Cost-effectiveness of nivolumab (Opdivo®) for the treatment of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults.

The NCPE has issued a recommendation regarding the cost-effectiveness of nivolumab (Opdivo®). Following NCPE assessment of the applicant's submission, nivolumab (Opdivo®) is not considered cost-effective for the treatment of non-squamous NSCLC 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) economic dossier on the cost effectiveness of nivolumab (Opdivo®). 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 **September 2016**

Summary

In April 2016, Bristol-Myers Squibb Pharmaceuticals submitted a dossier examining the cost effectiveness of nivolumab for the treatment of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy. Final data submitted by the Applicant was received on 12th September 2016.

The recommended dose is 3mg/kg by IV infusion every two weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. No specific dose reductions are recommended.

In the submission, docetaxel was the comparator investigated. This was considered appropriate by the NCPE.

1. Comparative effectiveness of nivolumab

Relative efficacy outcomes for the comparison with docetaxel were derived from the CheckMate-057 study. This study was an open-label, multi-national, Phase III randomised controlled trial of 582 patients with locally advanced or metastatic non-squamous NSCLC, after failure of prior platinum doublet-based chemotherapy. Patients were assigned to one of two arms, nivolumab 3mg/kg every 2 weeks or docetaxel 75mg/m^2 every three weeks. Treatment with nivolumab beyond progressive disease in the event of continuing clinical benefit was permitted; docetaxel treatment was continued until progressive disease or intolerable side-effects. Efficacy analyses were performed in the intent-to-treat population.

The study met its primary endpoint of overall survival (OS). Hazard ratios presented in the submission for OS cannot be considered valid since they are derived from a Cox proportional hazards model and the proportional hazards assumption is not shown to hold in this trial. Nivolumab was associated with a median OS of 12.2 months (95% CI 9.7, 15.5), compared to 9.4 months (95% CI 8.1, 10.7) with docetaxel treatment. The OS rate with nivolumab was 39% compared to 23% with docetaxel at 18 months. The OS rate at 24 months was 29% with nivolumab, compared to 16% with docetaxel. Docetaxel was associated with increased survival for the first seven months of the trial. Nivolumab was associated a median progression free survival (PFS) of 2.3 months (95% CI 2.2, 3.3) compared to 4.2 months

(95% CI 3.5, 4.9) for docetaxel. The PFS rate at 12 months was higher for nivolumab than for docetaxel (18.5% versus 8.1%). At the 24 month data cut off, the PFS rate was 12% in patients treated with nivolumab, compared to 1% in docetaxel treated patients. There is considerable risk of bias in the PFS estimates given that they are investigator assessed, and due to the open-label nature of the trial. As with OS, the HRs submitted for PFS cannot be considered valid due to violation of the proportional hazards assumption.

While crossover between treatment arms was not permitted during the trial period, patients could receive further lines of treatment in the follow up period; no attempt is made to adjust the survival benefit for this, and thus the treatment effects attributed to nivolumab and docetaxel may not be the result of these interventions alone. The European Medicines Agency considered that some of the survival benefit seen in the nivolumab treatment arm could be attributed to subsequent treatment with docetaxel, and therefore the trial results may overestimate the OS benefit of nivolumab. Subgroup analysis suggests that a relative survival benefit with nivolumab is only seen in patients whose tumours express PD-L1. Subgroup analysis of those aged over 75 years failed to show any treatment benefit for nivolumab in this patient cohort. The number of patients over 75 recruited to the trial was small, which prevents any conclusions being drawn around efficacy in this patient group, but since 37% of Irish patients are over 75 years of age when diagnosed, there is uncertainty over the generalizability of the trial outcomes to this patient population.

2. Safety of nivolumab

Safety data from all the available trials of nivolumab in non-squamous NSCLC were presented in the submission (CheckMate 057, 003 and 153). Overall the safety profile of nivolumab in non-squamous NSCLC is consistent with previous findings. There was a higher incidence of Grade 3-4 adverse events in the docetaxel arm of CheckMate 057 than in the nivolumab arm (67% versus 46%). There was one death in each arm considered to be treatment related. The most common all cause grade 3-4 AEs associated with nivolumab treatment were dyspnoea (5%), fatigue (3%), and pneumonia (3%).

3. Cost effectiveness of nivolumab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were time to treatment discontinuation (TTD) and overall survival (OS). Inputs for the comparison of nivolumab and docetaxel were derived from CheckMate 057. Cost effectiveness was investigated using a health state model with a 20 year time horizon. The model simulates patients through three health states: 'Progression-free', 'Progressive disease', and 'Death'. All health states are mutually exclusive, and death is the absorbing state. All patients start in the progression-free state; transitions to the death state could occur from either the progression-free or progressive disease states. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from CheckMate 057. Patients in the 'Progressive disease' state are assumed to receive one third line treatment, based on the proportion of patients who received subsequent systemic therapy in Checkmate 057. Third line treatments included in the model are docetaxel, carboplatin, pemetrexed, erlotinib, gemcitabine, and best supportive care (BSC).

TTD and OS results from CheckMate 057 are extrapolated to the full time horizon of the model, using parametric and spline-based extrapolations. The NCPE had concerns over a number of assumptions employed in these extrapolations and the sensitivity analyses showed that they were a major source of uncertainty in the model. In particular the economic model predicted an implausible PFS benefit with nivolumab, much greater than that seen in the CheckMate 057 trial. In addition, survival extrapolation had to be modified to ensure that the TTD didn't exceed the OS, and that the OS didn't fall below the general population mortality; these modifications to prevent the implausible scenarios predicted by the model are indicative of flawed assumptions in the extrapolation of the trial data.

Resource use in the model was based on studies identified by a literature review and validated by market research, and captured costs for drug acquisition and administration, hospital and home care resource use, monitoring and follow up, management of AEs and terminal care costs. AEs which were of Grade≥3 severity and occurred in ≥2% in either arm of the trial population were included in the economic model. A utility weight is applied per health state in the model.

The NCPE implemented a number of changes to the model:

- Excluded Grade 3-4 AEs with less than 5% occurrence in the trial, to maintain consistency with previous squamous NSCLC submission.
- Updated the distribution of subsequent treatments to reflect Irish clinical practice.
- Implemented OS extrapolation for nivolumab using the 2-knot spline model in the base case, since this was the statistically best fitting model.

The NCPE also believe that it would have been more appropriate to use PFS to model the state transitions and TTD to model the treatment costs; however this functionality was not incorporated into the model despite a specific request by the NCPE. Implementing the above NCPE preferred set of assumptions produced an ICER of €202,393 (incremental costs €88,117, incremental QALYs 0.44). The NCPE believe that this ICER may overestimate the ICER, (since PFS and TTD could not be used to model state transitions) but believe that it is much closer to the true ICER than that generated by the company base case of €136,030/QALY (incremental costs €92,205, incremental QALYs 0.68).

The probability of nivolumab being cost-effective relative to docetaxel using both the company and the NCPE preferred set of assumptions, at a WTP threshold of €45,000/QALY, is 0%. The company presented a variety of scenario analyses and performed appropriate sensitivity analyses. The NCPE performed a number of additional sensitivity analyses to test assumptions made in the model.

4. Budget impact of nivolumab

The company estimate that 302 patients will be eligible for treatment annually, and predict market share of 43% in year 1, rising to 75% thereafter.

The list price of nivolumab is €589 and €1,474 for the 40mg and 100mg vials respectively. This price is further subject to VAT. The estimated cost per patient per treatment course is €50,425 (including VAT), assuming patients receive 12.6 doses of nivolumab.

The gross cumulative drug impact of introducing nivolumab from 2017 to 2021 is approximately €57.1 million, assuming a market share of 75%.

The net cumulative budget impact of the introduction of nivolumab from 2017 to 2021 is approximately €56.33 million.

5. Conclusion

Following review of the company submission, nivolumab is not considered to be cost-effective relative to docetaxel for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer in adults after prior chemotherapy, at a threshold of €45,000/QALY.