Cost-effectiveness of pembrolizumab in combination with axitinib (Keytruda® with Inlyta®) for the first-line treatment of advanced renal cell carcinoma in adults.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of pembrolizumab in combination with axitinib (Keytruda® with Inlyta®). Following assessment of the Applicant's submission, the NCPE recommends that pembrolizumab in combination with axitinib 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 assessment of the Applicant's (Merck Sharp & Dohme) economic dossier on the cost effectiveness of pembrolizumab (Keytruda®) in combination with axitinib. 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 Applicant 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 **December 2020**

Summary

In May 2020, Merck Sharp & Dohme submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of pembrolizumab in combination with axitinib (pembro+axi) for the first line treatment of advanced renal cell carcinoma (aRCC) in adults.

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 pathway mediated inhibition of immune response. Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGF)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth and metastatic progression of cancer.

Pembrolizumab is administered by intravenous (IV) infusion at a dose of 200mg once every three weeks. Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Concurrent treatment with axitinib is at a dose of 5mg twice daily orally. Axitinib should continue as long as clinical benefit is observed or until unacceptable toxicity that cannot be managed by concomitant medicines or dose adjustments.

The comparators are sunitinib and pazopanib in the overall population (i.e. patients in all risk groups). Other comparators, licensed specifically for use in the intermediate-/poor-risk subgroup (as defined by the International Metastatic RCC Database Consortium (IMDC) score), include cabozantinib, and nivolumab in combination with ipilimumab (nivo+ipi). Their inclusion as comparators for the intermediate-/poor-risk subgroup is considered appropriate.

1. **Comparative effectiveness of pembrolizumab in combination with axitinib**

The clinical efficacy of pembro+axi compared with sunitinib was examined in KEYTNOTE-426 which is a phase 3, randomized, multicentre, open label study in the first-line treatment of aRCC in adults. Patients (all risk groups) were randomised to receive pembrolizumab IV at a dose of 200mg once every three weeks (q.3.w.) in combination with axitinib at a dose of

5mg twice daily orally (n=432) or sunitinib at a dose of 50mg once daily orally on days 1 to 28 of a 42-day cycle (n=429). Treatment was continued until disease progression, the development of unacceptable toxicity or physician/patient decision to discontinue. However, pembrolizumab was administered for a maximum of 35 doses (approximately two years). The Review Group notes that this stopping rule does not align with the posology in the Summary of Product Characteristics.

Patient characteristics were generally balanced between arms; median age was 62 (range 26 to 90 years), 73% were male and 79% were white. IMDC risk category was favourable for 31.2% of patients, intermediate for 56.2%, and poor for 12.5%. The primary efficacy endpoints were overall survival (OS) and progression-free survival (PFS), in the intention-to-treat population, as assessed by blinded independent central review. The Applicant submitted results from a number of data cuts, including interim analysis 1 (IA1, dated 24 August 2018) and IA2, the most recent data cut (dated 6 January 2020). The median follow-up times were 12.8 months (range of 0.1 to 22.0 months) and 27.0 months (range of 0.1 to 38.4 months) for IA1 and IA2, respectively.

In IA1, pembro+axi demonstrated a statistically significant benefit over sunitinib in both OS (hazard ratio (HR) of 0.53; 95% CI 0.38 to 0.74; p=0.00005) and PFS (HR of 0.69; 95% CI 0.56 to 0.84; p=0.00012) in the overall population (i.e. all risk groups). In IA2, a benefit in OS (HR of 0.68; 95% CI 0.55 to 0.85, p=0.00034) and PFS (HR of 0.71; 95% CI 0.60 to 0.84; p=0.00003) was also observed in the overall population. While the study was not powered to evaluate efficacy in subgroups, results across IMDC risk subgroups in IA1 and IA2 remained generally consistent with the primary endpoints with the exception of OS benefit in the IMDC favourable-risk subgroup. OS benefit was not observed in either data cut in the IMDC favourable-risk subgroup. The Review Group notes that the IA2 follow-up only slightly exceeds two years. Thus, the impact of 35-dose stopping rule (pembrolizumab) on treatment effectiveness is unclear.

Estimates of relative efficacy vs sunitinib for the economic evaluation were based on the KEYNOTE-426 trial. For the comparison with pazopanib, the Applicant assumed equal efficacy of pazopanib and sunitinib based on the COMPARZ study. This was a phase III, open-

label randomised controlled trial, designed to show the non-inferiority of pazopanib vs sunitinib.

The efficacy of cabozantinib and nivo+ipi in the intermediate-/poor-risk subgroup was based on results of a network-meta analysis (NMA). This utilised data from three randomised controlled trials (RCTs); KEYNOTE-426, CABOSUN (cabozantinib vs sunitinib) and Checkmate 214 (nivo+ipi vs sunitinib). Results (based on IA2) indicated that pembro+axi was associated with a statistically significant increase in OS vs sunitinib (HR 0.63; 95% CrI 0.49 to 0.80), but not vs cabozantinib (HR 0.78; 95% CrI 0.47 to 1.23), or nivo+ipi (HR 0.95, 95% CrI 0.70 to 1.30). Also, pembro+axi was associated with a statistically significant increase in PFS vs sunitinib (HR 0.69; 95% CrI 0.56 to 0.84), but not vs cabozantinib (HR 1.44; 95% CrI 0.89 to 2.33), or nivo+ipi (HR 0.91, 95% CrI 0.69 to 1.19). The Review Group notes that the NMA results for cabozantinib should be interpreted with caution given the small patient numbers in CABOSUN, between-trial clinical heterogeneity and inconsistencies in outcome measurements.

The Review Group requested an evaluation in the favourable-risk subgroup to be provided. The Applicant declined to present these results citing uncertainty. The Review Group consider this a limitation of the evaluation.

2. Safety of pembrolizumab in combination with axitinib

In KEYNOTE-426 (IA1), adverse events were observed in similar proportions of patients in the pembro+axi arm (98.4%) and the sunitinib arm (99.5%). Adverse events observed in the pembro+axi arm were in line with the safety profiles of pembrolizumab and axitinib monotherapies, although higher incidence was observed for some. The following were reported more frequently in the pembro+axi arm compared with the sunitinib arm: Grade 3-5 adverse events (75.8% vs 70.6%), Grade 3-5 drug-related adverse events (62.9% vs 58.1%), serious adverse events (SAEs) (40.3% vs 31.3%), drug-related SAEs (23.8% vs 14.1%) and drug discontinuations due to adverse events (30.5% vs 13.9%). The Committee for Medicinal Products for Human Use concluded that the safety profile of pembro+axi was '*overall manageable'* and that '*permanent discontinuation of treatment due to adverse*

events does not seem to negatively affect either the outcome of patients on subsequent treatments nor their prognosis if left untreated'.

Safety data from IA2 were generally in line with IA1.

3. Cost effectiveness of pembrolizumab in combination with axitinib

A partitioned survival model with a life time horizon was used. OS, PFS and time-on-treatment were based on Kaplan-Meier data from KEYTNOTE-426. Patient characteristics were derived from KEYNOTE-426 and are in line with the population for which the treatment is licensed. Utilities were estimated from KEYNOTE-426. The Review Group identified a number of limitations in the Applicant's cost-effectiveness model, which were addressed in the NCPE-adjusted base case. The Applicant used the IA1 data cut. The NCPE Review Group used the IA2 data cut. The Applicant assumed different parametric extrapolations for OS for pembro+axi and sunitinib. The Review Group considered that the exponential model was the most appropriate choice for both treatments based on model fit and clinical plausibility. The exponential model was used to extrapolate PFS for both treatments in both the Applicant base case and the NCPE adjusted base case. The Applicant assumed a lifetime treatment benefit after stopping pembrolizumab at 35 doses. This assumption was not supported by the short follow-up time in KEYNOTE-426. In order to account for the uncertainty of this lifetime benefit a treatment waning effect at five years was implemented in the NCPE adjusted base case.

In the Applicant's base case pembrolizumab time-on-treatment from IA1 was extrapolated but truncated at two years to reflect a 35-dose stopping rule for pembrolizumab. The Review Group removed this truncation and used the available Kaplan-Meier data from IA2 to model pembrolizumab time-on-treatment. However, in the NCPE adjusted base case analysis the majority of patients who had not progressed did stop pembrolizumab at around two years (as a consequence of the use of the KEYNOTE-426 data). As a stopping rule is not included in the Summary of Product Characteristics nor the NCCP Chemotherapy Regimen the Review Group consider that this stopping rule may not be implemented in clinical practice. Consequently, the total costs in the NCPE adjusted base case may be underestimated.

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in 1 and Table 2, respectively. The difference in ICERs between the two analyses is driven mainly by the assumption of treatment waning in the NCPE base case, the choice of parametric extrapolation, the removal of the time-on-treatment truncation, and the choice of data-cut.

Table 1 NCPE adjusted base case analysis

	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)*
Overall population (all risk groups)**			
Pembro+axi			
Sunitinib	139,405	0.585	238,136
Pazopanib	138,554	0.585	236,682
Intermediate-/poor-risk subgroup			
Pembro+axi			
Sunitinib	144,460	0.687	210,177
Cabozantinib	48,417	0.361	134,127
Nivo+ipi	61,702	0.076	815,519

QALY: Quality adjusted life year, **ICER:** Incremental cost effectiveness ratio.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.
** Population for which pembro+axi is licensed.

Table 2 Applicant base case analysis

	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)*
Overall population (all risk groups)**			
Pembro+axi			
Sunitinib	157,716	2.187	72,121
Pazopanib	156,873	2.187	71,735
Intermediate-/poor-risk subgroup			
Pembro+axi			
Sunitinib	155,436	2.160	71,958
Cabozantinib	42,648	1.323	32,246
Nivo+ipi	76,414	0.664	115,090

QALY: Quality adjusted life year, **ICER:** Incremental cost effectiveness ratio.
* Figures in the table are rounded, and so calculations will not be directly replicable.
** Population for which pembro+axi is licensed.

In both the NCPE adjusted base case and Applicant's base case, the probabilistic ICERs of pembro+axi vs sunitinib were similar to the deterministic ICERs. In the NCPE adjusted base case the probability of pembro+axi being cost-effective vs sunitinib in the overall population (all risk groups) population was estimated at 0% at both the €20,000 per QALY and €45,000 per QALY thresholds. In the Applicant's base case the probability of pembro+axi being cost-effective vs sunitinib was estimated at 0% and 3.8% at the €20,000 per QALY and €45,000 per QALY thresholds, respectively.

Deterministic one-way sensitivity analysis indicated that the most influential parameters in both the Applicant's and NCPE adjusted base case models (with the exception of discount rate) related to the parameters used in the models for extrapolation of OS and time-on-treatment.

4. Budget impact of pembrolizumab in combination with axitinib

The price to wholesaler for pembrolizumab 25mg/ml concentrate for solution for infusion (4ml vial) is €3,263.09.

In the budget impact model the Applicant estimated treatment costs for pembro+axi and sunitinib using median treatment durations reported in the early KEYNOTE-426 data cut (IA1). The Applicant estimated treatment durations of other comparators using median time-on-treatment reported in relevant trials. As treatment was still ongoing in 20% of patients in KEYNOTE-426, the Review Group considered that more plausible predictions of treatment duration for pembro+axi and sunitinib were the mean time of treatment estimated from the time-on-treatment curve in the cost-effectiveness model (IA2). In line with assumptions on equivalent efficacy, the Review Group assumed that the treatment duration of pazopanib was equivalent to sunitinib.

Under NCPE adjusted base case assumptions, the total drug-acquisition cost of pembro+axi including VAT, but excluding administration costs, was €243,994 per patient per treatment course. The cost under the Applicant's budget impact assumptions was €159,913 per patient per treatment course.

The Applicant predicted that 213 patients will be treated in Year 1 rising to 231 patients in Year 5, resulting in a total of 1,111 receiving treatment over five years. The 5-year cumulative gross budget impact of pembro+axi, assuming a 70% market share and NCPE adjusted base case assumptions, was an estimated €189.7 million. The Applicant's estimate was €124.33 million. Under the assumption that sunitinib and pazopanib have the remaining market share the 5-year cumulative net budget impact was an estimated €146.96 million under NCPE adjusted base case assumptions. The Applicant's estimate was €104.27 million.

5. Patient submissions

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

The NCPE recommends that pembrolizumab in combination with axitinib 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 Medicinal Goods) Act 2013.