Cost effectiveness of Nivolumab (Opdivo®) as monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults.

The NCPE has issued a recommendation regarding the cost-effectiveness of nivolumab. Following NCPE assessment of the applicant's submission, nivolumab is not considered cost effective as monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Bristol-Myers Squibb Pharmaceuticals) dossier on the cost effectiveness of nivolumab. 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 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 **March 2017**

Summary

In October 2016, Bristol-Myers Squibb Pharmaceuticals made a submission on nivolumab (Opdivo®) monotherapy for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults. Final data was submitted by the applicant on 13th March 2017.

The licensed dose for this indication is 3mg/kg by intravenous (IV) infusion every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until no longer tolerated.

Axitinib is the primary comparator for the evaluation. Comparisons against everolimus and best supportive care are also presented.

1. Comparative effectiveness of nivolumab

The CheckMate 025 trial was used to inform the relative effectiveness of nivolumab versus everolimus. The Review Group note that the trial population had clear-cell advanced RCC. This is a sub-group of the entire licensed population.

This was a Phase III, multicentre, open-label, active-controlled randomised controlled trial in patients (≥18 years) with clear-cell advanced RCC for which they had received previous treatment with one or two regimens of antiangiogenic therapy (prior cytokine therapy was also allowed). Patients were randomised (1:1) to nivolumab (3 mg/kg IV infusion every 2 weeks) or everolimus (10mg daily orally). Of the 821 patients randomly assigned, 803 underwent treatment (406 received nivolumab and 397 received everolimus). Treatment beyond progression was permitted if the patient had clinical benefit and was tolerating drug as determined by the investigator. The study was initiated in October 2012, and the primary data presented here are based on a database lock of June 2015. This database lock was used to inform the cost-effectiveness model.

The intention-to-treat population was evaluated for primary efficacy analysis of overall survival (OS). The study stopped early after an interim analysis showed an OS benefit. Median OS was 25.0 months (95% CI: 21.8 - not estimable) with nivolumab and 19.6 months (95% CI: 17.6 - 23.1) with everolimus. The hazard ratio for death for nivolumab versus everolimus = 0.73 (98.5% CI, 0.57 - 0.93); p=0.002 (98.5% CI width was used to coincide

with the O'Brien-Fleming alpha-spending function). Secondary end points included investigator assessed progression free survival (PFS). This was an open label trial; thus there is a potential for bias with this outcome. Median PFS was 4.6 months (95% CI: 3.7 - 5.4) and 4.4 months (95% CI: 3.7 - 5.5) with nivolumab and everolimus respectively; hazard ratio for death or progression was 0.88 (95% CI: 0.75 - 1.03). The 6-month PFS rate was 39% in both arms. The Kaplan-Meier PFS curves overlap until about 6 months and then separate. The 1-year rates were 23% (nivolumab) and 19% (everolimus).

In conclusion, in Checkmate 025 nivolumab extended OS compared to everolimus in the trial population. No significant improvement in PFS was seen.

Evidence synthesis was required to compare nivolumab to axitinib and best supportive care. To compare to best supportive care, the network linked CheckMate 025 with RECORD-1 (everolimus vs. best supportive care). To compare to axitinib, the network linked both CheckMate 025 and RECORD-1 to TARGET (best supportive care vs. sorafinib) and AXIS (sorafenib vs. axitinib). The Review Group note that:

- patients in AXIS had a poorer prognosis than those in CheckMate 025.
- CheckMate 025 recruited patients who had had 1 or 2 previous treatments; the other trials recruited patients who had only had one. Previous lines of treatments varied between trials.
- the base case network meta-analysis used cross-over adjusted results from TARGET and RECORD-1. An alternative analysis used data that are crossover adjusted/crossover free (where available).
- the base case OS analysis used ITT hazard ratios available for each of the trials with the exception of AXIS. Data for the subgroup in AXIS who had been treated with sunitinib were utilised to better reflect the trial population of CheckMate 025 (and the target population for nivolumab in clinical practice).
- In CheckMate 025, AXIS and TARGET, PFS was assessed by the investigator. In the other trials, it was assessed by an independent review committee.

The hazard ratio for OS benefit for nivolumab vs. everolimus was 0.73 (95% CI: 0.6 - 0.89). Hazard ratios for the comparisons of nivolumab vs. axitinib and vs. best supportive care are 0.72 (95% CI: 0.46 - 1.15) and 0.64 (95% CI: 0.45 - 0.90), respectively. Using the crossover adjusted/crossover free network, the respective hazard ratios were 0.61 (95% CI: 0.21-1.82) and 0.44 (95% CI: 0.16- 1.22).

The hazard ratio for PFS for nivolumab vs. everolimus was 0.88 (95% CI: 0.75 - 1.03). Hazard ratios for the comparisons of nivolumab vs. axitinib and vs. best supportive care are 0.77 (95%CI: 0.50 - 1.19) and 0.29 (95%CI: 0.21 - 0.40) respectively. Those for the comparisons of everolimus vs. axitinib and vs. best supportive care are 0.87 (95% CI: 0.58 - 1.31) and 0.33 (95% CI: 0.25 - 0.43) respectively. The hazard ratio for everolimus vs. nivolumab is 1.14 (95% CI: 0.97- 1.33).

2. Safety of nivolumab

The all-treated population of Checkmate 025 was evaluated for the safety analyses. The majority of patients in both arms experienced ≥ one adverse event (any grade). Grade 3/4 all-causality adverse events reported more frequently with nivolumab were hypercalcaemia, increased alanine aminotransferase, and malignant neoplasm progression. Those reported more with everolimus were anaemia, hyperglycaemia, hypertriglyceridemia, stomatitis, and mucosal inflammation. Adverse events with a potential immunological cause were investigated. More patients treated with nivolumab reported those belonging to the endocrine, hepatic and hypersensitivity/infusion reaction categories. More with everolimus reported those belonging to the gastrointestinal, pulmonary and skin categories.

3. Cost effectiveness of nivolumab

This submission evaluates the cost effectiveness of nivolumab according to the population of CheckMate 025 (advanced or metastatic clear-cell RCC). Cost effectiveness is not evaluated in the entire licensed population.

A Markov model with a 30 year time horizon was utilised. It has six health states: 'PFS on treatment', 'PFS off treatment', 'Post-progression (PPS) on treatment' and 'PPS off treatment'. All patients enter in 'PFS on Treatment'. 'Terminal Care' is a transitory state which patients transition to prior to moving into 'Death'. Future costs and health-related outcomes are discounted at 5% per annum.

Parametric and spline-based extrapolations of OS, PFS and time to treatment discontinuation data from ChecckMate 025 inform the proportion of patients in each health state in each cycle in the nivolumab and everolimus arms. The NCPE had a number of concerns regarding the assumptions employed in the extrapolations of the survival data; sensitivity analyses

indicated that they were a major source of uncertainty in the model. Of note, a substantial increase in PFS with nivolumab relative to everolimus was predicted. Likewise, a substantial increase in the OS benefit associated with nivolumab was estimated. For the axitinib and best supportive care model arms, hazard ratios for PFS and OS from network meta-analyses were applied to everolimus survival curves. Unlike the other drugs, axitinib treatment was assumed to continue until disease progression or death.

Health state utility values for pre- and post-progressive disease for nivolumab and everolimus were derived from EQ-ED data from Checkmate 025. For axitinib, values were derived from EQ-5D data from AXIS. Estimates taken from AXIS are much lower than those from CheckMate 025. In AXIS a higher proportion of patients had a poorer prognosis. It is assumed that estimates for AXIS are applicable to best supportive care. Differential health state utility values are not applied while patients are on or off treatment. Patients off treatment in the nivolumab arm will continue to accrue more utility benefits than those off treatment in comparator arms. Disutilites were applied to treatment-emergent Serious Grade 3/4 adverse events that occurred in CheckMate 025. The decrement for anaemia was derived from an assessment of pazopanib for first-line treatment of advanced RCC (NICE TA215b). Decrements for the others were drawn from discussions involving one Irish oncologist and a small number of UK oncologists. Decrements for everolimus are assumed to be applicable to axitinib.

Resource use assumptions were derived from an assessment of axitinib (NICE TA333) and from previous submissions on nivolumab for RCC in other jurisdictions. Validation was sought from one anonymous oncologist in Ireland. Costs considered included those for drug acquisition and administration, monitoring and follow up, management of adverse events and terminal care costs. It is assumed that nivolumab will always be administered in a day case setting. It is assumed that 2 hours will be sufficient for a patient to be admitted, be seen by a consultant, receive nivolumab (over 60 minutes) and be monitored. Drug acquisition costs are based on relative dose intensities of 92% for nivolumab, 94% for everolimus (both derived from CheckMate 025) and 102.0% for axitinib (derived from AXIS). Different methodologies are used to estimate relative dose intensities in the trials. Patient-level weight data from CheckMate 025 patients (from Western Europe) were used. No vial sharing was assumed. The applicant used a ‘method of moment’s calculation’ resulting in 1.73 x 100mg vials and 1.99 x 40mg vials being required for an average patient. Costing of treatment-

emergent Serious Grade 3/4 adverse events was informed by one anonymous Oncologist. Decreased appetite, hyperglycaemia, hypertriglyceridaemia and anaemia (all occur more frequently with everolimus) are assumed to be treated in the inpatient setting. The costing of adverse events for everolimus is assumed to applicable to axitinib.

According to the applicant's preferred assumptions, the ICERs are €43,749/QALY vs. axitinib (incremental cost €63,110; incremental QALY 1.4426), €69,655/QALY vs. everolimus (€71,245; 1.0228) and €60,795/QALY vs. best supportive care (€109,016; 1.7932). Probabilities of cost effectiveness at the €45,000/QALY threshold are best supportive care (52.7%), everolimus (41.7%), axitinib (5.3%) and nivolumab (0.28%).

Alternatively, the NCPE have assumed that 2 x 100mg + 2 x 40mg vials are required for an average patient and that the relative dose intensity is 100% for all drugs. If all other applicant assumptions remain unchanged we estimate ICERs of €55,864/QALY vs. axitinib (€63,110; QALY 1.4426), and €86,740/QALY (€71,245; QALY 1.0228) vs. everolimus.

The company presented a variety of scenario analyses and sensitivity analyses. The NCPE performed a number of additional such analyses.

4. Budget impact of nivolumab

The list price of nivolumab is €1,474.00 per 100mg vial and €589.00 per 40mg vial. Using the applicant's assumptions, the per-person acquisition cost for a course of treatment with nivolumab will be about €113,300 (inclusive of VAT). Using the NCPE alternative assumptions, of numbers of vials required and relative dose intensities (see section 3), this cost would be about €135,800.

The applicant estimates an expected gross cost for nivolumab treatment to be about €3.81 million in the first year increasing to about €4.96 million by the fifth year. The total 5 year cumulative budget would be about €22.61 million. Using the NCPE alternative assumptions, the expected gross impact would be about €4.51 million in the first year increasing to about €5.86 million by the fifth year. The total 5 year cumulative figure would be about €26.73 million.

5. Conclusion

The efficacy and cost effectiveness of nivolumab according to the entire license (i.e. as monotherapy for the treatment of advanced RCC after prior therapy in adults) has not been investigated. Therefore is not recommended for reimbursement in this setting.

Further, following the NCPE assessment of the applicant's submission, nivolumab is not considered cost effective for the treatment of advanced or metastatic clear-cell RCC and therefore is not recommended for reimbursement at the submitted price.