NCPE report on the cost effectiveness of nivolumab (Opdivo®) for the treatment of advanced (unresectable or metastatic) melanoma 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 advanced (unresectable or metastatic) melanoma in adults, 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 advanced (unresectable or metastatic) melanoma in adults. Final data submitted by the Applicant was received on 10th 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 ipilimumab and dacarbazine for BRAF negative patients, and ipilimumab, vemurafenib and dabrafenib for BRAF positive patients.

1. **Comparative effectiveness of nivolumab**

Relative efficacy outcomes for the comparison with dacarbazine were derived from the CheckMate-066 study. This study was a double-blind, placebo controlled, multi-national Phase III randomised controlled trial of 418 patients with advanced metastatic melanoma. Patients had not received any previous treatments, and only BRAF negative patients were eligible for inclusion. Patients were assigned to one of two arms, nivolumab 3mg/kg every 2 weeks or dacarbazine 1000mg/m^2 every three weeks, plus matched placebo infusions. In both arms, treatment continued until there was documented disease progression or unacceptable toxicity. Treatment beyond RECIST v1.1 defined progressive disease (PD) was permitted in patients who, as judged by the Investigator, were receiving clinical benefit from the study drug and not experiencing side-effects. There was no maximum duration of treatment with study drug specified. Efficacy analyses were performed in the intent-to-treat population.

The study was halted prematurely, 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) 0.42, 99.79% CI 0.25-0.73, p<0.001). The OS rates for nivolumab versus dacarbazine at 6 and 12 months were 84.1% and 72.9% respectively. The median OS was 10.8 months for dacarbazine and not yet reached for nivolumab.

The HR for progression or death was 0.43 (95% CI 0.34-0.56, p<0.001). The PFS rate at 6 months was 48% for nivolumab and 18.5% for dacarbazine, and at 12 months was 41.8% for

nivolumab and not produced for the dacarbazine group as all patients had progressed. The median PFS in the nivolumab arm was 5.1 months versus 2.2 months in the dacarbazine arm

While crossover between treatment arms was not permitted in the data-cut outlined above, patients could receive further lines of treatment in the follow up period such as ipilimumab; no attempt is made to adjust survival benefits for same and thus the treatment effects attributed to nivolumab and dacarbazine may not be the result of these interventions alone.

CheckMate-067 is a Phase III randomised controlled trial, comparing nivolumab, ipilimumab and a combination of both treatments. OS data from this study is not available at present, and thus an evidence synthesis is required to compare nivolumab to the primary comparator for BRAF negative patients, ipilimumab. It is also required to compare nivolumab to the comparators for BRAF positive patients, ipilimumab, vemurafenib and dabrafenib. The company state that a 'mixed treatment comparison' (MTC) between all the comparators of interest was not possible, and so two indirect comparison networks were created. For the comparison with ipilimumab, the company presented a covariate adjusted survival model using patient-level data from MDX010-20 (the pivotal registration study for ipilimumab) and CheckMate-066. This analysis is associated with significant uncertainty as a number of assumptions regarding equivalent treatment effects and prognostic variables are required, and there was considerable heterogeneity in patient populations between the trials. For the comparison with vemurafenib and dabrafenib, the company presented a covariate adjusted analysis, using BRIM-3 (the pivotal registration study for vemurafenib) and CheckMate-066, thereby assuming that dabrafenib and vemurafenib have equivalent clinical effects. The BRIM-3, Checkmate-66 and BREAK-3 (the pivotal registration study for dabrafenib) trials recruited a very heterogeneous patient mix, and there is doubt over the comparability of these trials for an indirect treatment comparison. The company presented a variety of scenario analyses for the indirect treatment comparisons.

2. Safety of nivolumab

In CheckMate-066, adverse events (AEs) of any grade occurred in >90% patients in both arms. The incidence of Grade 3-4 AEs were similar in both arms. Treatment-related AEs reported in ≥15% nivolumab patients were fatigue (19.9%), pruritus (17%), nausea (16.5%), diarrhoea (16%) and rash (15%). Safety data from the CheckMate-067 study was also

provided; Grade 3-4 AEs were experienced by less patients receiving nivolumab than ipilimumab (43.5% v 55.6%).

3. Cost effectiveness of nivolumab

The key model inputs are TTP (time to progression), PrePS (pre-progression survival) and PPS (post-progression survival) for BRAF negative patients, and PFS (progression free survival) and OS for BRAF positive patients. Inputs for the comparison of nivolumab and dacarbazine were derived from CheckMate-066. Inputs for the comparison of nivolumab and ipilimumab, vemurafenib and dabrafenib were derived from an indirect treatment comparison. Cost-effectiveness was investigated using a de-novo semi-Markov model with a 40 year time horizon.

The model simulates patients through three main survival states: 'Progression-free', 'Progressed', 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 progressed states. Patient characteristics for the BRAF negative patients are based on CheckMate-066, and for the BRAF positive patients, on BRIM-3. Utility measurements and AE frequency are based on data collected in CheckMate-066. Nivolumab treatment costs are modelled to reflect 'Time on Treatment' in the CheckMate-066 study. The model base case caps treatment duration with nivolumab at 2 years regardless of progression status. This treatment rule has a large effect on the treatment costs associated with nivolumab in the model, with no impact on the QALY gain

A proportion of patients in the 'Progressive disease' state are assumed to receive second line treatment with ipilimumab, based on the proportion of patients who received subsequent ipilimumab in CheckMate-066.

TTP, PrePS and PPS results from CheckMate-066 are extrapolated to the full time horizon of the model, using parametric 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. Nevertheless, the model outputs predict similar results to the clinical trial at 1 and 2 years.

Resource use in the model was based on studies identified by a literature review, and captured costs for drug acquisition, administration, hospital and home care resource use, monitoring and follow up, management of AEs and terminal care costs. AEs which were of Grade ≥3, diarrhoea ≥Grade 2, and any endocrine AEs were included in the economic model. A combination of 'time to death' and progression based utility states were implemented in the model.

The NCPE implemented a number of changes to the model:

- Implementing a time horizon of 30 years to ensure consistency with previous melanoma submissions.
- Implementing 'progression based' utilities from CheckMate-066 to ensure consistency with previous melanoma submissions.
- Removing the cap on the duration of treatment with nivolumab, to ensure consistency with CheckMate-066, the licensed indication and international clinical guidelines.
- Removed the possibility of re-treatment with ipilimumab in line with Irish practice.

The implementation of these changes resulted in significant increase in the ICER compared to the company base case. The final ICER versus ipilimumab for BRAF negative patients was approximately €101,282 / QALY, and for BRAF positive patients was €76,540/ QALY. The final ICER versus vemurafenib was €29,018/ QALY and versus dabrafenib was €46,276/ QALY for BRAF positive patients. The probability of nivolumab being cost-effective relative to ipilimumab at a WTP threshold of €45,000/ QALY is 0% in BRAF negative patients and 6% in BRAF positive patients. It should be noted that the NCPE previously found ipilimumab and vemurafenib not to be a cost effective treatments for metastatic melanoma, and dabrafenib only cost effective relative to vemurafenib

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 budget impact model after request for clarifications from the Review Group.

The company estimate that the gross cost of the adoption of nivolumab using the base case model and list price of all treatments is €98.8 million over 5 years. This figure assumes 100% market share after year 1, incorporates the costs of subsequent ipilimumab treatment, and is based on treatment with nivolumab being capped to a maximum of two years treatment duration.

The company estimate that the net budget impact of the adoption of nivolumab using the revised base case model and the list price of all treatments, is €17.6 million from 2016-2020. This is based on treatment with nivolumab being capped to a maximum of two years treatment duration. The Review Group consider this figure may potentially under-estimate the gross budget impact since there is no evidence to support the discontinuation of treatment at two years.

5. Conclusion

Following review of the company submission, nivolumab is not considered to be cost-effective for the treatment of advanced (unresectable or metastatic) melanoma at a threshold of €45,000/QALY.