Cost effectiveness of pembrolizumab (Keytruda), in combination with platinum and fluoropyrimidine-based chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10

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 unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an appraisal 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 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 drugs for cancer, 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.

National Centre for Pharmacoeconomics **December 2022**

Summary

In March 2022, MSD Ireland submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of pembrolizumab (Keytruda®) for use in combination with platinum and fluoropyrimidine-based chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or human epidermal growth factor receptor-2 (HER-2) negative gastroesophageal junction adenocarcinoma in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive scoring (CPS) ≥ 10. Reimbursement is sought under the Oncology Drugs Management System.

Pembrolizumab binds to the programmed cell death-1 (PD-1) receptor and blocks its interactions with ligands PD-L1 and PD-L2, which are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment. This blockade stops the PD-1 mediated inhibition of immune response. Pembrolizumab is administered by intravenous infusion at a dose of 200mg once every three weeks or 400mg once every six weeks. The licence allows for any combination of platinum and fluoropyrimidine-based chemotherapy. In the pivotal trial, cisplatin was administered by intravenous infusion at a dose of 80 mg/m^2 once every three weeks, in combination with 5-fluorouracil (5-FU) by intravenous infusion at a dose of 800 mg/m^2 on Days 1 to 5 of every three-week cycle, or as per local standard for 5-FU administration. For each drug, treatment should be continued until disease progression, unacceptable toxicity or to the maximum duration of treatment specified in the corresponding Summary of Product Characteristics (SmPC). Of note, no maximum duration of treatment is specified, in the SmPC, for pembrolizumab; however, a 35-cycle (approximately two years) stopping rule was implemented in the pivotal trial.

The Applicant anticipates that pembrolizumab will be used in line with its licensed indication. Comparators, relevant to clinical practice in Ireland, include a number of doublet and triplet systemic chemotherapy regimens (typically, platinum- and fluoropyrimidine-based regimens, with or without an anthracycline). For the purpose of this assessment, these are collectively termed 'Standard of Care [SOC] chemotherapy'.

1. Comparative Effectiveness of Pembrolizumab

Direct comparative evidence

KEYNOTE-590 is a phase III, double-blind, randomised controlled trial designed to evaluated the safety and efficacy of pembrolizumab in combination with cisplatin and 5-FU (herein pembrolizumab plus chemotherapy) versus cisplatin and 5-FU (herein chemotherapy). Trial participants included adult patients with locally advanced, unresectable or metastatic oesophageal, or HER2-negative gastroesophageal junction, carcinoma who had not received prior therapy for advanced or metastatic disease. The trial recruited an 'all-comer' population (i.e. did not restrict recruitment by PD-L1 status). Results relating to the subpopulation whose tumours expressed PD-L1 with CPS ≥10 are the focus of this assessment. A total of 749 participants were randomised. Of those, 383 participants had tumours which expressed PD-L1 CPS ≥10 (pembrolizumab plus chemotherapy n=186; chemotherapy n=197). Treatment was continued until progression of disease or unacceptable toxicity. Duration of treatment for pembrolizumab was capped at 35 cycles (approximately two years). No crossover between treatment arms was permitted. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS) in the overall population and subpopulation of patients whose tumours were positive for PD-L1 with CPS ≥10, with comparisons adjusted to control for multiplicity.

Results from two data cut-offs were available: July 2020 and July 2021. At the July 2021 data cut-off, median PFS in the CPS ≥10 subpopulation was 7.5 months with pembrolizumab plus chemotherapy versus 5.5 months with chemotherapy (HR 0.51; 95% confidence interval [CI] 0.41, 0.65). At the same data cut-off, median OS was 13.6 months with pembrolizumab plus chemotherapy versus 9.4 months with chemotherapy. A comparison of the OS results, in the CPS ≥10 subpopulation, at the available data cut-offs indicated there was a numerically less favourable benefit for pembrolizumab versus chemotherapy in July 2021, as compared to July 2020 (0.64 [95% CI 0.51, 0.80] and OS HR 0.62 [95% CI 0.49, 0.78], respectively). Of the CPS ≥10 subpopulation, 210/383 (54.8%) were based in Asia. The results of the subgroup analysis for OS (July 2020) demonstrated a potentially greater treatment benefit for patients based in Asia, as compared to the Rest of the World. Thus there is uncertainty as to the generalisability of the treatment effect observed in the trial to clinical practice in Ireland.

Indirect comparative evidence

KEYNOTE-590 provided direct comparative evidence versus cisplatin plus 5-FU. However, the Applicant indicated a number of other treatments, including doublet and triplet regimens, may be considered as comparators relevant to clinical practice in Ireland. The Applicant conducted a systematic literature review (SLR) and evaluated the feasibility of conducting an indirect treatment comparison (ITC) of the efficacy and safety of pembrolizumab plus chemotherapy versus comparators relevant to clinical practice in Ireland. The Applicant did not consider it feasible to conduct an ITC using any of the available trials which included systemic cytotoxic chemotherapies.

Of note, nivolumab was recently licensed for use in combination with chemotherapy as a first-line treatment in advanced or metastatic oesophageal and gastroesophageal junction cancer, and the relevant trials were identified by the Applicant following SLR. The Review Group noted that while the licensed populations are not directly aligned, there is considerable overlap in terms of patient eligibility for the treatments. The Applicant did not consider an ITC using the available clinical data to be feasible due to potential limitations and high likelihood of uncertainty. The Review Group acknowledged such comparisons would have been subject to uncertainty, but contested that a comparison, acknowledging the inherent limitations, would still have been informative for decision-making.

2. Safety of Pembrolizumab

The safety profile of pembrolizumab plus chemotherapy was consistent with the known safety profile of the individual components. No new safety concerns were identified. As noted in the EPAR, the addition of pembrolizumab to chemotherapy did not substantially increase the overall toxicity profile relative to chemotherapy alone. However, there was a trend towards an increased toxicity for patients aged 75 years and older, raising concern about the tolerability of pembrolizumab plus chemotherapy in the elderly.

3. Cost Effectiveness of Pembrolizumab

A *de novo* cohort-level state transition model was used to investigate the cost effectiveness of pembrolizumab. The model comprised three health states: 'Progression-free',

'Progressed disease', and the absorbing death state. State occupancy during each cycle was informed from survival curves that estimated cohort-level PFS and OS at each point in time, using data from KEYNOTE-590. In the absence of any comparative evidence for the intervention versus the components of SOC chemotherapy, it was assumed that the clinical efficacy and safety of all treatments in this arm were equivalent to the chemotherapy arm in KEYNOTE-590. The Review Group acknowledged that this assumption was supported by international clinical practice guidelines. Of note, only data from the earlier (July 2020) data cut-off from KEYNOTE-590 were used to inform the cost-effectiveness model, despite a more recent data cut-off being available (July 2021).

The Review Group considered the assumptions and inputs used by the Applicant in the cost-effectiveness model, and highlighted the following key issues:

- Treatment effectiveness was primarily modelled by estimating PFS ad OS from KEYNOTE-590, and extrapolating over the model time horizon using a piecewise modelling approach. Extrapolation of OS is a key source of uncertainty in the cost-effectiveness model. Multiple contributing factors were noted:
    - The failure to use the most up-to-date OS data is a key concern. A numerically less favourable benefit for pembrolizumab versus chemotherapy was observed in the July 2021 data cut-off (compared to the July 2020 data cut-off). The generalisability of the KEYNOTE-590 OS data is an additional source of uncertainty, given the distribution of effect modifiers (namely participant location) in the trial population versus the population expected to receive treatment in Ireland.
    - The Applicant's approach to selecting survival extrapolations was not systematic and may introduce bias. The Applicant's preference for a piecewise model over a fully parametric approach (the only two modelling approaches considered) was not supported by the data provided. Furthermore, the selection of the 40-week cut point (used to model OS) was unfounded.
    - There is no evidence to support the Applicant's assertion that pembrolizumab will result in a life-long treatment effect being maintained.
- Utility data were derived from EQ-5D-3L data collected during KEYNOTE-590. The

utility values used in the Applicant's base case (estimated using a time-to-death approach) were implausibly high, matching values expected in the general population for patients >360 days from death. The modelled population comprised patients with advanced and metastatic oesophageal cancer; thus the Review Group had concerns regarding the face validity of these values. Acknowledging all approaches to utility estimation are associated with strengths and limitations, the utilities estimated using the progression-based approach were deemed more appropriate on the basis of face validity.

- Costs applied in the model included drug acquisition costs, drug administration costs, cost of PD-L1 testing, costs of subsequent therapies, health care resource use costs, adverse event-related costs and end-of-life care costs.
    - A strict two-year stopping rule for pembrolizumab was applied in the model, but is not stipulated in the SmPC, meaning treatment may be continued beyond this timeframe in clinical practice. It is not possible to explore the implications for this in terms of efficacy. The Applicant declined to implement a scenario where the implications in terms of cost were examined.

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. Of note, the NCPE-adjusted base case could not address a number of key uncertainties relating to the modelling of OS. These include failure to use the most up-to-date clinical data, or adjusting for potentially important treatment effect modifiers of relevance to the Irish context. An additional uncertainty, not investigated, is the impact of removing the two-year stopping rule, which was implemented in KEYNOTE-590 but not provided for in clinical practice.

Table 1 Results of the Applicant's base case cost-effectiveness analysis

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Pembrolizumab plus chemotherapy	86,682	1.98			
SOC chemotherapy	14,237	1.00	72,445	0.98	73,791

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
A discount rate of 4% is applied to costs and outcomes. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2 Result of the NCPE-adjusted base case cost-effectiveness analysis

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Pembrolizumab plus chemotherapy	87,685	1.66			
SOC chemotherapy	14,237	0.93	73,448	0.73	100,158

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
A discount rate of 4% is applied to costs and outcomes. Figures in the table are rounded, and so calculations will not be directly replicable.

In both the Applicant's and the NCPE-adjusted base case, the probabilistic ICERs were similar to the deterministic ICERs. Under the Applicant's base case, the probability of pembrolizumab plus chemotherapy being cost effective at a willingness-to-pay threshold of €20,000 per QALY is 0.0%, and at a €45,000 per QALY threshold is 3.8%. Under the NCPE-adjusted base case, the probabilities of cost effectiveness are 0.0% and 0.2% at the €20,000 and €45,000 per QALY thresholds, respectively. An analysis of the price-ICER relationship was conducted using the NCPE-adjusted base case. The price reductions required to achieve cost effectiveness at the €20,000 per QALY and €45,000 per QALY thresholds were approximately 85% and 60%, respectively (inclusive of 7.75% Framework Agreement rebate).

4. Budget Impact of Pembrolizumab

The price-to-wholesaler of a 100mg vial of pembrolizumab is €3,221.79. VAT is applicable to pembrolizumab. Treatment costs were based on a mean duration of treatment for each of the component drugs from KEYNOTE-590 (pembrolizumab: 12.2 x three-week cycles; 5-FU: 9.1 x three-week cycles; cisplatin 4.3 x three-week cycles), and were adjusted to reflect the relative dose intensity observed in KEYNOTE-590. The estimated total treatment cost per patient is €86,700 (€69,421 excluding VAT).

The eligible population was defined as patients with stage III and IV oesophageal cancer with HER2-negative, PD-L1 CPS ≥10 disease (herein full licensed population). The Applicant applied additional modifiers to the eligible population calculations, which reduced the size of the eligible population, based on eligibility for 'a curative plan' and receipt of 'palliative pharmacological treatment' (herein restricted population). The Review Group highlighted that these assumptions were not aligned with the licensed indication, and therefore did not consider these modifiers to be appropriate. Budget impact analyses are presented for both the full licensed population (NCPE-adjusted base case, patient numbers ranged from 180 in

2022 to 205 in 2026) and the restricted subpopulation (Applicant's base case, patient numbers ranged from 61 in 2022 to 70 in 2026). Furthermore, the Review Group considered the Applicant's proposed market share for pembrolizumab to be low, given the poor prognosis and limited number of therapies available in this disease area. Overall, the Review Group considered the budget impact results to be subject to considerable uncertainty. Based on the Applicant assumptions, the cumulative five-year gross drug budget impact was estimated to be €6.70 million (€5.46 million excluding VAT). Under the NCPE-adjusted base case, the cumulative five-year gross drug budget impact was €19.65 million (€15.73 million excluding VAT). Cost offsets due to drugs and other health-related costs were marginal, meaning the net drug and net health budget impact results were only slightly lower than the gross estimates.

5. Patient Submissions

No Patient Organisation Submissions were received during the course of this assessment.

6. Conclusion

Pembrolizumab demonstrated an OS benefit in KEYNOTE-590; however, it is uncertain if a treatment benefit of this magnitude will be observed in clinical practice in Ireland. Pembrolizumab is not cost effective at pre-specified decision-making thresholds under both the Applicant's base case and the NCPE-adjusted base case.

The NCPE recommends that pembrolizumab not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

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