Cost-effectiveness of nivolumab (Opdivo®) plus ipilimumab (Yervoy ®) for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of nivolumab (Opdivo ®) plus ipilimumab (Yervoy ®). Following assessment of the Applicant's submission, the NCPE recommends that nivolumab (Opdivo ®) plus ipilimumab (Yervoy ®) 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.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Bristol Myers Squibb) Health Technology Assessment dossier on nivolumab (Opdivo ®) plus ipilimumab (Yervoy ®). 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 2022**

Summary

In January 2022, Bristol Myers Squibb (BMS) submitted a dossier of clinical, safety and economic evidence on nivolumab (Opdivo ®) plus ipilimumab (Yervoy ®) for the treatment of adults with unresectable malignant pleural mesothelioma (MPM). BMS are seeking reimbursement through the Oncology Drug Reimbursement Scheme.

Nivolumab is a humanised monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity. Thus nivolumab potentiates T-cell immune responses, including anti-tumour responses. Ipilimumab is a humanised monoclonal antibody, and a CTLA-4 inhibitor. CTLA-4 inhibition blocks inhibitory T-cell signals, allowing a T-cell mediated immune response against tumour cells. Nivolumab plus ipilimumab act simultaneously at different points within the T-cell immune response pathway, producing a synergistic effect. For this indication, the recommended dose is 360 mg nivolumab administered intravenously over 30 minutes once every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes once every 6 weeks. Treatment is continued for up to 24 months in patients without disease progression.

1. Comparative effectiveness of nivolumab plus ipilimumab

Clinical evidence, for the regulatory approval of nivolumab plus ipilimumab, is from the CheckMate 743 phase III, open-label, randomised controlled trial. Nivolumab plus ipilimumab (n=303) was compared to standard of care (SoC) chemotherapy (n=302) in treatment naïve patients with unresectable MPM. Baseline characteristics of the population appear to be generalisable to those patients in Ireland who have an ECOG performance status of 0 to 1. Nivolumab plus ipilimumab was administered until progressive disease or unacceptable toxicity, or for up to 24 months. SoC chemotherapy consisted of pemetrexed plus carboplatin or pemetrexed plus cisplatin (herein 'pemetrexed plus carboplatin or cisplatin'). This was administered until progressive disease, unacceptable toxicity, or the completion of six cycles. The comparator arm was considered reflective of SOC in Ireland.

At the pre-specified primary analysis of the intention to treat (ITT) population, treatment with nivolumab plus ipilimumab reduced the risk of all cause death by 26% compared with

pemetrexed plus carboplatin or cisplatin (HR 0.74, 95% CI 0.61 to 0.89, p=0.002) at a minimum follow up of 22.1 months. Median overall survival (OS) was 18.1 months (95% CI 16.8 to 21.4) with nivolumab plus ipilimumab versus 14.1 months (95% CI 12.4 to 16.2) with pemetrexed plus carboplatin or cisplatin. There was no statistically significant increase in progression free survival (PFS). Outcomes were consistent at an updated analysis (minimum follow up of 35.5 months) and across most subgroups.

The Review Group highlight a number of key limitations in the clinical evidence and its generalisability to clinical practice in Ireland.

- The OS results were potentially confounded by the subsequent use of immunotherapies in CheckMate 743 trial. Following treatment discontinuation, patients were eligible to receive subsequent systemic treatment. In total 3% of patients in the nivolumab plus ipilimumab arm and 20% in the pemetrexed plus carboplatin or cisplatin arm received subsequent immunotherapy. The magnitude and direction of any bias in the OS results is unclear.
- A numerically smaller OS benefit was observed in the subgroup with epithelioid histology (HR 0.85, 95% CI 0.68 to 1.06). The CheckMate 743 study was not powered to detect a difference in efficacy in histology subgroups. However, the efficacy results in this subgroup are of interest as epithelioid histology is predominant in patients with MPM in Ireland. It accounts for 60 to 80% of all cases of MPM.

2. Safety of nivolumab plus ipilimumab

The safety profile of nivolumab plus ipilimumab was consistent with the known safety profile of nivolumab plus ipilimumab. The overall frequencies of adverse events (AEs) in CheckMate 743 were similar between the nivolumab plus ipilimumab (100%) and pemetrexed plus carboplatin or cisplatin (98%) arms. Occurrence of immune mediated AEs (IMAEs) in the nivolumab plus ipilimumab arm was as follows (% of subjects with any grade IMAE | % of those subjects with grade 3 to 4 IMAE): rash (13.0% | 61.5%), hypothyroidism/thyroiditis (11.7% | 25.7%), diarrhoea/colitis (8.7% | 92.3%), and pneumonitis (6.7% | 65.0%). The CHMP and Applicant report that the majority of events

were considered manageable, with resolution occurring when corticosteroids were administered.

3. Cost effectiveness of nivolumab plus ipilimumab

Methods

The Applicant presented a cohort partitioned survival model to assess the cost effectiveness of nivolumab plus ipilimumab compared with the current SOC. The model consisted of three mutually exclusive health states: 'progression-free,' 'progressed disease' and 'death.' The model structure was in line with previous submissions, to the NCPE, in this therapeutic area. Treatment effects for the comparison with pemetrexed plus carboplatin or cisplatin were derived from an updated analysis from the CheckMate 743 trial (minimum follow up of 35.5 months). To estimate PFS and OS over the 20-year modelled time horizon, the Applicant fitted parametric survival curves to patient-level data. The generalisability of OS from CheckMate 743 to the target population was uncertain due to the 20% of patients in the SOC arm who switched to immunotherapy following disease progression. This would not be expected to occur in clinical practice. To account for this, the Applicant adjusted the OS data in the SOC arm to attempt to remove the effect of treatment switching. This resulted in a reduction in estimated OS in the SOC arm. No OS adjustment was made in the nivolumab plus ipilimumab arm. The impact of switching in this arm is likely to have been minimal given the small proportion of patients (3%) who received subsequent immunotherapy.

Results

In the Applicant's base case, nivolumab plus ipilimumab was associated with an incremental cost of €82,800 and an incremental QALY of 0.73 versus SoC, resulting in an incremental cost effectiveness ratio (ICER) of €113,278/QALY. The probability of cost effectiveness at both the €20,000/QALY and €45,000/QALY thresholds is 0%.

The NCPE-adjusted base case comprised a number of changes to the Applicant's base case:

- Removal of the Applicant's assumption of a persistent treatment effect on discontinuation of nivolumab plus ipilimumab through the implementation of treatment waning from 5 years.
- Treatment duration informed by time-to event data (adjusted by relative dose intensity) rather than by mean dosage data from the CheckMate 743 trial.

- Implementation of health state utilities across arms, rather than treatment-specific utilities.
- Removal of the cost of subsequent immunotherapies from both arms in line with Irish clinical practice.

In the NCPE-adjusted base case, nivolumab plus ipilimumab was associated with an incremental cost of €79,650 and an incremental QALY of 0.46; ICER of €172,475/QALY. The probability of cost effectiveness at both the €20,000/QALY and €45,000/QALY thresholds is 0%. The Review Group note that estimates of OS in the model may remain biased despite the adjustment for treatment switching; the magnitude and direction of this bias remains unclear.

Table 1 Results of cost-effectiveness analysis under the Applicant and NCPE's adjusted base case assumptions

Treatment	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
Applicant Base Case					
Nivolumab plus ipilimumab	117,588	1.76			
Pemetrexed plus carboplatin or cisplatin	34,788	1.02	82,800	0.73	113,278
NCPE Adjusted Base Case					
Nivolumab plus ipilimumab	112,917	1.51			
Pemetrexed plus carboplatin or cisplatin	33,266	1.05	79,650	0.46	172,475

QALY: quality-adjusted life-year**; ICER:** incremental cost effectiveness ratio.
A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

In both the NCPE-adjusted and Applicant's base case, the probabilistic ICERs were similar to the deterministic ICERs. Sensitivity analysis indicated that the adjustment of OS for treatment switching had a considerable impact on the ICER. When this adjustment was removed from the NCPE-adjusted base case the ICER increased to €207,948/QALY. The ICER was also sensitive to the choice of parametric curves used to model OS, as well as the

assumptions made regarding the duration of treatment effect. When the NCPE-adjusted base case adopted a lifetime duration of treatment effect, the ICER decreased to €164,071/QALY.

No scenario analyses investigating cost effectiveness in the subgroups with epithelioid and non-epithelioid histology were presented. The Review Group considers it likely that cost effectiveness would differ considerably between these two subgroups given differences in OS observed in CheckMate 743.

4. Budget impact of nivolumab plus ipilimumab

The price to wholesaler (exc. VAT) for one vial of nivolumab 240mg/24ml is €2,987.97, for one vial of 100mg/10ml is €1,227.90, and for one vial of 40mg/4ml is €491.39. The price to wholesaler (exc. VAT) of one vial of ipilimumab 200mg/40ml is €14,833.33 and for one vial of 50mg/10ml is €3,723.93.

The estimated total drug acquisition cost of nivolumab plus ipilimumab per patient per treatment course is €102,920 (including VAT) and €82,380 (excluding VAT). The duration of therapy of nivolumab plus ipilimumab was informed by the CheckMate 743 trial. The Applicant estimates that 11 patients in Ireland will be eligible for treatment for MPM annually. The Review Group estimates that the 5-year gross and net budget impacts associated with the reimbursement of nivolumab plus ipilimumab for MPM are €5,660,618 and €5,258,557 respectively.

5. Patient Submission

No patient organisation submissions were received during the course of this evaluation.

6. Conclusion

The NCPE recommends that nivolumab plus ipilimumab 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.