Cost effectiveness of nivolumab (Opdivo®)
for the adjuvant treatment of adult patients with oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy

The National Centre for Pharmacoeconomics (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. 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 appraisal of the Applicant's (Bristol-Myers Squib) Health Technology Assessment 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 drugs for cancer, 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 **February 2023**

Summary

In May 2022, Bristol-Myers Squib submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of nivolumab (Opdivo®) for the adjuvant treatment of adult patients with oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy. Reimbursement is sought under the Oncology Drugs Management System.

Nivolumab is a humanised monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with programmed death-ligand 1 (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. Nivolumab is administered by intravenous infusion at a dose of 240 mg once every two weeks or 480 mg once every four weeks, for 16 weeks, then at a dose of 480 mg once every four weeks, beginning at week 17. Treatment should be continued until disease recurrence or until no longer tolerated by the patient, for a maximum total duration of one year.

The Applicant anticipates that nivolumab will be used in line with its licensed indication (as stated above). No other active treatments are currently licensed for use in the adjuvant setting; patients undergo 'routine surveillance' as current standard of care. If reimbursed, nivolumab would be used in the adjuvant setting in addition to current standard of care.

1. Comparative effectiveness of nivolumab

CheckMate 577 is a phase III, double-blind, randomised, placebo-controlled trial designed to evaluate the safety and efficacy of nivolumab versus placebo. Participants were adult patients with stage II or III cancer of the oesophagus or gastro-oesophageal junction, who had residual pathologic disease following neoadjuvant chemoradiotherapy. A total of 794 participants were randomised on a 2:1 basis to receive either nivolumab (n=532) or placebo (n=262). Treatment was continued for a maximum of one year or until recurrent disease, unacceptable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed disease-free survival (DFS), with overall survival (OS) measured as a key secondary endpoint. In line with the statistical analysis plan, OS is tested using a hierarchical testing

procedure, with testing conditional upon demonstration of superiority in DFS at either the interim or final analyses for all randomized subjects. At the time of completing this appraisal, OS data have not been released.

Results from two data cut-offs were available: July 2020 and February 2021. At the most recently available data cut-off (February 2021), median DFS was 22.4 months with nivolumab versus 10.4 months with placebo (HR 0.67; 95% confidence interval 0.55, 0.81). The Review Group's main concern regarding the clinical evidence is the absence of OS data.

2. Safety of nivolumab

Overall, the safety data from CheckMate 577 were consistent with the known safety profile of nivolumab. No new risks were identified. Nonetheless, as outlined in the EPAR, this study has been performed in a new clinical scenario where no other treatments have been licensed yet. Adverse effects of nivolumab, although known and relatively manageable, are not minor and long-term follow-up is considered necessary.

3. Cost effectiveness of nivolumab

The cost-effectiveness evaluation was informed by direct evidence from CheckMate 577; placebo was considered a proxy for 'routine surveillance' (current standard of care). A de novo semi-Markov model was developed, containing three health states: 'Disease free', 'Recurred disease', and an absorbing 'Death' state. Health state occupancy during each cycle in the 'Disease free' state was estimated based on extrapolated patient-level data from CheckMate 577 (February 2021 data cut-off) and from background mortality derived from Irish life tables. Health state occupancy in the 'Recurred disease' state was estimated based on data sourced from the academic literature. OS is modelled indirectly, with the effect of nivolumab on survival captured via the increased length of time spent in the 'Disease free' health state. The Review Group considered the Applicant's approach to extrapolating DFS to be reasonable, but noted that the ICER was sensitive to variation in modelling approach used. The Review Group did not consider the data source used to inform post-recurrence survival to be the most appropriate modelling choice. Data from an alternative source has been used in the NCPE-adjusted base case.

Health state utility values estimated for the 'Disease free' health state, using CheckMate 577 data, were higher than the general population values. The Applicant instead assumed the use of general population utility values (from an age- and sex-matched cohort) for this health state. The Review Group considered this assumption to be subject to considerable uncertainty. Scenario analysis demonstrated that the incremental cost-effectiveness ratio (ICER) increased when lower values were applied in this health state. No definitive alternative values could be identified. Values for the 'Recurred disease' health state were sourced from the literature. The following costs were included: drug acquisition costs, drug administration costs, costs of subsequent therapies, health care resource use costs, adverse event-related costs and end-of-life care costs. The Review Group considered the costs applied in the 'Recurred disease' health state to be unrealistically high. The Applicant provided details of a scenario where alternative values were used; these values are applied in the NCPE-adjusted base case.

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2.

Table 1 Results of the Applicant's base case cost-effectiveness analysis

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab	125,448	5.46			
Routine surveillance	89,467	4.24	35,980	1.22	29,521

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

Table 2 Results of the NCPE-adjusted base case cost-effectiveness analysis

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab	80,080	4.77			
Routine surveillance	31,193	3.36	48,888	1.41	34,569

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

In both the Applicant's and the NCPE-adjusted base case analyses, the mean probabilistic sensitivity analysis outputs were generally consistent with the deterministic analyses. Under the NCPE-adjusted base case, the probabilities of cost effectiveness of nivolumab versus routine surveillance at the €20,000/QALY and €45,000/QALY thresholds were 0.0% and

93.7%, respectively. The price reduction required to achieve cost-effectiveness at the €20,000/QALY was approximately 47% (inclusive of 7.75% rebate).

The Review Group highlighted that, under the NCPE-adjusted base case, the cost-effectiveness model predicts an incremental life year gain of approximately 1.8 years. OS data from CheckMate 577 have not been released, and thus the benefit of nivolumab versus routine surveillance, in terms of OS, has not been demonstrated. OS is modelled indirectly, with the effect of nivolumab on survival captured via the increased length of time spent in the 'Disease free' health state. It was not feasible to implement a scenario where nivolumab is not associated with a survival benefit. The Review Group emphasized that this prediction is subject to considerable uncertainty, and there is no comparative data demonstrating an OS benefit for nivolumab over routine surveillance for this indication.

4. Budget impact of nivolumab

The price-to-wholesaler of a 240 mg vial of nivolumab is €2,987.97. VAT is applicable. Treatment was assumed to be continued for one year, and drug costs were not adjusted for dose intensity, discontinuations or mortality. The Review Group acknowledged this was a conservative assumption, and in clinical practice treatment costs may be lower. The estimated total treatment cost per patient is €89,842 (€71,913 excluding VAT).

The eligible population was defined as patients with oesophageal and gastro-oesophageal junction cancer, with stage II or III disease, who had residual pathologic disease following neoadjuvant chemoradiotherapy. The Applicant assumed 30% of patients with stage II or III disease would receive neoadjuvant chemoradiotherapy and undergo surgery, resulting in estimated patient numbers ranging from 65 in Year 1 to 67 in Year 5. It was noted that clinical opinion, obtained by the Applicant, indicated that an assumption of 50% may be more reflective of clinical practice in Ireland. This assumption has been adopted as the NCPE-adjusted base case, and resulted in estimated patient numbers ranging from 108 in Year 1 to 112 in Year 5. Based on the Applicant's assumptions, the five-year cumulative gross drug budget impact was estimated to be €20.83 million (€16.67 million excluding VAT). Under the NCPE-adjusted base case, the five-year cumulative gross drug budget impact was estimated to be €34.71 million (€27.78 million excluding VAT). Reimbursement

of nivolumab for this indication is not expected to result in displacement of other drugs. Therefore, the net drug budget impact is the same as the gross drug budget impact.

5. Patient submissions

No Patient Organisation Submissions were received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant's submission, 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.