NCPE Technical Summary

Nivolumab (Opdivo®)

HTA ID 21049

11 July 2023

Applicant: Bristol-Myers Squibb

Nivolumab is indicated in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥5.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of nivolumab (Opdivo®) for this indication. Following assessment of the Applicant's submission, the NCPE recommends that nivolumab (Opdivo®) in combination with chemotherapy not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. *

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Bristol-Myers Squibb [BMS]) Health Technology Assessment of nivolumab. 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 (HRQoL) 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.

Summary

In October 2022, BMS submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of nivolumab in combination with chemotherapy for the first line treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥5. 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 PDL2. 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 licensed for use in combination with fluoropyrimidine and platinum-based chemotherapy. It is administered by intravenous infusion at a dose of 360 mg once every three weeks in combination with XELOX (capecitabine in combination with oxaliplatin), or 240 mg once every two weeks in combination with FOLFOX (5-fluorouracil [5-FU] in combination with folinic acid and oxaliplatin). Treatment should be continued until disease progression or unacceptable toxicity, for a maximum total duration of 24 months.

The Applicant anticipates that nivolumab will be used in line with its licensed indication (as stated above). The current standard of care for the treatment of this patient population in Ireland is chemotherapy, typically either XELOX or FOLOX. If reimbursed, nivolumab will be used in addition to either XELOX or FOLFOX. Clinical opinion, in Ireland, obtained by the Applicant indicated that the choice of chemotherapy would not be impacted by the addition of nivolumab (i.e., if reimbursed, a patient expected to receive XELOX would be considered for nivolumab in combination with XELOX; a patient expected to receive FOLFOX would be considered for nivolumab in combination with FOLFOX). XELOX and FOLOX are both considered to be relevant comparators here.

Of note, pembrolizumab recently underwent evaluation, by the NCPE, for use in combination with chemotherapy as a first-line treatment for locally advanced unresectable or metastatic carcinoma of the oesophagus, or HER2-negative GEJ cancer, in adults whose tumours express PD-L1 with a CPS ≥10. The Review Group noted that while the licensed population are not directly aligned, there is considerable overlap in terms of patient eligibility for the treatments. Despite the Review Group's request, the Applicant declined to perform a comparison versus pembrolizumab plus chemotherapy. While the Review Group acknowledged that such a comparison would be subject to uncertainty, a comparison (acknowledging the inherent limitations) would still have been informative for decision-making.

Comparative effectiveness of nivolumab in combination with chemotherapy

CheckMate 649 is an ongoing, phase III, open-label, active comparator-controlled trial designed to evaluate the safety and efficacy of nivolumab in combination with chemotherapy (herein, nivolumab plus chemotherapy) versus chemotherapy. The trial enrolled adult patients with previously untreated, unresectable, non-HER2-positive gastric, GEJ, or oesophageal adenocarcinoma, regardless

of PD-L1 expression. The trial randomised patients on a 1:1:1 basis to one of three treatment arms: nivolumab plus chemotherapy, nivolumab plus ipilimumab or chemotherapy alone. The nivolumab plus ipilimumab arm is not of relevance to this submission; comparative evidence derived from the nivolumab plus chemotherapy and chemotherapy arms is the focus of this assessment. Treatment was continued until unacceptable toxicity or loss of clinical benefit, for a maximum duration of 24 months. Patients randomised to nivolumab plus chemotherapy could continue treatment beyond disease progression, if there was evidence of clinical benefit as determined by the clinical investigator. The co-primary endpoints were overall survival (OS) and progression free survival (PFS), assessed by a blinded independent central review, in patients whose tumours expressed PD-L1 with a CPS ≥5.

Of the intent-to-treat population (N=1,581), 955 patients had tumours which expressed PD-L1 with a CPS ≥5 and thus correspond to the licensed population (nivolumab plus chemotherapy: n=473; chemotherapy: n=482). Results from two data cut-offs were available: July 2020 (12-month minimum follow-up) and July 2021 (24-month minimum follow-up). At the July 2021 data cut-off, median PFS in the CPS ≥5 subpopulation was 8.1 months with nivolumab plus chemotherapy versus 6.1 months with chemotherapy (HR 0.70; 95% confidence interval [CI] 0.60, 0.81). At the same data cut-off, median OS was 14.4 months with nivolumab plus chemotherapy versus 11.1 months with chemotherapy (HR 0.70; 95% CI 0.61, 0.81). Efficacy data from a later data cut-off (July 2022; 36-month minimum follow-up) were published during the course of the evaluation. The hazard ratios for OS, PFS were numerically comparable at the July 2021 and July 2022 data cut-offs.

The Review Group's main concerns regarding CheckMate 649 related to protocol-mandated treatment beyond progression in those randomised to nivolumab plus chemotherapy (23% received treatment beyond progression) but not chemotherapy (0% received treatment beyond progression). This is not aligned with the product licence, which specifies treatment should be continued until disease progression. Generalisability of the clinical efficacy data to clinical practice in Ireland is uncertain.

Safety of nivolumab in combination with chemotherapy

The adverse events observed in CheckMate 649 were reflective of the known safety profile of nivolumab plus chemotherapy; no new safety issues were identified. However, as highlighted by the European Medicines Agency, the severity of toxicity is considerable and should be weighed against the observed benefit in patients with advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma. It was highlighted that patients who had baseline Eastern Co-operative Oncology Group performance status ≥2; untreated central nervous system metastases; active, known, or suspected autoimmune disease; or, medical conditions requiring systemic immunosuppression were

excluded from the CheckMate 649 trial, and that nivolumab plus chemotherapy should be used with caution in these populations.

Cost effectiveness of nivolumab in combination with chemotherapy

Methods

A *de novo* cohort-level state transition model was used to investigate the cost effectiveness of nivolumab plus chemotherapy. The model comprised three health states: 'Progression free', 'Progressed disease', and the absorbing state 'death'. The health states are aligned with the co-primary endpoints (PFS and OS) in the CheckMate 649 trial. Efficacy data from the July 2021 data cut-off (24-month minimum follow-up) informed the model; data from a later July 2022 data cut-off (36-month minimum follow-up) were published during the evaluation but have not been used in the model.

The Applicant performed pairwise comparisons for nivolumab plus FOLFOX versus FOLFOX, and nivolumab plus XELOX versus XELOX, as it anticipated that the choice of chemotherapy in Ireland would not be impacted by the addition of nivolumab. For many model inputs (including treatment effectiveness and utilities), the Applicant assumed equivalence between FOLFOX and XELOX; differences in relative cost-effectiveness profiles between comparisons were driven by cost.

The Review Group identified a number of limitations in the Applicant's cost-effectiveness model, which were addressed through changes in the NCPE-adjusted base case. Long-term OS extrapolations are uncertain and are key drivers in the cost-effectiveness model. Using a piecewise modelling approach, the Applicant selected a Gompertz distribution. The NCPE-adjusted base case models OS using a piecewise model with a log-logistic tail, which represents the most conservative of the equally plausible modelling options. The Review Group highlighted that the use of the more recent data cut-off from CheckMate 649 (outlined above) may have reduced uncertainty associated with OS extrapolations, but the Applicant did not update the model to incorporate these data. Further changes to the NCPE-adjusted base case included: the application of a treatment waning effect; an increase in the modelled population starting age to better reflect the target population in Ireland; and the removal of the strict two-year stopping rule for nivolumab, to reflect treatment continuation beyond 24 months as was observed in CheckMate 649.

There were a number of uncertainties associated with the Applicant's modelling approach which the Review Group were unable to address in the NCPE-adjusted base case. All survival models were

estimated under a relative survival framework that adjusts trial hazards based on individual patient demographics. The Review Group consider that there was no clear empirical justification for this approach here. It was not possible for the Review Group to ascertain the impact of this modelling decision on the cost-effectiveness results.

Results

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: Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab[b] plus XELOX	81,620	2.03	-	-	-
XELOX	20,849	1.05	60,771	0.98	61,855
Nivolumab[b] plus FOLFOX	86,707	2.03	-	-	-
FOLFOX	26,110	1.05	60,597	0.98	61,679

ICER: incremental cost-effectiveness ratio; **QALY**: quality adjusted life years
[a] Corresponding probabilistic ICER using 1,000 iterations = €65,122/QALY (XELOX). Corresponding probabilistic ICER using 1,000 iterations = €63,963/QALY (FOLFOX). Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes. [b] A CIC PAS has been proposed for nivolumab, not included here.

Table 2: NCPE-adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab[b] plus XELOX	82,643	1.72	-	-	-
XELOX	21,169	1.11	61,475	0.61	101,665
Nivolumab[b] plus FOLFOX	87,887	1.72	-	-	-
FOLFOX	26,426	1.11	61,461	0.61	101,642

ICER: incremental cost-effectiveness ratio; **QALY**: quality adjusted life years
[a] Corresponding probabilistic ICER using 1,000 iterations = €101,585/QALY (XELOX). Corresponding probabilistic ICER using 1,000 iterations = €101,040/QALY (FOLFOX). Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes. [b] A CIC PAS has been proposed for nivolumab, not included here.

Under the Applicant's base case, the probability of nivolumab plus chemotherapy being cost effective at a willingness-to-pay threshold of €20,000 per QALY is 0.0% (XELOX) and 0.0% (FOLFOX), and at a €45,000 per QALY threshold is 9.7% (XELOX) and 10.4% (FOLFOX). Under the NCPE-adjusted base case, the probabilities of cost effectiveness are 0.0% (XELOX and FOLFOX) at both the €20,000 and €45,000 per QALY thresholds. An analysis of the price-ICER relationship was conducted using the NCPE-adjusted base case. The price reductions (inclusive of 8.25% Framework Agreement rebate) required to achieve cost effectiveness at the €45,000 per QALY thresholds were approximately 64.0% (XELOX) and 66.5% (FOLFOX), and for the €20,000 per QALY thresholds were approximately 88.5% (XELOX) and 92.0% (FOLFOX).

Budget impact of nivolumab in combination with chemotherapy

The price to wholesaler for nivolumab is €1,463.45 per 120 mg vial, and €2,971.96 per 240 mg vial. VAT (23%) is applicable on this. Treatment costs were calculated based on the licensed dosing schedules, and duration of treatment was estimated from CheckMate 649 data. The estimated total treatment cost per patient for nivolumab plus XELOX is €60,016 (€48,248 excluding VAT) and for nivolumab plus FOLFOX is €65,102 (€52,142 excluding VAT).

The eligible population was defined as patients with locally advanced or metastatic gastric cancer, GEJ or oesophageal adenocarcinoma who are eligible for treatment with first-line chemotherapy and have a HER2-negative status and tumours express PD-L1 with a CPS ≥5. This resulted in an estimated total population of 119 patients per year eligible for treatment under the product licence. Based on market share projections for this eligible population, the Applicant estimated the number of patients treated with nivolumab plus chemotherapy would increase from 42 patients in Year 1 to 89 patients in Year 5.

The Applicant elected to present the drug budget impact results for nivolumab plus XELOX and nivolumab plus FOLFOX separately (i.e. 100% of patients receive either nivolumab plus XELOX or nivolumab plus FOLFOX). Given clinical opinion obtained by the Applicant indicated FOLFOX and XELOX are used at a ratio of 80:20, respectively, a weighted average would fall between the estimates provided (and be slightly lower than the results presented for nivolumab plus FOLFOX). The five-year cumulative gross drug budget impact for nivolumab plus XELOX was estimated at €19.6 million (€15.8 million excluding VAT), or for nivolumab plus FOLFOX was €21.3 million (€17.0 million excluding VAT). The corresponding five-year cumulative net drug budget impacts were €18.0 million (€14.5 million excluding VAT) or €19.7 million (€15.8 million excluding VAT), respectively.

Patient submission

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

Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that nivolumab (Opdivo®) in combination with chemotherapy not be considered for reimbursement unless 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.