Cost-effectiveness of pembrolizumab (Keytruda®) as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a combined positive score≥1

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 assessment of the Applicant's (MSD) economic dossier on the cost effectiveness 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 **May 2021**

In August 2020, MSD submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of pembrolizumab as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express programmed death ligand-1 (PD-L1) with a combined positive score (CPS) ≥1.

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. Treatment may continue until disease progression or unacceptable toxicity. If administered in combination with platinum (cisplatin or carboplatin) and 5-FU chemotherapy, the chemotherapy would usually be administered until disease progression, unacceptable toxicity, or up to six cycles of treatment.

Current treatments for metastatic or unresectable recurrent HNSCC in Ireland include the EXTREME regimen (cetixumab, platinum (cisplatin or carboplatin) with 5-FU) or platinum (cisplatin or carboplatin) with 5-FU.

1. Comparative effectiveness of pembrolizumab

The clinical efficacy of pembrolizumab monotherapy (PEM) or pembrolizumab in combination with platinum and 5-FU (PEM+CHEMO) was examined in the KEYNOTE-048 trial. This trial was a randomised, phase III, multicentre, open label trial comparing PEM or PEM+CHEMO to the EXTREME regimen, in adult patients with metastatic or unresectable recurrent HNSCC. The trial was not powered to compare PEM to PEM+CHEMO. Pembrolizumab was administered for a maximum of 35 cycles; this stopping rule does not align with the posology in the Summary of Product Characteristics. The co-primary endpoints were overall survival (OS) and progression free survival (PFS), in the intention to treat population, and in the populations with CPS≥20 and CPS≥1. Trial results were available from the final analysis, dated 25 February 2019.

The majority of patients recruited to the trial were white, male, aged less than 65 years with metastatic HNSCC (stage IVc), were ex or current smokers, with an ECOG PS 1, and were human papillovirus negative. The trial outcomes in the CPS≥1 population are provided (

Table **1**).

Table 1 KEYNOTE-048 clinical outcomes in the CPS≥1 population

Outcome	PEM (n=257)	EXTREME (n=255)	PEM+CHEMO (n=242)	EXTREME (n=235)
Progression Free Survival				
Median PFS (months, 95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
HR for PFS	1.13 (0.94, 1.36); p=0.896		0.84 (0.69, 1.02), p=0.037	
PFS at 12 months (%, 95% CI)	20.6 (15.9, 25.8)	13.6 (9.6, 18.2)	19.7 (14.8, 25.0)	12.5 (8.6, 17.3)
Overall Survival				
Median OS (months, 95% CI)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
HR for OS	0.74 (0.61, 0.90); p=0.001		0.65 (0.53, 0.80), p<0.00002	
ORR* (%, 95% CI)	19.1 (14.5, 24.4)	34.9 (29.1, 41.1)	36.4 (30.3, 42.8)	35.7 (29.6, 42.2)

CPS: combined positive score, **PFS:** progression free survival, **OS**: overall survival, **ORR:** overall response rate, **HR**: hazard rate , **CI:** confidence interval, PEM:pembrolizumab monotherapy, PEM+CHEMO: pembrolizumab with platinum and 5-FU, EXTREME: cetuximab, platinum and 5-FU

More patients treated with PEM or PEM + CHEMO died in the early months of treatment compared with those treated with the EXTREME regimen; the OS curves for PEM and PEM+CHEMO cross the EXTREME curve at approximately eight months and a survival advantage is maintained for PEM and PEM+CHEMO therafter. Approximately 25% of patients in the EXTREME arm received subsequent treatment with an immunotherapy, biasing OS outcomes against PEM and PEM+CHEMO. Response rates with PEM+CHEMO were similar to EXTREME, and higher than with PEM alone, but median duration of response was greater with PEM. There were no statistical differences in global quality of life scores between the treatment arms up to week 15 of the trial.

The median OS benefit for PEM or PEM+CHEMO versus EXTREME is approximately three months, with durable responses of greater than 24 months seen in a small proportion of patients. This should be considered alongside the risk of early death and faster progression

seen with PEM or PEM+CHEMO in some patients. Also, no demonstrated benefit in terms of quality of life was seen with PEM or PEM+CHEMO (versus EXTREME).

Estimates for the relative efficacy of PEM or PEM+CHEMO versus a platinum and 5-FU chemotherapy regimen were derived from a fractional polynomials network meta-analysis (NMA). This approach was adopted as the proportional hazards assumption was inappropriate in the KEYNOTE-048 trial. The outcomes of the NMA found that pembrolizumab-containing regimens were associated with improved PFS and OS outcomes compared with platinum and 5-FU. The Review Group highlight concerns regarding the heterogeneity of the included trials, and while the qualitative outcomes are plausible, the quantitative outcomes are highly uncertain.

2. Safety of pembrolizumab

The safety profile of pembrolizumab was consistent with that seen in previous clinical trials that investigated pembrolizumab. The overall safety profile of pembrolizumab is mainly characterised by immune-related adverse reactions, classified as general (fatigue, decreased appetite), gastrointestinal (nausea, diarrhoea, constipation), respiratory (cough, dyspnoea), and skin (pruritus, rash) disorders. Overall, PEM+CHEMO seems to have a slightly worse safety profile compared to the EXTREME regimen. PEM monotherapy has a significantly better safety profile compared to the EXTREME regimen. The Summary of Product Characteristics contains a specific recommendation for physicians to consider the benefit/risk of PEM and PEM+CHEMO before initiating treatment for the indication under consideration.

3. Cost effectiveness of pembrolizumab

A partitioned survival economic model with a 20-year time horizon was used. OS, PFS and time-on-treatment were modelled based on data from KEYNOTE-048; parameters from the NMA were also used. The model comprised three mutually exclusive health states: pre-progression, post-progression and death. Survival outcomes were extrapolated to the full time horizon of the model using a piecewise extrapolation approach. Utilities were estimated using data from KEYNOTE-048. Patient characteristics were derived from KEYNOTE-048. Treatment effects for PEM versus EXTREME and PEM+CHEMO versus EXTREME were modelled separately based on the trial arms in KEYNOTE-048, leading to

different outcomes in the EXTREME arm depending on the intervention under consideration, which lacks face validity. The Review Group identified a number of limitations in the Applicant's cost-effectiveness model which were largely addressed by the Applicant during the course of the evaluation.

Analyses presented in this summary document are based on the list prices of the interventions. The model outcomes are described in Table 2 and Table 3. The Applicant failed to address the uncertainty in the NMA outputs through the probabilistic sensitivity analysis. Overall the Review Group have limited confidence in the model outcomes for the comparisons with platinum and 5-FU. Furthermore, long-term projections of survival with PEM and PEM+CHEMO are subject to great uncertainty. Incremental cost-effectiveness ratios (ICERs) were highly sensitive to assumptions regarding an ongoing treatment effect beyond treatment discontinuation at 24 months, and subsequent treatments.

Table 2 Applicant base case model outcomes (Pairwise analysis)

Technologies	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
PEMBROLIZUMAB MONOTHERAPY					
PEM	102,059	1.66	-	-	-
EXTREME	73,937	0.95	28,122	0.7	39,657
Platinum +5-FU	40,764	0.77	61,295	0.89	68,784
PEMBROLIZUMAB + CHEMO					
PEM + CHEMO	115,542	2.08	-	-	-
EXTREME	73,615	0.89	41,926	1.18	35,489
Platinum +5-FU	39,777	0.75	75,765	1.32	57,346

PEM: pembrolizumab, **EXTREME:** cetuximab, platinum chemotherapy and 5-fluorouracil, **PEM+CHEMO:** pembrolizumab, platinum chemotherapy and 5-fluorouracil, **QALY:** quality adjusted life year, **ICER:** incremental cost effectiveness ratio. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 3 Applicant base case model outcomes (incremental analysis)

Technologies	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Platinum +5-FU	40,764	0.77	-	-	-
EXTREME	73,937	0.95	-	-	Extended dominance*
PEM	102,059	1.66	-	-	Extended dominance*
PEM + CHEMO	115,542	2.08	74,778	1.31	57,149

PEM: pembrolizumab, **EXTREME:** cetuximab, platinum chemotherapy and 5-fluorouracil, **PEM+CHEMO:** pembrolizumab, platinum chemotherapy and 5-fluorouracil, **QALY:** quality adjusted life year, **ICER:** incremental cost effectiveness ratio. Figures in the table are rounded, and so calculations will not be directly replicable.
*Extended dominance: the ICER for a given alternative, is higher than that of the next, more effective, alternative.

The probability of cost-effectiveness of PEM and PEM+CHEMO (vs EXTREME) was 53.9% and 71.6% respectively at the €45,000 per QALY threshold.

4. Budget impact of pembrolizumab

The price to wholesaler for a vial of pembrolizumab 25mg/ml concentrate for solution for infusion (4ml) is €3,263.09. The estimated cost per patient for a treatment course (pembrolizumab costs only) is €78,740.60 (€63,407.97 ex VAT). The Applicant has proposed a commercial in confidence patient access scheme for consideration by the HSE.

The Applicant used estimates from the National Cancer Registry of Ireland and the literature to derive estimates of the annual numbers of patients eligible for treatment, with 100 patients eligible for treatment in year 1, rising to 103 patients by year 5. The Review Group considered the expectations of market share were unreflective of clinical opinion and updated the budget impact model to assume a 40:60 split between usage of PEM and PEM+CHEMO respectively, and a market share of 50% in year 1, rising to 80% in years 2 to 5, so that 50 patients are treated in year 1, and 82 patients in years 2 to 5.

Using the Review Group's estimates of market share, the predicted 5-year cumulative gross budget impact is approximately €31.24 million (incl VAT) and the 5-year cumulative net budget impact is approximately €25.75 million (incl VAT). The Applicant's estimate of 5-year cumulative gross budget impact is approximately €13.76 million, and the 5-year cumulative net budget impact is approximately €11.34 million.

5. Patient Submissions

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

6. Conclusion

The NCPE recommends that pembrolizumab 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.