Cost effectiveness of nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination therapy

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

The HSE asked the NCPE to carry out an appraisal of the Applicant's (Bristol Myers Squibb Ireland) Health Technology Assessment of nivolumab (Opdivo®) in combination with 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 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 **December 2022**

Summary

In January 2022, Bristol Myers Squibb Ireland submitted a dossier, which investigated the clinical effectiveness, cost effectiveness, and potential budget impact of nivolumab in combination with ipilimumab (NIVO+IPI) for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination therapy. 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 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. When used in combination, NIVO+IPI act simultaneously at different points within the T-cell immune response pathway, producing a synergistic effect. For this indication, the recommended dose is 3mg/kg nivolumab in combination with 1mg/kg ipilimumab, both administered intravenously once every three weeks for four doses. This is then followed by a monotherapy phase, in which nivolumab monotherapy is administered intravenously at a dose of 240mg once every two weeks. Treatment should be continued for as long as clinical benefit is observed or until no longer tolerated. No maximum duration of treatment with nivolumab is specified.

The Applicant anticipates that NIVO+IPI will be used in the second- and third-line setting for the treatment of adult patients with MSI-H or dMMR (MSI-H/dMMR) metastatic colorectal cancer after prior fluoropyrimidine-based combination therapy. This is in line with the licensed indication. Current treatments for the second-line treatment of metastatic colorectal cancer in Ireland include FOLFOX (folinic acid, fluorouracil, oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, irinotecan) in combination with bevacizumab (herein 'FOLFOX+Bevacizumab' or 'FOLFIRI+Bevacizumab'). Trifluridine-tipiracil or best supportive care (BSC) are used in the third-line metastatic setting. These are the comparators considered in this assessment. Based on clinical opinion, FOLFIRI+Bevacizumab is considered to be the comparator of most relevance to the decision maker.

1. Comparative Effectiveness of Nivolumab plus Ipilimumab

CheckMate-142 Trial

The CheckMate-142 trial is an on-going, phase II, open-label, multi-cohort trial in patients with recurrent or metastatic colorectal cancer. For regulatory purposes, the Committee for Medicinal Products for Human Use (CHMP) only considered data from the relevant patient cohort i.e. those patients who received NIVO+IPI for previously treated MSI-H/dMMR metastatic disease. Data from the other cohorts are not presented here. The clinical evidence, that supports this submission, is thus derived from single-arm data.

Eligible patients must have received prior treatment, for metastatic disease, with a fluoropyrimidine, and oxaliplatin or irinotecan, or have actively refused standard-of-care chemotherapy for the treatment of metastatic or locally advanced disease. Patients who received oxaliplatin in an adjuvant setting should have progressed during or within six months of completion of adjuvant therapy in order for oxaliplatin to count as a prior therapy needed for entry. Patients who received prior treatment with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody were excluded. Ipilimumab was administered for a maximum of four doses, while nivolumab was administered until disease progression, discontinuation due to toxicity, death, withdrawal of consent, or study end. A stopping rule was not applied. However, patients could discontinue after a minimum of 24 months of treatment if they achieved maximum clinical benefit, as assessed by the investigator. The primary endpoint of the trial was investigator-assessed objective response rate. Overall survival (OS) and progression-free survival (PFS) were exploratory endpoints.

Trial results were presented for the October 2020 interim analysis; median duration of follow up was 51.5 months. A total of 119 patients were treated with NIVO+IPI and were included in the treated population analysis. Investigator-assessed objective response rate was 64.7% (95% CI 55.4 to 73.2). Median OS and median investigator-assessed PFS were not reached. Median blinded independent central review-assessed PFS was 56.3 months (95% CI 30.3 to not estimable). Of note, nine of the 119 treated patients progressed during or within six months of completion of adjuvant therapy; one patient did not receive any prior line and refused chemotherapy in order to enter the study, per inclusion criteria. Thus, ten patients did not receive prior treatment in the metastatic setting. All patients, treated in the Irish

setting, are expected to receive prior treatment in the metastatic setting. Patients in CheckMate-142 are expected to be more heavily pre-treated than those in Irish clinical practice, which results in uncertainty in the generalisability of outcomes to Irish clinical practice. The open-label nature of this single-arm data and the immaturity of the survival data limit interpretation of the results and the conclusions that can be drawn.

Indirect Comparative Evidence

No direct comparative evidence was available for NIVO+IPI versus the comparators of interest for this indication. Estimates for the relative efficacy of NIVO+IPI versus the defined comparators were derived by means of an unanchored matching-adjusted indirect comparison (MAIC). The outcomes defined in the MAIC were mean OS and mean PFS. Efficacy of FOLFIRI+Bevacizumab was informed by ML18137 (an open-label randomised trial in the second-line metastatic colorectal cancer setting). Efficacy of FOLFOX+Bevacizumab was informed by E3200 trial (an open-label, randomised trial in the previously treated metastatic setting). Trifluridine-tipiracil and BSC efficacy data were derived from RECOURSE (a double-blind, randomised trial in patients who had received two or more regimens for metastatic disease). Results of the unanchored MAICs indicated that NIVO+IPI is associated with a considerable survival benefit versus each comparator. However, the Review Group had concerns regarding the bias associated with the unanchored nature of the MAIC. Heterogeneity was noted between the patient populations of the trials; a number of key prognostic factors and effect modifiers could not be adjusted for. Notably, CheckMate-142 was the only trial to specify MSI-H/dMMR disease as a requirement for treatment. The impact of this heterogeneity on the magnitude and direction of effect estimates is unknown. The Review Group did not consider the evidence to be robust; results are highly uncertain and should be interpreted with caution.

2. Safety of Nivolumab plus Ipilimumab

In CheckMate-142 (October 2020 data cut), any grade, all-causality adverse events (AEs) were reported in 99.2 % of patients. The most common AEs were diarrhoea (58.0%), pyrexia (44.5%), cough, pruritus (each 35.3%), and fatigue (34.5%). All-causality grade 3-4 AEs occurred in 62.2% of patients. The most common grade 3-4 AEs were increased lipase,

aspartate transferase, and alanine aminotransferase. Drug-related any-grade serious AEs reported in at least 1% of patients (February 2019 data cut) were colitis and pyrexia (each 2.5%), abdominal pain, increased transaminase, acute kidney injury, anaemia, and hypophysitis (each 1.7%).

Overall, the safety profile of NIVO+IPI for the treatment of patients with MSI-H/dMMR metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy was consistent with the established safety profile of NIVO+IPI, and no new safety concerns were identified.

3. Cost Effectiveness of Nivolumab plus Ipilimumab

Methods

A de novo cohort-level partitioned survival model was submitted. This model included three mutually exclusive health states: pre-progression, post-progression, and death. The pre-progression and post-progression health states were divided into sub-health states of on- and off-treatment. A time horizon of 50 years and a cycle length of one week were used. OS, PFS, and time-on-treatment data for NIVO+IPI were extrapolated to the time horizon of the model, using a semi-parametric approach (from Kaplan-Meier 6.44 month cut-off). To model OS and PFS of the comparator treatments, the Applicant fitted an exponential model such that the area under the curve equated to the mean survival estimated from the MAIC. Utility data were derived from EQ-5D-3L data collected during the CORRECT study (which investigated regorafenib in patients with previously treated metastatic colorectal cancer). The costs included in the model were drug acquisition, administration, disease management, AEs, subsequent treatment, and terminal care. Of note, the cost of MSI-H/dMMR testing was not included in the model as this is routinely conducted for patients in Irish clinical practice. The Review Group corrected a calculation error in the Applicant's base case. Thus, the Applicant base case is herein referred to as the Applicant corrected base case.

Results

Analyses presented in this document are based on the list prices of interventions. Results of the Applicant's corrected base case analyses are presented in Table 1. In this analysis,

patients in the NIVO+IPI arm experienced prolonged post-progression survival; post-progression survival was longer than PFS. The Review Group considered this prolonged post-progression survival to lack clinical and biological rationale and thus, had major concerns regarding the validity of the Applicant's corrected base case estimates.

Table 1 Applicant corrected base case pairwise analyses*

Treatment Strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
NIVO+IPI§	210,438	6.8			
FOLFIRI+Bevacizumab†	46,551	0.8	163,887	6.0	27,357
FOLFOX+Bevacizumab	50,060	1.3	160,378	5.4	29,574
Trifluridine-Tipiracil	36,991	0.6	173,447	6.1	28,210
BSC	26,466	0.4	183,971	6.3	29,088

BSC: Best supportive care; **FOLFIRI:** Folinic acid, 5-fluorouracil plus irinotecan; **FOLFOX:** Folinic acid, 5-fluorouracil plus oxaliplatin; **ICER:** Incremental cost-effectiveness ratio; **NIVO+IPI:** Nivolumab in combination with ipilimumab; **QALY:** Quality-adjusted life years.
*Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.
†Main comparator of relevance to the decision maker.
§Based on the list price of nivolumab and ipilimumab.

To investigate the impact of the prolonged post-progression survival of NIVO+IPI, the Review Group conducted an exploratory analysis. Here, the relative survival input for NIVO+IPI was adjusted (from 6.44 months) using the difference in PFS and OS all-cause survival curves of the comparator regimen. This exploratory analysis resulted in lower post-progression survival for NIVO+IPI than comparator therapies. The Review Group acknowledged that this is a conservative assumption. However, based on the available data, the most plausible assumption is difficult to determine. Other changes implemented in this exploratory analysis included alternative assumptions regarding disease management, subsequent treatment and terminal care costs. The results of the NCPE exploratory analysis are presented in Table 2.

Table 2 NCPE exploratory pairwise analyses*

Treatment Strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
NIVO+IPI§	228,657	4.4			
FOLFIRI+Bevacizumab†	36,201	0.8	192,456	3.6	53,096
NIVO+IPI§	230,608	4.6			
FOLFOX+Bevacizumab	44,015	1.3	186,593	3.3	57,348
NIVO+IPI§	228,318	4.4			
Trifluridine-Tipiracil	26,975	0.6	201,342	3.8	53,685
NIVO+IPI§	227,833	4.3			
BSC	12,669	0.4	215,165	3.9	55,478

BSC: Best supportive care; **FOLFIRI:** Folinic acid, 5-fluorouracil plus irinotecan; **FOLFOX:** Folinic acid, 5-fluorouracil plus

oxaliplatin; **ICER:** Incremental cost-effectiveness ratio; **NIVO+IPI:** Nivolumab in combination with ipilimumab; **QALY:** Quality-adjusted life year.
*Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.
†Main comparator of relevance to the decision maker.
§Based on the list price of nivolumab and ipilimumab.

The Review Group highlight that the Applicant corrected base case and NCPE exploratory ICERs are highly uncertain. Key concerns, in both analyses, include the likely highly biased survival estimates derived from the MAIC. Model inputs and outputs could not be fully interrogated by the Review Group due to model design, which further increases the uncertainty.

Sensitivity Analysis

In the NCPE exploratory analysis, the mean probabilistic ICERs were closely aligned with the deterministic ICERs. NIVO+IPI had a 14.4% probability of cost effectiveness, versus FOLFIRI+Bevacizumab, at the €45,000 per QALY threshold. There was a 0% probability of cost effectiveness at the €20,000 per QALY threshold. In the Applicant corrected base case, NIVO+IPI had a 98.5% and 0.8% probability of cost effectiveness (versus FOLFIRI+Bevacizumab), at the €45,000 per QALY and €20,000 per QALY thresholds, respectively.

In one-way sensitivity analysis, the main driver of cost effectiveness, for all comparisons, was the time horizon. This was followed by the discount rate on outcomes.

4. Budget Impact of Nivolumab plus Ipilimumab

The price-to-wholesaler of a 240mg vial of nivolumab is €2,987.97. The price-to-wholesaler of a 200mg vial of ipilimumab is €14,833.33; a 50mg vial is €3,723.93. Based on a mean of 51 doses of nivolumab and 3.7 doses of ipilimumab (derived from CheckMate-142), the total cost per-patient, per-treatment course of NIVO+IPI is €207,384.94 (€165,997.93 excluding VAT).

The Applicant used estimates from several sources to inform the eligible population estimates. These included the National Cancer Registry Ireland, clinical opinion, and the literature. Based on these data, the Applicant assumed that 31 patients will be eligible for

treatment in year one, increasing to 33 patients by year five. Population estimates were rounded up to the nearest whole number by the Review Group. Assuming a market share of between 55% (year one) and 70% (year two onwards), the total population treated with NIVO+IPI over five years was estimated to be 111 patients. Employing alternative assumptions, the Review Group estimated the total population treated with NIVO+IPI over five years to be 173 patients. The Review Group considered the population estimates to be subject to considerable uncertainty.

Based on the NCPE assumptions, the cumulative five-year gross drug budget impact was estimated to be €33.5 million (€26.8 million excluding VAT). The cumulative five-year net drug budget impact was estimated to be €30.8 million (€24.6 million excluding VAT).
Based on the Applicant assumptions, the cumulative five-year gross drug budget impact was estimated to be €21.4 million (€17.1 million excluding VAT). The cumulative five-year net drug budget impact was estimated to be €19.7 million (€15.7 million excluding VAT).

5. Patient Organisation Submissions

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

6. Conclusion

The NCPE recommends that NIVO+IPI not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*. This recommendation is based on the assumption that patients have not received treatment with prior pembrolizumab (or any anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody therapy). The Review Group reiterate that there is considerable uncertainty associated with the outcomes presented in this appraisal. The MAICs and survival modelling employed in the cost-effectiveness model are subject to notable limitations. The true magnitude of benefit of NIVO+IPI, versus the comparators of relevance, is unknown.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.