NCPE Assessment Summary

Pembrolizumab (Keytruda®)

HTA ID 24049

24 July 2026

Applicant: MSD Ireland

Pembrolizumab, in combination with carboplatin and paclitaxel, for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pembrolizumab (Keytruda®), in combination with carboplatin and paclitaxel, for first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

Following assessment of the Applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®) be considered for reimbursement, within its licensed indication in the mismatch repair proficient (pMMR) subpopulation, if cost-effectiveness can be improved relative to existing treatments*. There is insufficient information available on the comparative effectiveness of pembrolizumab in combination with carboplatin and paclitaxel versus dostarlimab in combination with carboplatin and paclitaxel to reliably inform cost-effectiveness in the mismatch repair deficient (dMMR) subpopulation.

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 November 2025, MSD Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of pembrolizumab (Keytruda®) in combination with CP (carboplatin and paclitaxel) for the first-line treatment of primary advanced or recurrent endometrial carcinoma (EC) in adults who are candidates for systemic therapy. MSD Ireland is seeking reimbursement of pembrolizumab on the Oncology Drug Management System (ODMS).

Pembrolizumab is administered by intravenous infusion at a dose of 200mg once every three weeks or 400mg once every six weeks, and is used in combination with platinum-based chemotherapy for this indication. Administration of pembrolizumab should continue according to the recommended schedule until disease progression or unacceptable toxicity. Two separate subpopulations are considered in this assessment, depending on DNA mismatch repair (MMR) status. Based on current practice, the most relevant comparator for the proficient MMR (pMMR) subpopulation is CP. Dostarlimab in combination with CP is the most relevant comparator for the deficient MMR (dMMR) subpopulation.

1. Comparative effectiveness of pembrolizumab

KEYNOTE-868 (NRG-GY018) is an ongoing, randomised, double-blind, multicentre, placebo-controlled phase III trial. Participants were randomised in a 1:1 ratio to two treatment arms, pembrolizumab in combination with CP (n=408), or placebo in combination with CP (n= 411). Randomisation was stratified based on MMR status (pMMR, n=597 or dMMR, n=222), ECOG Performance Status (0 or 1 versus 2), and prior adjuvant chemotherapy (yes/no). Pembrolizumab was administered intravenously at a dose of 200mg once every three weeks in combination with CP for six cycles, followed by pembrolizumab 400mg once every six weeks for up to 14 cycles.

The primary endpoint of the study was investigator-assessed PFS, in two distinct populations (pMMR and dMMR), and secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR). The primary endpoint was met in both subpopulations. Median PFS in the pMMR subpopulation for pembrolizumab in combination

with CP was 11.4 months (95% CI 10.9 to 15.1) and for CP was 10.6 months (CI 8.7 to 11.3); hazard ratio [HR] 0.74 (CI 0.60 to 0.91). Median PFS in the dMMR subpopulation for pembrolizumab in combination with CP was not reached and for CP was 8.3 months (CI 6.5 to 12.7); HR 0.35 (CI 0.23-0.52). The study was unblinded after the pre-planned IA (when statistical significance was reached for the primary endpoint in both subpopulations) and the majority of participants in the placebo in combination with CP arm discontinued soon after unblinding. Many participants initiated subsequent treatment prior to investigator-assessed progressive disease, which included subsequent immunotherapy in many cases. Statistical analysis of OS outcome was descriptive in nature and OS results should therefore be interpreted with caution. At the August 2023 data cut off, an OS benefit was observed in the pMMR and dMMR subpopulations. Median OS in the pMMR subpopulation for pembrolizumab in combination with CP was 28.9 months (CI 26.8 to not reached) and for CP was 28.7 months (CI 24.0 to 34.6); HR 0.80 (CI 0.59 to 1.08). Median OS in the dMMR subpopulation for pembrolizumab in combination with CP was not reached and for CP was 42.7 months (CI 42.7 to not reached); HR 0.57, CI 0.31-1.04. These OS findings are also limited by the immaturity of the OS data, and the extent of subsequent immunotherapy therapy use after IA.

Direct comparative trials of pembrolizumab in combination with CP versus dostarlimab in combination with CP, in the dMMR subpopulation, were not available. The Applicant conducted a network meta-analysis (NMA) informed by data from the KEYNOTE-868 (NRG-GY018) and Ruby-1 trials (the pivotal trial for dostarlimab in combination with CP) for the PFS outcome, and assumed equivalence (i.e. a constant HR of 1) for OS. The results of the NMA were unstable, showing extreme fluctuation in both direction and magnitude of treatment effect. Therefore, there is insufficient evidence to determine if there a treatment benefit of pembrolizumab in combination with CP over dostarlimab in combination with CP, in the dMMR subpopulation.

2. Safety of pembrolizumab

The safety analysis set for KEYNOTE-868 (NRG-GY018) trial comprised 779 participants (all patients who received at least one dose of study intervention). The most frequently reported adverse events were fatigue, anaemia, alopecia, nausea, constipation, diarrhoea, peripheral

sensory neuropathy, peripheral neuropathy, and white blood cell count decreased. Reporting of adverse events ≥ grade 3 were higher for the pembrolizumab in combination with CP treatment arm compared to placebo in combination with CP (65.7% versus 49.2% respectively). The overall incidence of participants with drug-related adverse events ≥ grade 3 was 49.9% in the pembrolizumab in combination with CP arm and 34.0% in the placebo in combination with CP arm.

3. Cost effectiveness of pembrolizumab

Methods

The Applicant compared pembrolizumab in combination with CP, to CP alone in the pMMR subpopulation. Pembrolizumab in combination with CP was compared to dostarlimab in combination with CP in the dMMR subpopulation. A three-state partitioned survival model (PSM) developed in Microsoft Excel® was used. The PSM included three mutually-exclusive health states: progression-free (PF), progressed disease (PD), and death. The treatment effects captured by the cost-effectiveness model (CEM) were the delay of disease progression and death, modelled over a lifetime horizon. The key efficacy inputs were PFS and OS, modelled using parametric distributions fitted to time-to-event data from KEYNOTE-868 (NRG-GY018). As PFS and OS data were not fully mature, extrapolation of patient-level data beyond the trial period was required. The Applicant adjusted the observed OS in the trial for "treatment-switching" to account for subsequent use of immunotherapies, as this is not representative of standard-of-care in Ireland. In the pMMR subpopulation, the Applicant's chosen survival extrapolations overestimated OS with CP at ten years, and implied a persistence of treatment benefit for the intervention after treatment discontinuation. The NCPE adjusted-base case uses alternative distributions which align with clinical expectations of survival with CP and incorporate a waning of treatment effect over time. To inform the PFS and OS survival curves in the dMMR subpopulation, the Applicant assumed equivalent treatment efficacy between both pembrolizumab in combination with CP and dostarlimab in combination with CP, for both outcomes. The Review Group considers that this assumption is highly uncertain, and the potential for dostarlimab in combination with CP to have a treatment benefit over pembrolizumab in combination with CP cannot be excluded.

Health state utility (a measure of quality of life) values for the PF state and PD state were derived from KEYNOTE-B21 and KEYNOTE-158. The Applicant applied disutilities due to adverse events to hypertension and anaemia only. Direct medical costs were included for drug acquisition, drug administration, disease management, subsequent treatments and adverse events. Duration of treatment was informed by time to treatment-discontinuation data from KEYNOTE-868 (NRG-GY018), which applied a two-year stopping-rule for pembrolizumab. As this stopping-rule is not required by the pembrolizumab product license, it is uncertain whether such a stopping-rule will be applied in practice. The duration of dostarlimab was based on an extrapolation of the pembrolizumab time to treatment-discontinuation data, truncated at three years, based on the stopping rule in the dostarlimab product license. Differences in drug costs and treatment duration should be interpreted with caution since the application of a stopping-rule to pembrolizumab (at 2 years) and dostarlimab (at 3 years) in clinical practice is uncertain. Importantly, the potential for there to be no difference in treatment duration cannot be excluded. A once-off end-of-life cost was also applied.

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. The Review Group made several changes to the Applicant's base case in the pMMR sub-population, based on more plausible alternative assumptions as described in the previous section. In the Applicant base case in the dMMR subpopulation, pembrolizumab in combination with CP is less costly and less effective than dostarlimab in combination with CP. Due to assumptions of equal treatment effect in PFS and OS, the difference in QALYs is extremely small and driven by adverse events disutilities which are highly uncertain and should be interpreted with caution. The NCPE Review Group considers that there is insufficient evidence to generate reliable cost-effectiveness results in the dMMR subpopulation due to the absence of robust evidence on comparative effectiveness and duration of treatment in clinical practice. The NCPE adjusted base case was therefore only presented for the pMMR subpopulation.

Table 1: Applicant base case incremental cost-effectiveness results [a, b, c, d]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
pMMR subpopulation					
CP	36,207	1.98			
Pembrolizumab+CP	117,142	2.92	80,935	0.94	86,061
dMMR subpopulation					
Dostarlimab+CP	181,166	5.59			
Pembrolizumab+CP	148,971	5.59	-32,194	-0.00074	Less costly, less effective [d]
Full-licensed population (all-comer)[c]					
Weighted comparator *(CP in pMMR, dostarlimab+CP in dMMR)*	75,926	2.96			
Pembrolizumab+CP	125,863	3.65	49,938	0.68	73,163

CP: carboplatin and paclitaxel; **dMMR:** mismatch repair deficient; **ICER:** incremental cost-effectiveness ratio; **PAS:** patient access scheme; **pMMR:** mismatch repair proficient; **QALY:** quality-adjusted life years.

[a] Corresponding probabilistic ICER in the pMMR subpopulation, using 1,000 iterations =€90,786/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 commercial in confidence PAS is in place for pembrolizumab and dostarlimab, not reflected in this table.

[c] The Applicant's base-case weighted ICER is based on dMMR and pMMR proportions from the KEYNOTE-868 (NRG-GY018) trial.

[d] ICER of dostarlimab+CP against pembrolizumab+CP is €43,444,457/ QALY, though caution must be exercised when interpreting ICERs in the setting of "dominated" treatments, as willingness-to-pay thresholds may not necessarily extend linearly to the southwest quadrant of the incremental cost-effectiveness plane.

Table 21: NCPE base case incremental cost-effectiveness results [a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
pMMR					
CP	36,066	1.83			
Pembrolizumab+CP	116,528	2.16	80,461	0.32	248,781

CP: carboplatin and paclitaxel; **ICER:** incremental cost-effectiveness ratio; **PAS:** patient access scheme; QALY**:** quality-adjusted life years.

[a] Corresponding probabilistic ICER using 1,000 iterations =312,165/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 commercial in confidence PAS is in place for pembrolizumab and is not reflected in this table.

Sensitivity analysis

Sensitivity analysis indicated that modelling approaches to OS extrapolation had a much greater impact on the model than other individual parameters. A price-ICER analysis, conducted using the NCPE-adjusted base case, in the pMMR subpopulation only, indicated that an 86.5% and a 96% 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 pembrolizumab

The price to wholesale (PtW) for two vials each containing pembrolizumab at 25mg/ml concentrate for solution for infusion is €5,970.05. The Applicant assumed a total cost, per patient, per treatment course of pembrolizumab in combination with CP, of €119,343 corresponding to a mean treatment duration of 11.87 months. This duration is based on data from the "all-comer" population in KEYNOTE-868 (NRG-GY018), in which a two-year stopping-rule was applied. The Applicant's approach to the duration of dostarlimab in the budget impact model was similar to that taken in the CEM, resulting in a considerably longer duration of treatment compared to pembrolizumab, and the prediction of considerable cost-offsets due to the displacement dostarlimab.

For the "all-comer" population, it is estimated that 77 patients will receive treatment in Year 1, increasing to 127 patients in Year 5. The cumulative five-year gross drug-budget impact is estimated to be €64.3 million (including VAT). The cumulative net drug-budget impact is estimated to be €47.2 million (including VAT). However, as discussed in the previous section, the duration of both pembrolizumab and dostarlimab in clinical practice, and the corresponding potential for cost-offsets due to dostarlimab-displacement, is highly uncertain.

5. Patient Organisation Submission

A patient organisation submission was received from Irish Society for Gynaecological Oncology. 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 (Keytruda®) be considered for reimbursement, within its licensed indication in the pMMR subpopulation, if cost-effectiveness can be improved relative to existing treatments*. There is insufficient information available on the comparative effectiveness of pembrolizumab in combination with CP versus dostarlimab in combination with CP to reliably inform cost-effectiveness in the dMMR subpopulation.

*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.