Cost-effectiveness of nivolumab in combination with ipilimumab (Opdivo with Yervoy®) for the first line treatment of adult patients with intermediate- and poor-risk advanced or metastatic renal cell carcinoma.

The NCPE has issued a recommendation regarding the cost-effectiveness of nivolumab in combination with ipilimumab (Opdivo with Yervoy®). Following assessment of the Applicant's submission, the NCPE recommends that nivolumab in combination with ipilimumab 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Bristol Myers Squibb) economic dossier on the cost effectiveness of nivolumab in combination with ipilimumab. 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 **January 2020**

Summary

In April 2019, Bristol Myers Squibb (BMS) submitted a dosser which investigated the cost-effectiveness of nivolumab in combination with ipilimumab (nivo+ipi) for the first line treatment of adult patients with intermediate- and poor-risk advanced renal cell carcinoma (RCC). BMS are seeking reimbursement in the hospital setting.

Nivolumab is a humanised monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity; thus nivolumab potentiates T-cell immune responses, including anti-tumour responses. Ipilimumab is a humanised monoclonal antibody, and a CTLA-4 inhibitor. CTLA-4 inhibition blocks inhibitory T-cell signals, allowing a T-cell mediated immune response against tumour cells. Nivo+ipi act simultaneously at different points within the T-cell immune response pathway, producing a synergistic effect with concomitant administration.

For the combination phase of treatment, nivolumab is administered at a dose of 3mg/kg every three weeks for four doses, in combination with ipilimumab at a dose of 1mg/kg every three weeks for four doses. For the monotherapy phase, treatment with nivolumab can be administered at a dose of 240mg every two weeks or 480mg every four weeks. Treatment with nivolumab monotherapy should be continued as long as clinical benefit is observed or until the patient no longer tolerates treatment. Both agents are formulated as concentrate for solution for infusion, available in multiple vial sizes.

The main comparators for this submission are sunitinib and pazopanib; tivozanib is included as a scenario analysis. These were considered appropriate by the Review Group and in line with current practice in the Irish setting. The Review Group note that cabozantinib, although not included in the submission, may also be considered a relevant comparator.

1. Comparative effectiveness of nivolumab in combination with ipilimumab

Clinical evidence for the approval of nivo+ipi comes from the CheckMate 214 trial. CheckMate 214 was a Phase III, open-label, international randomised controlled trial, comparing nivo+ipi with sunitinib monotherapy in patients with previously untreated

advanced clear-cell RCC. A total of 1096 patients were randomised across 28 countries, with 550 allocated to nivo+ipi and 546 to sunitinib in the intention-to-treat population, and 425 to nivo+ipi and 422 to sunitinib in the intermediate-/poor-risk population.

Data presented by the Applicant suggested that the proportional hazards assumption was unlikely to hold in CheckMate 214, and so reported hazard ratios (HRs) should be interpreted with caution. Nivo+ipi was associated with a statistically significant increase in overall survival (OS) (HR 0.63, 95% CI 0.44 to 0.89; p<0.001) and objective response rate compared to sunitinib, but no increase was demonstrated in progression free survival (HR 0.82, 95% CI 0.64 to 1.05; p=0.03). With 25.2 months follow-up, median OS was not reached with nivo+ipi, and was 26 months with sunitinib. Outcomes were consistent with additional follow-up, and across most sub-groups. There was no statistically significant difference in OS outcomes by PD-L1 status. Additional supportive evidence from single-arm trials was also considered. The Review Group had concerns regarding the generalisability of the trial to the Irish setting given the low uptake of second line treatment with nivolumab in the sunitinib arm of the trial. As the proportional hazards assumption was found not to hold, reported HRs should be interpreted with caution.

Estimates of relative efficacy versus sunitinib for the economic evaluation were based on the CheckMate 214 trial. For the comparison with pazopanib, the Applicant assumed equal efficacy of pazopanib and sunitinib based on the COMPARZ study, a randomised trial designed to show non-inferiority of pazopanib to sunitinib. For the comparison with tivozanib, the Applicant presented a network meta-analysis

2. Safety of nivolumab in combination with ipilimumab

In CheckMate 214, in all treated subjects, the overall frequency of adverse events (AEs) was >99% in both arms. Grade 3-4 AEs were reported in 65.3% of patients treated with nivo+ipi, compared to 76.1% of patients treated with sunitinib. With nivo+ipi, the most frequently reported grade 3-4 AEs were increased lipase (11%), increased amylase (6.2%) and fatigue (6.2%). With sunitinib, the most frequently reported grade 3-4 AEs were hypertension (17.6%), fatigue (10.1%), palmar-plantar erythrodyesthesia syndrome (9.3%), increased lipase (7.7%) and decreased platelet count (7.1%).

Similar proportions of patients experienced grade 5 AEs (death) in both arms (3.1% with nivo+ipi and 3.4% with sunitinib), although none of these were classified as treatment-related in the nivo+ipi arm and 0.4% in the sunitinib arm. The EPAR states that deaths of seven patients (1.3%) were attributable to study drug toxicity with nivo+ipi, compared to four patients (0.7%) with sunitinib. The recorded causes of the seven deaths in the nivo+ipi arm were necrotizing pneumonia, sudden death, hepatic failure, pneumonitis, immune-mediated bronchitis, lower gastrointestinal haemorrhage and haemophagocytic syndrome. The recorded causes of the four deaths in the sunitinib arm were heart failure, cardiac arrest and multiple organ failure. The EPAR concludes, "The safety profile of nivo+ipi in the current dossier seems to compare unfavourably with nivolumab monotherapy in second line treatment of RCC, as well as with nivolumab monotherapy in other tumour types. It is clear that addition of ipilimumab contributes substantially to toxicity….the contribution to benefit of ipilimumab in the first line treatment of RCC remains unclear".

3. Cost effectiveness of nivolumab in combination with ipilimumab

A de novo partitioned survival model was developed to investigate the cost-effectiveness of nivo+ipi. Data from CheckMate 214 and the network meta-analysis were used to inform the model. There was an assumption of equal efficacy between sunitinib and pazopanib. Patient characteristics were based on the characteristics of the intermediate- and poor-risk patients enrolled in CheckMate 214. A time horizon of 40 years was applied in the model. The model comprised of six mutually exclusive health states. Comparators were sunitinib, pazopanib and tivozanib. In the Applicant's base case model, all costs were estimated based on time to treatment discontinuation, which was not a pre-defined endpoint of the CheckMate 214 trial. Utilities were estimated using data from CheckMate 214.

Survival outcomes from CheckMate 214 were extrapolated to the full time horizon of the model using parametric extrapolation. OS data from CheckMate 214 is immature and long-term projections are therefore subject to great uncertainty. Incremental cost-effectiveness ratios (ICERs) for all comparisons were highly sensitive to choice of parametric curve fitting for time to treatment discontinuation. Resource use in the model was based on studies identified by a literature review and captured costs for drug acquisition and administration,

hospital resource use, monitoring and follow-up, management of AEs and terminal care costs.

The Review Group applied changes to derive their preferred base case, choosing an alternative model for time to treatment discontinuation, removing an assumption of long-term cure for responding patients, applying a utility increment for subsequent treatments, and utility decrements for AEs. The NCPE preferred ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1 NCPE preferred base case analysis*

Treatment	Incremental Costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Nivo+ipi	-	-	-
Sunitinib	91,413	1.41	64,614
Pazopanib	93,271	1.41	65,992
Tivozanib	61,587	1.98	31,058

*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. **QALY:** Quality adjusted life year, **ICER:** Incremental cost effectiveness ratio.

Table 2 Applicant base case ICERs*

Treatment	Incremental Costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Nivo+ipi	-	-	-
Sunitinib	59,986	1.37	43,745
Pazopanib	62,161	1.37	45,388
Tivozanib	29,815	1.85	16,147

*The Review Group identified a number of errors in the submitted model, which were rectified to produce the results shown. Figures in the table are rounded, and so calculations will not be directly replicable. **QALY:** Quality adjusted life year, **ICER:** Incremental cost effectiveness ratio.

For the probabilistic analysis of the NCPE preferred base case, the ICERs are similar to the deterministic model. The probability of nivo+ipi being the most cost-effective intervention was estimated at 0% at both the €20,000 per QALY and €45,000 per QALY thresholds, when compared with sunitinib and pazopanib. Tivozanib was not included in this analysis.

In the probabilistic sensitivity analysis using the Applicant's base case model, there is a moderate increase in the ICERs for nivo+ipi compared with all of the comparators, which

indicates uncertainty around some of the parameters included in the model. The probability that nivo+ipi is cost-effective at a threshold of €20,000 per QALY is 3.60%, and at a threshold of €45,000 per QALY is 48.80%, when compared with sunitinib and pazopanib.

Budget impact of nivolumab in combination with ipilimumab

The drug costs for nivo+ipi are described in Table 3, based on the list price and exclusive of commercial in confidence rebates.

Table 3 Costs per vial for nivolumab and ipilimumab

	Nivolumab		
		Strength	
	240mg	100mg	40mg
Price to wholesaler	€3,022.82	€1,229.58	€492.79
Pharmacy fee	N/A	N/A	N/A
Rebate of 5.5%	€166.26	€67.63	€27.10
Total drug cost to the HSE	€2,858.56	€1,161.95	€465.69
	Ipilimumab		
		Strength	
	200mg	**50mg**	-
Price to wholesaler	€15,193.87	€3,812.50	-
Pharmacy fee	N/A	N/A	-
Rebate of 5.5%	€835.66	€209.69	-
Total drug cost to the HSE	€14,358.21	€3,602.81	-

The drug cost for nivo+ipi per patient was estimated using the above costs per vial, and the extrapolated time to treatment discontinuation curve from CheckMate 214, as €119,168 per patient per treatment course.

The Review Group amended the estimated number of eligible patients to include patients with non-clear cell RCC, in line with the marketing authorisation. With this amendment included, it is estimated that 111 patients will be eligible for treatment in year 1, rising to 134 patients by year 5. Using Review Group estimates, the gross drugs budget impact is €2.7 million in year 1, rising to €7.1 million by year 5, giving a cumulative total of €25.9 million (inclusive of VAT). This cost is inclusive of drug administration costs and subsequent therapy costs, which account for approximately 5% and 6%, respectively of the total cost. The Applicant estimates the cumulative five-year gross budget impact at €15.5 million.

The net budget impact assumes that nivo+ipi will replace other treatments as first line treatment. Using Review Group estimates, the net drugs budget impact is €0.9 million in year 1, increasing to €3.3 million by year 5, giving a cumulative total of €10.98 million (inclusive of VAT). The Applicant estimates the net budget impact at €6.6 million. Estimated budget impact is sensitive to assumptions regarding treatment duration, numbers of eligible patients, and the assumption that subsequent treatments are replaced by nivo+ipi rather than displaced to further lines of treatment.

4. State if any patient submissions were received, and name submitting organisations.

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

5. Conclusion

The NCPE recommends that nivolumab in combination with ipilimumab be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*. The clinical and cost-effectiveness of nivolumab in combination with ipilimumab for the first line treatment of RCC should be reconsidered upon publication of the outcomes of the EMA-mandated post-authorisation efficacy study comparing combination therapy to nivolumab monotherapy for this indication.

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