Cost effectiveness of pembrolizumab (Keytruda®) for the first-line treatment of metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults

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®) be considered for reimbursement if 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 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.

National Centre for Pharmacoeconomics **October 2022**

Summary

In January 2022, MSD Ireland submitted a dossier, which investigated the clinical effectiveness, cost effectiveness and potential budget impact of pembrolizumab for the first-line treatment of metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults. Reimbursement is sought under the Oncology Drugs Management Scheme. Pembrolizumab was the first immunotherapy to be authorised for the first-line treatment of metastatic MSI-H/dMMR disease.

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. Both doses are considered to be clinically equivalent. For this indication, treatment may continue until disease progression or unacceptable toxicity.

The Applicant anticipates that pembrolizumab will be used in line with its licensed indication, in the first-line metastatic setting for patients with MSI-H/dMMR colorectal cancer. Current treatments for the first-line treatment of metastatic colorectal cancer in Ireland include mFOLFOX6 (folinic acid, fluorouracil, oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, irinotecan), either alone or in combination with bevacizumab (herein 'mFOLFOX6+Bevacizumab' or 'FOLFIRI+Bevacizumab'). For patients with RAS wild-type disease, mFOLFOX6 or FOLFIRI may be used in combination with either cetuximab (herein 'mFOLFOX6+Cetuximab' or 'FOLFIRI+Cetuximab') or panitumumab (herein 'mFOLFOX6+Panitumumab' or 'FOLFIRI+Panitumumab'). The Applicant also proposed XELOX (capecitabine in combination with oxaliplatin) to be a relevant comparator. For this assessment, the main comparator of relevance, standard-of-care (SOC), comprised treatments administered in the comparator arm of KEYNOTE-177. These were mFOLFOX6, mFOLFOX6+Bevacizumab, mFOLFOX6+Cetuximab, FOLFIRI, FOLFIRI+Bevacizumab, and FOLFIRI+Cetuximab.

1. Comparative Effectiveness of Pembrolizumab

Direct Comparative Evidence

The clinical efficacy of pembrolizumab was examined in the KEYNOTE-177 trial. This was a phase III, open-label, randomised controlled trial (RCT) designed to evaluate the safety and efficacy of pembrolizumab versus SOC chemotherapy (as described above). Eligible patients were randomised 1:1 to pembrolizumab (n=153) or SOC chemotherapy (n=154). The chemotherapy regimen received in the SOC arm was determined prior to randomisation. Adult patients with treatment-naive MSI-H/dMMR stage IV colorectal cancer were eligible for inclusion. Pembrolizumab was administered at a dose of 200mg once every three weeks, for a maximum of 35 cycles. The majority of participants in the SOC arm were treated with mFOLFOX6+Bevacizumab (44.8%) or FOLFIRI+Bevacizumab (25.2%). The co-primary endpoints of the trial were progression-free survival (PFS) and overall survival (OS).

Trial results were available from the final analysis, dated 19 February 2021. Based on this, pembrolizumab was associated with a statistically significant PFS benefit compared to SOC (hazard ratio (HR) 0.59; 95% confidence interval (CI) 0.45 to 0.79). There was no statistically significant OS benefit for pembrolizumab (HR 0.74; 95% CI 0.53 to 1.03). As the proportional hazards assumption was violated, the reported HRs should be interpreted with caution. Restricted mean survival time, based on 36 months of data, indicated that pembrolizumab was associated with a non-significant increase in OS, 1.6 months (95% CI -1.4 to 4.6). The Review Group highlight the high rate of crossover from the SOC arm to the pembrolizumab arm (36%), as well as the large proportion of patients who received immunotherapy as subsequent treatment (23%). This is likely to have an important impact on trial OS outcomes. Sensitivity analyses outputs, adjusting for crossover, were generally consistent with the unadjusted analysis outputs. While pembrolizumab demonstrated a significant PFS benefit, failure to demonstrate a significant OS benefit in the final analysis is a notable limitation.

Indirect Comparative Evidence

Estimates for the relative efficacy of pembrolizumab versus mFOLFOX6+Panitumumab and versus XELOX were derived by means of a fractional polynomial network meta-analysis (fpNMA). Efficacy of mFOLFOX6+Panitumumab was informed by the PRIME study. This

assumed that mFOLFOX6+Panitumumab has equal efficacy to that of FOLFOX4+Panitumumab (as evaluated in the PRIME study). This was considered reasonable by the Review Group. Efficacy of XELOX was informed by the NO16966, TREE-1, and Porschen (2007) studies. The outcomes of the fpNMA indicated that pembrolizumab was associated with improved PFS and OS outcomes compared with mFOLFOX6+Panitumumab and XELOX. However, the Review Group had concerns regarding the heterogeneity of the included trials and patient populations. Notably, KEYNOTE-177 was the only trial to specify MSI-H/dMMR disease as a requirement for treatment. The impact of this heterogeneity on the magnitude and direction of effect estimates is unknown. Results should be interpreted with caution.

2. Safety of Pembrolizumab

The safety profile of pembrolizumab was consistent with that seen in previous clinical trials that investigated pembrolizumab. In KEYNOTE-177, pembrolizumab demonstrated a favourable overall safety profile relative to SOC, with a different adverse event profile as expected. Important identified risks with pembrolizumab include immune-related adverse reactions such as immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies. Grade 3-5 adverse events occurred in 56.2% of patients treated with pembrolizumab, compared with 77.6% of patients in the SOC arm. Treatment discontinuation due to adverse events (all causality and drug-related) was more frequently reported in the pembrolizumab arm compared to the SOC arm (discontinuation due to drug-related adverse events: 9.8% versus 5.6%). Of the 15 patients who discontinued pembrolizumab due to drug-related adverse events, 13 were due to gastrointestinal and hepatic events.

3. Cost Effectiveness of Pembrolizumab

Methods

A de novo cohort-level state transition model was used to investigate the cost effectiveness of pembrolizumab. This model comprised three health states; progression-free, progressed disease, and death. Direct evidence for pembrolizumab versus SOC was available from KEYNOTE-177 (February 2020 data cut). PFS, time-to-progression, and post-progression survival data were used to inform transitions in the model. Outcomes were extrapolated to

the full time horizon of the model using a piecewise modelling approach. Parameters from the fpNMA were used to inform the comparison of pembrolizumab versus mFOLFOX6+Panitumumab. Efficacy of XELOX was assumed equivalent to that of SOC (as derived from KEYNOTE-177). Justification for this assumption was based primarily on clinical opinion, obtained by the Applicant, which indicated that mFOLFOX6, FOLFIRI, and XELOX are considered equivalent. However, the majority of patients in KEYNOTE-177 received a bevacizumab-containing regimen, which is associated with improved survival outcomes. Thus, the Review Group considered this assumption to potentially overestimate the efficacy of XELOX. A time horizon of 40 years and a cycle length of one week were employed. Utility data were derived from EQ-5D-3L data collected during KEYNOTE-177. The cost categories considered in the model were drug acquisition, administration, disease management, surgery, adverse events, subsequent treatment, and terminal care.

Results

Analyses presented in this document are based on the list prices of interventions. The NCPE implemented a number of changes to the Applicant's base case assumptions to reflect the NCPE preferred assumptions. The most notable of these included: the use of pooled health-state utility values, assuming time-on-treatment of mFOLFOX6+Panitumumab was equivalent to that of SOC, and applying the relative dose intensity of SOC, derived from KEYNOTE-177, to the mFOLFOX6+Panitumumab and XELOX arms of the model. The results of the NCPE-adjusted and Applicant base case analyses are presented in Table 1 and Table 2, respectively.

Table 1 NCPE-adjusted base case pairwise analyses

Treatment Strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
Pembrolizumab§	147,083	4.09			
SOC†	61,078	2.30	86,005	1.79	48,077
mFOLFOX6+Panitumumab	80,779	2.47	66,304	1.62	41,040
XELOX	38,157	2.30	108,926	1.79	60,889

mFOLFOX6: Folinic acid, 5-fluorouracil plus oxaliplatin; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year; **SOC:** Standard-of-care; **XELOX:** Capecitabine in combination with oxaliplatin.

*Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

†Main comparator of relevance to the decision maker.

§There is a CIC PAS in place for pembrolizumab; not shown in this table.

Table 2 Applicant base case pairwise analyses

Treatment Strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
Pembrolizumab§	160,499	4.15			
SOC†	68,580	2.25	91,919	1.90	48,316
mFOLFOX6+Panitumumab	136,316	2.39	24,183	1.77	13,696
XELOX	43,868	2.26	116,632	1.90	61,481

mFOLFOX6: Folinic acid, 5-fluorouracil plus oxaliplatin; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year; **SOC:** Standard-of-care; **XELOX:** Capecitabine in combination with oxaliplatin.
*Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.
†Main comparator of relevance to the decision maker.
§There is a CIC PAS in place for pembrolizumab; not shown in this table

Sensitivity Analysis

In the NCPE-adjusted base case, the mean probabilistic ICERs were closely aligned with the deterministic ICERs. In the NCPE-adjusted analysis, pembrolizumab had a 14% probability of cost effectiveness, versus SOC, at the €45,000 per QALY threshold. In the one-way sensitivity analysis, the main driver of cost effectiveness, for all comparisons, was the discount rate on outcomes. This emphasises that a large proportion of the outcome gain in the model occurs after year one in the model, in the extrapolated phase.

4. Budget Impact of Pembrolizumab

The price-to-wholesaler of a 100mg vial of pembrolizumab is €3,221.79. VAT is applicable to pembrolizumab. Based on a mean treatment duration of 19.45 cycles (derived from KEYNOTE-177), the estimated total treatment cost per patient is €144,440 (€115,615 excluding VAT).

The Applicant used estimates from several sources to inform the eligible population estimates. These included the National Cancer Registry Ireland, clinical opinion, and the literature. Based on these data, the Applicant assumed that 47 patients will be eligible for treatment in year one, increasing to 51 patients by year five. Assuming a market share of 100%, the total population treated with pembrolizumab over five years was estimated to be 246. The Review Group considered the population estimates to be subject to considerable uncertainty.

Based on the Applicant assumptions, the cumulative five-year gross drug budget impact was estimated to be €35,547,794 (€28,453,657 excluding VAT). The Review Group made a number of changes to the Applicant's net drug budget impact assumptions, to align with assumptions used in the cost-effectiveness model. The subsequent cumulative five-year net drug budget impact was estimated to be €29,455,601 (€23,497,238 excluding VAT).

5. Patient Submissions

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

6. Conclusion

Pembrolizumab demonstrated a significant PFS benefit but failed to demonstrate a significant OS benefit versus SOC in KEYNOTE-177. The NCPE recommends that pembrolizumab be considered for reimbursement if cost effectiveness can be improved relative to existing treatments[*]. This recommendation assumes a maximum treatment duration of 35 treatment cycles. It also assumes that eligible patients would receive one course of treatment with a PD-1 inhibitor.

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