Cost-effectiveness of nivolumab (Opdivo®) for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

The NCPE has issued a recommendation regarding the cost-effectiveness of nivolumab (Opdivo®). Following assessment of the Applicant's submission, the NCPE recommends that nivolumab (Opdivo®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

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 (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 **October 2019**

In November 2018, Bristol Myers Squibb (BMS) submitted a dossier of clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of nivolumab (Opdivo®) for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Final data was submitted by the Applicant in April 2019. BMS are seeking reimbursement for nivolumab in the hospital setting.

Nivolumab (Opdivo®)

Nivolumab is a human, monoclonal immunoglobulin G4 (IgG4) antibody that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Through this action, nivolumab prevents inactivation of T-cells, restoring T-cell activity against tumour cells, resulting in destruction of the tumour. Nivolumab is currently approved for reimbursement for advanced (unresectable or metastatic) melanoma; the National Cancer Control Programme protocol (April 2019) specifies that patients will only be eligible for treatment with nivolumab if they have not had a previous PD-1 or PD-L1 inhibitor.

The recommended dose of nivolumab for the indication under consideration here is 3mg/kg intravenously every two weeks. Treatment continues for a maximum of one year. No specific dose reductions are recommended.

Routine surveillance was considered by the Applicant as the main comparator of interest. This was considered appropriate by the NCPE and in line with current standard of care in Ireland.

1. **Comparative effectiveness of nivolumab**

Clinical efficacy is primarily derived from the Checkmate 238 trial. This is a phase III multicentre, randomised controlled trial in which patients aged 18 years or older with stage III or stage IV disease were randomised to receive nivolumab 3mg/kg intravenously every two weeks (n=453) or ipilimumab 10mg/kg every three weeks for four doses then continuing every 12 weeks (n=453). Treatment was administered for one year or until disease recurrence, unacceptable toxicity or withdrawal of consent. The primary outcome was recurrence free survival (RFS) and secondary outcomes included overall survival (OS),

safety and tolerability, Health Related Quality of Life, and RFS according to PD-L1 status; distant metastasis free survival (DMFS) was an exploratory endpoint.
Median RFS was 30.8 months compared to 24.1 months respectively in the nivolumab and ipilimumab arms at minimum 24 month cut off. The EPAR notes that the median estimates provided are "unstable due to low number of patients and censoring with 24 months of follow-up". At 24 months the hazard ratio (HR) for RFS was 0.66 (95% CI 0.54 to 0.81). At 24 month cut off, approximately 30% of patients in the nivolumab group and 40% in the ipilimumab group received subsequent treatment. Median DMFS was not reached at 24 months. The HR for DMFS for nivolumab versus ipilimumab was 0.76 (95% CI 0.59 to 0.98). Subgroup analyses indicate that greater PD-L1 expression (>1%) results in lower risk of recurrence in nivolumab treated group compared to ipilimumab treated group. RFS benefit was demonstrated regardless of BRAF mutation status.

The Applicant provided additional clinical data in confidence to the NCPE for appraisal.

A formal analysis of OS was not yet available; formal analysis is expected at 48 month data point. The European Medicines Agency concluded that the OS data is too immature to confirm that the benefit observed for RFS will be borne out in the OS; however the data indicates that there is unlikely to be a detrimental effect on OS.

No direct evidence was available for nivolumab versus routine surveillance and therefore an evidence synthesis (patient level data meta-regression) was undertaken using data from Checkmate 238 and clinical trial comparing ipilimumab with placebo (CA 184-029). The common comparator between CheckMate 238 and CA 184-029 is ipilimumab, while placebo acts as a proxy for routine surveillance. The results of the evidence synthesis concluded that there was a correspondingly increased benefit in terms of RFS over placebo. In the absence of direct evidence for OS, the Applicant presents OS results based on assuming a surrogacy relationship between OS and RFS.

2. **Safety of** Nivolumab

The safety profile of nivolumab in CheckMate 238 was consistent with previous studies. Any grade adverse events (AEs) were reported in 96.9% of subjects in the nivolumab group and 98.5% of subjects in the ipilimumab group. In the nivolumab group, the most frequently reported AEs were fatigue (42.7%), diarrhoea (36.9%), pruritus (28.1%), rash (25.4%), headache (23.5%), and nausea (23.0%). In the ipilimumab group, the most frequently reported AEs were diarrhoea (54.5%), fatigue (40.8%), pruritus (36.9%), rash (33.1%), headache (31.3%), nausea (28.0%), and pyrexia (21.2%).

Grade 3-4 AEs were reported in 25.4% of subjects in the nivolumab group and 55.2% of subjects in the ipilimumab group. In the nivolumab group, the most frequently reported grade 3-4 AEs were lipase increased (4.9%), diarrhoea (2.4%), and amylase increased (2.4%). In the ipilimumab group, the most frequently reported grade 3-4 AEs were diarrhoea (10.6%), colitis (7.7%), and alanine aminotransferase (ALT) increased (6.2%). A similar AE pattern was seen in subjects with extended follow-up (100 days after last dose).
In the nivolumab group, of those who did not complete treatment (n=177), the most common reason for discontinuation was disease recurrence (n=121) followed by toxicity (n=41); in the ipilimumab group, 331 patients did not complete treatment (due to disease recurrence (n=101) and toxicity (n=208)).

3. Cost effectiveness of nivolumab

The Applicant presented both a partitioned survival analysis (Applicant base case) and a Markov model to consider the cost-effectiveness of nivolumab in the adjuvant setting. The NCPE chose to appraise the Markov model in detail, as it more closely aligns with previously published models in this disease area. Cost effectiveness was modelled over a 60 year time horizon.

Clinical efficacy inputs for the model were derived from the RFS and OS curves from the CheckMate 238 and CA184-029 trials, in addition to various other trials conducted in the metastatic setting and registry data. Patient characteristics were based on the CheckMate

238 and CA184-029 trial populations. For the base case, utilities were sourced from the EQ-5D-3L data from the CheckMate 238 trial, Mapping of the QLQ-C30 to the EQ-5D from the CheckMate 238 and CA 184-029 trials was also undertaken. Adverse event utilities were sourced from literature. The Applicant included relevant costs. The proportion of patients receiving subsequent therapies was derived from CheckMate 238. The Review Group consider that the evidence in relation to subsequent treatments is too immature to adequately inform proportions of treatments to be used following recurrence. Resource use was identified from the CheckMate 238 and CA 184-029 trials, from an academic study conducted to support the reimbursement of ipilimumab in the metastatic setting, and was validated using expert opinion from UK clinicians. While opinion was sought from clinicians specialising in melanoma in Ireland, it was only used in the applicant scenario analysis.

Despite no OS benefit being observed, the Applicant assumed a surrogacy relationship between RFS and OS; the data used to inform this relationship was based on older studies and treatments that are no longer used routinely. The Review Group considered the evidence presented to support this assumption to be insufficient to draw conclusion of OS benefit; this was also the opinion of the European Medicines Agency.

Analyses presented in this summary document are based on the list prices of all interventions included in the model (including subsequent treatments).

The NCPE adjusted a number of aspects of the model and calculated an ICER of €52,988 per QALY (nivolumab costs/QALY €140,160/7.43 vs routine surveillance €84,334/6.37). The Applicant had calculated an ICER of €48,906 per QALY (nivolumab costs/QALY €145,382/7.47 vs routine surveillance €89,878/6.34). There was little difference between probabilistic and deterministic ICERs. The probability of cost effectiveness (NCPE adjusted model) at a threshold of €45,000/QALY was 31%, and at a threshold of €20,000 per QALY was 0%. The Review Group was unable to remove the OS benefit from the model, to establish the cost-effectiveness of nivolumab in terms of RFS only. For this reason the ICERs calculated are likely to be a more positive representation of benefit, given the evidence available. The Review Group undertook a number of scenario analyses on the model to

explore this in other ways. The ICERs ranged from approximately €9,000 per QALY to €330,000 per QALY reflecting the uncertainty associated with survival extrapolations.
The Review Group highlight that this assessment of cost-effectiveness is based on highly uncertain and immature data. The cost-effectiveness estimates will change if the underlying assumptions change. These assumptions include the expected OS benefit and the number of PD-1 or PD-L1 inhibitors that patients can receive. Currently, patients in Ireland can receive a single treatment course with a PD-1 or PD-L1 inhibitor over the course of their disease. If in the future, patients can receive more than one treatment course with a PD-1/PD-L1 inhibitor, cost effectiveness should be re-evaluated.

4. Budget impact of nivolumab

The cost (price of wholesaler exc. VAT) to the HSE of one vial of nivolumab 100mg/10ml is €1,311.26 for the 40mg/4ml vial is €524.56. Treatment duration in the adjuvant setting is limited to one year. The cost for nivolumab for one year (26 cycles), is €96,143.32 inclusive of VAT and mandatory rebate. Fewer cycles were given in the Checkmate trial and the mean number from the trial was used to inform the cost-effectiveness model. The patient population who would receive nivolumab in the adjuvant setting is greater (approximately 50% more patients) than those who would receive it in the metastatic setting. This is partly because some patients receiving adjuvant treatment may never have progressed.
The gross budget impact of adjuvant nivolumab treatment in year 1 is estimated to be €6,591,161, in year 2 €9,946,062, in year 3 €10,065,773, in year 4 €10,065,773 and in year 5 €10,126,167. As the current treatment is routine surveillance and does involve immunotherapy the net budget impact is similar to the gross budget impact. The cumulative 5 year budget impact is €46,734,901.

5. Patient Organisation Submissions

A Patient Organisation Submission was received from Melanoma Support Ireland.

6. Conclusion

The NCPE recommends that nivolumab 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.*