NCPE report on the cost effectiveness of nivolumab (Opdivo®) for the treatment of locally advanced or metastatic squamous non-small cell lung cancer 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 is not considered cost effective for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy, and therefore it 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) economic dossier. 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 2016**

Background

In October 2015, Bristol-Myers Squibb (BMS) submitted a dossier examining the cost effectiveness of nivolumab for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy. Final data submitted by the Applicant was received on 5th February 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, comparators investigated were docetaxel and erlotinib. The primary comparator in the analysis was docetaxel with the erlotinib comparison presented as a scenario analysis. 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-017 study. This study was an open-label, multi-national, Phase III randomised controlled trial of 272 patients with locally advanced or metastatic squamous cell 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 was halted prematurely, at a pre-specified interim analysis point, as it was judged to have met its primary endpoint of overall survival (OS). Nivolumab is associated with a statistically significant increase in OS (hazard ratio (HR) 0.59, 96.85% CI 0.43, 0.81, p=0.0002). The OS rates for nivolumab versus docetaxel at 6 and 12 months are 63.7% v 50.4%, and 42.1% v 23.7% respectively. The median OS was 9.23 months with nivolumab versus 6.01 months with docetaxel. The PFS rate at 6 months is 38.4% with nivolumab versus 21.9% with docetaxel, and at 12 months was 20.8% v 6.4%. 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. A HR presented in the submission for PFS cannot be considered valid

since it was derived from a Cox proportional hazards model and the proportional hazards assumption is not shown to hold in this trial.

While crossover between treatment arms was not permitted, patients could receive further lines of treatment in the follow up period; no attempt is made to adjust survival benefits for same and thus the treatment effects attributed to nivolumab and docetaxel may not be the result of these interventions alone. In addition, trials terminated early for benefit may lead to an overestimation of treatment effect. Results from an 18-month data cut presented by the company show a decrease in the OS endpoints compared to the data quoted above.

There are no head to head trials comparing nivolumab to erlotinib. The company undertook an indirect treatment comparison to generate comparative efficacy estimates. There was considerable heterogeneity in patient populations between the trials included in the analysis. Because of the uncertainty associated with the results of the ITC, the comparison of nivolumab and erlotinib is presented as a scenario analysis. The ICER generated cannot be considered a reasonable estimate of the relative costs and benefits of the treatments.

2. Safety of nivolumab

In CheckMate-017, adverse events (AEs) of any grade occurred in 96.9% patients in both arms of the trial. Grade ≥3 AEs occurred in fewer patients in the nivolumab arm than the docetaxel arm, and the incidence of serious AEs was less also. The most commonly reported treatment related AEs with nivolumab were fatigue (16%), decreased appetite (11%), asthenia (10%) and nausea (9%) and diarrhoea (8%). The most commonly reported Grade 3-4 treatment-related AEs with nivolumab were fatigue, decreased appetite, pneumonitis, and leukopenia (<1%).

3. Cost effectiveness of nivolumab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were progression free survival and overall survival. Inputs for the comparison of nivolumab and docetaxel were derived from CheckMate-017. Inputs for the comparison of nivolumab and erlotinib were derived from an indirect treatment comparison and are presented as a scenario analysis. Cost effectiveness was investigated using a health state model with a 20 year time horizon.

The model simulates patients through three main 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. The model assumes patients continue to receive treatment until disease progression, which is contrary to the licensed dosing for nivolumab and to the nivolumab dosing implemented in the CheckMate-017 trial, where treatment was continued beyond progressive disease in a proportion of patients. Patient characteristics (with the exception of patient weight), dose intensity, utility measurements and adverse event frequency used in the model are derived from CheckMate-017. 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-017. Third line treatments included in the model are docetaxel, platinum doublet, erlotinib, gemcitabine, and vinorelbine, and best supportive care (BSC).

PFS and OS results from CheckMate-017 are extrapolated to the full time horizon of the model, using parametric and spline 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, there is an assumption of continued efficacy for nivolumab after treatment has been discontinued, meaning that nivolumab is associated with a much longer survival in the post progression phase than docetaxel. The bulk of the survival gain in the model comes from the period after progressive disease has been confirmed, which is not reflected in the trial results.

Resource use in the model was based on studies identified by a literature review, 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 ≥5% in either arm of the trial population were included in the economic model; eight AEs were incorporated into the model in total. A utility weight is applied per state in the model.

The NCPE implemented a number of changes to the model:

- Used results from an updated data-cut from 18 months.
- Changed the modelled patient weight to reflect the patients in the CheckMate-017

trial.

- Updated administration and AE costs.

The implementation of these changes resulted in significant increase in the ICER compared to the company base case. The final ICER was €136,215/ QALY. The probability of nivolumab being cost-effective relative to docetaxel 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 submitted a revised base case budget impact analysis at the request of the NCPE due to significant underestimation of patient numbers, market share, and inappropriate calculations.

In the revised model, the company make a conservative estimate of market share at 43% in year 1, rising to 75% from year 2 onwards. The NCPE believe this may underestimate the potential market share, based on the results from CheckMate-017.

The gross cumulative drug impact of introducing nivolumab from mid-2016 to 2020 is approximately €35.3 million using the Review Group estimates, compared to €28.1 million using the company estimates.

The net cumulative budget impact of the introduction of nivolumab from mid-2016 to 2020 is €26 million using the Review Group estimates, compared to €20.6 million according to the company estimates.

5. Conclusion

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