) were higher in the KEYNOTE-091 safety population versus the reference safety dataset.

3. Cost effectiveness of pembrolizumab

In line with the licensed indication, the cost-effectiveness analysis is informed by the prior adjuvant chemotherapy population of the KEYNOTE-091 trial. The Applicant provided comparisons to (i) active monitoring in the PD-L1 TPS < 50% subpopulation, (ii) atezolizumab in the PD-L1 TPS ≥ 50% subpopulation and (iii) active monitoring in the full licensed population.

The Review Group considers that the cost-effectiveness results presented by the Applicant for the full licensed population (comparison with active monitoring) are not suitable for decision-making. Active monitoring is not a relevant comparator in the PD-L1 TPS ≥ 50% subpopulation which constitutes a sizeable proportion of the full licensed population. In the

NCPE adjusted base case the cost-effectiveness results for the full licensed population were obtained by weighting the results from the two PD-L1 TPS subpopulations (PD-L1 TPS < 50% (versus active monitoring) and PD-L1 TPS ≥ 50% (versus atezolizumab)). This weighting was based on the distribution of the PD-L1 TPS subgroups in KEYNOTE-091.

Methods

The cost-effectiveness model uses a semi-Markov cohort-level state transition approach, comprising four mutually exclusive health states based on disease stage: disease free (DF), local-regional recurrence (LRR), distant metastases (DM) and an absorbing health state for Death. All patients enter the model in the DF state and receive either pembrolizumab or the relevant comparator (active monitoring or atezolizumab). In each model cycle, patients either remain in their current state, transition from the DF to LRR or DM, or transition from LRR to DM. Transitions to Death are possible from all health states. A lifetime horizon of 36.5 years was used. The cycle length was one week, and a half-cycle correction was applied. In each cycle, patients accrue quality-adjusted life years (QALYs) and incur costs specific to the treatment arm and health state occupied.

Transitions, from DF, were informed by individual patient-level data from the KEYNOTE-091 trial with the placebo arm acting as a proxy for active monitoring in clinical practice. Results from the post-hoc analysis of the PD-L1 TPS < 50% and PD-L1 TPS ≥ 50% subgroups of the prior adjuvant chemotherapy population were used to inform the comparisons in the relevant PD-L1 TPS subpopulations. All post-recurrence transitions were based on external sources and modelled using exponential distributions (i.e. a constant hazard was applied). Transitions from LRR were based on real-world evidence from the US. Transitions from DM to Death were mainly informed by randomised controlled trials in patients with previously untreated locally advanced or metastatic NSCLC. The Applicant calibrated the post-recurrence transitions so that the resulting OS curves more closely matched the observed OS from the KEYNOTE-091 trial. Utility data were derived from KEYNOTE-091.

The Review Group made a number of changes to the Applicant base case. These included:

- selection of an alternative parametric distribution (with improved statistical fit) to model the DF to LRR transition in the PD-L1 TPS < 50% subpopulation,

- use of a linear mixed effect regression model to derive utility values rather than a descriptive analysis in order to account for correlation of repeated measures in the same individuals over time
- discontinuation rates for subsequent treatments based on treatment duration data reported in clinical trials, rather than progression-free survival data in order to avoid overestimation of subsequent treatment costs.

The cost-effectiveness evaluation remains uncertain. In particular, the model structure depends on the validity of DFS as a surrogate outcome for OS. There is no evidence that improvements in DFS with adjuvant pembrolizumab will lead to improved OS. Efficacy data informing the PD-L1 TPS subpopulations is based on a post-hoc analysis of the KEYNOTE-091 trial and may be subject to bias. The modelling of post-recurrence outcomes is very uncertain. Also, the OS calibration is likely to introduce bias and may result in long-term extrapolations which are overfitted to the trial data thereby limiting generalisability to patients in clinical practice.

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 (pairwise comparisons)

	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licensed population [a]					
Active monitoring	134,291	6.31			
Pembrolizumab	172,650	7.06	38,360	0.75	51,455
PD-L1 TPS < 50% subpopulation [b]					
Active monitoring	130,216	6.01	-	-	-
Pembrolizumab	174,148	6.86	43,932	0.86	51,266
PD-L1 TPS ≥ 50% subpopulation (comparison with atezolizumab) [c]					
Atezolizumab	129,703	8.70	-	-	
Pembrolizumab	160,375	7.64	30,672	-1.06	Dominated
PD-L1 TPS ≥ 50% subpopulation (comparison with active monitoring) [d]					
Active monitoring	109,070	7.14	-	-	-
Pembrolizumab	160,375	7.64	51,305	0.50	102,872

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; PD-L1: programmed death-ligand 1 tumour proportion score.

[a] Corresponding probabilistic using 1,000 iterations for the full licenced population is €51,057/QALY;
[b] Corresponding probabilistic ICER using 1,000 iterations PD-L1 TPS < 50% subpopulation is €50,250/QALY;
[c] Corresponding probabilistic average incremental costs is €30,326 and average incremental QALYs is -0.98 using 1,000 iterations. Pembrolizumab is dominated by atezolizumab (i.e. pembrolizumab is more costly, less effective) in the deterministic and probabilistic analyses
[d] Corresponding probabilistic ICER using 1,000 iterations for the PD-L1 TPS ≥ 50% subpopulation is €115,354/QALY.
Figures in the table are rounded, and so calculations may not be directly replicable. 4% discount rate is applied to costs and outcomes.

Table 1: NCPE base case incremental cost-effectiveness results

	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
PD-L1 TPS < 50% subpopulation [a]					
Active monitoring	120,649	5.92	-	-	-
Pembrolizumab	170,857	6.63	50,208	0.71	71,053
PD-L1 TPS ≥ 50% subpopulation (comparison with atezolizumab) [b]					
Atezolizumab	129,703	8.33	-	-	-
Pembrolizumab	160,375	7.35	30,672	-0.98	Dominated
Full licensed population (weighted ICER) [c]					
Weighted comparator	123,194	6.60			
Pembrolizumab	167,909	6.83	44,715	0.23	192,523

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; PD-L1 TPS: programmed death-ligand 1 tumour proportion score.
[a] Corresponding probabilistic using 1,000 iterations for the PD-L1 TPS < 50% subpopulation is €63,429/QALY
[b] Corresponding probabilistic average incremental costs is €30,326 and average incremental QALYs is -0.98 using 1,000 iterations. Pembrolizumab is dominated by atezolizumab (i.e. pembrolizumab is more costly, less effective) in the deterministic and probabilistic analyses
[c] Total QALYs and total costs for each comparison were weighted by the distribution of the PD-L1 TPS subgroups in the prior adjuvant chemotherapy population of KEYNOTE-091 (i.e. PD-L1 TPS < 50% assumed to account for 72% of the full licensed population and the PD-L1 ≥ 50% subgroup assumed to account for 28% of the full licensed population). Weighted comparator refers to active monitoring in the TPS < 50% subpopulation and atezolizumab in the ≥ 50% subpopulation.
Figures in the table are rounded, and so calculations may not be directly replicable. 4% discount rate is applied to costs and outcomes.
CIC PAS are in place for pembrolizumab and atezolizumab; these are not included in this table.

Sensitivity analysis

In relation to the full licensed population, the Review Group was unable to determine the probability of cost effectiveness or present a Price-ICER analysis under the NCPE adjusted base case. This is because the Review Group weighted the cost-effectiveness results for the PD-L1 TPS subpopulations from two separate cost-effectiveness models.

The Review Group does not consider the probabilities of cost effectiveness for the full licensed population under the Applicant base case (presented in Table 2) to be suitable for decision-making. This comparison is against active monitoring only which is not a relevant comparator in the PD-L1 TPS ≥ 50% subpopulation. The probability of cost effectiveness in both the Applicant and NCPE adjusted base cases for the PD-L1 TPS < 50% subpopulation is also presented in Table 3. For the PD-L1 ≥ 50% subpopulations, pembrolizumab remained dominated by atezolizumab in the probabilistic analysis so the probability of cost-

effectiveness, in both the Applicant and NCPE adjusted base cases is zero.

Table 2: Probability of cost effectiveness for pembrolizumab vs active monitoring (Applicant assumptions)

	Probability of cost effectiveness	
Threshold (€/QALY) Full licensed population	Applicant base case	NCPE adjusted base case
20,000	1.9%	N/A[b]
45,000	40.5%	N/A[b]
PD-L1 TPS < 50% subpopulation		
20,000	1.9%	0%
45,000	42.3%	22.4%

[a] Results based on probabilistic analysis using 1,000 iterations
[b] Probabilities could not be determined for the NCPE adjusted base case as a weighted ICER from two separate cost-effectiveness models has been presented

Under the NCPE adjusted base case a total rebate of about 72% and 41% on the price to wholesaler of pembrolizumab would be required for it to be considered cost effective in the PD-L1 TPS < 50% subpopulation at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY, respectively.

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 time-on-treatment data and relative dose intensity from KEYNOTE-091 the mean cost per treatment course per patient is estimated to be approximately €90,000 (including VAT).

The treatment landscape in the neoadjuvant, perioperative and adjuvant NSCLC settings is rapidly evolving meaning the future budget impact of adjuvant pembrolizumab is uncertain. The Applicant assumes that pembrolizumab will only be used for adjuvant treatment of patients with fully resected stage II disease and a PD-L1 TPS < 50%. This assumption is uncertain as it is based on the opinion of a small number of clinicians. Under this assumption, the Applicant estimates the five-year cumulative gross-budget impact to be €15.13 million (including VAT). As there is no displacement of an active treatment, the gross and net- drug-budget impacts are the same. The Review Group notes that the budget impact estimates are based on a population much narrower than the full licensed population. A confidential PAS is in place for pembrolizumab; this is not included in budget impact estimated here.

5. Patient Organisation Submission

A patient organisation submission was received from the Irish Lung Cancer Community.

6. Conclusion

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 treatment.*

Further, Clinical Opinion has advised that treatment, for this indication, would be individualised based on PD-L1 TPS status. The NCPE recommends that pembrolizumab (Keytruda®) not be considered for use in patients with a PD-L1 TPS ≥ 50%. Atezolizumab is expected to be more effective and less costly in this subpopulation.

Thus, if reimbursement is considered for the subpopulation with a PD-L1 TPS < 50%, it is recommended that appropriate management strategies are in place.

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