NCPE Assessment

Technical Summary

Nivolumab (Opdivo®)

HTA ID:22046

February 2024

Applicant: Bristol-Meyers Squibb

Nivolumab as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥1%, who are at high risk of recurrence after undergoing radical resection of MIUC.

NCPE
National Centre for Pharmacoeconomics, Ireland

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®) for this indication 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-Meyers Squibb) 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 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 January 2023, Bristol-Meyers Squibb submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of nivolumab (Opdivo®) as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥1%, who are at high risk of recurrence after undergoing radical resection of MIUC. 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 as an intravenous (IV) infusion at a dose of 240mg once every two weeks or 480mg once every four weeks. The current appraisal (cost-effectiveness analysis and budget impact analysis) and associated clinical trial (CheckMate 274) are based on the 240mg dose. Treatment should be continued as long as clinical benefit is observed or until no longer tolerated by the patient, for a maximum total duration of one year.

The Applicant anticipates that nivolumab will be used according to its licensed indication (as stated above). In line with the current standard of care in Ireland, the proposed primary comparator is best supportive care (BSC) in the form of routine surveillance. The Review Group notes that the European Society for Medical Oncology do not currently recommend adjuvant immune checkpoint inhibitors (ICIs) i.e. nivolumab, in MIUC, stating that evidence of an overall survival (OS) advantage is needed before ICIs can be recommended as standard therapy. In addition, the Society for Immunotherapy of Cancer state that the full results of CheckMate 274 are awaited to guide the potential use of ICIs in the adjuvant setting.

1. Comparative effectiveness of nivolumab (Opdivo®)

The clinical evidence, supporting regulatory approval of nivolumab, comes from the ongoing CheckMate 274 trial. CheckMate 274 is a phase III, double-blind, randomised controlled trial (RCT) designed to evaluate the safety and efficacy of nivolumab versus placebo. Participants

were adults post radical surgical resection for MIUC, considered at high-risk of recurrence based on pathological staging of radical surgery tissue. A total of 709 participants were randomised in a 1:1 ratio. Treatment was continued for a maximum of one year or until recurrent disease, unacceptable toxicity or discontinuation from the study.

The primary analysis was evaluated in two populations: the intention-to-treat (ITT) population (n=709) and the population with a tumour PD-L1 ≥1% (PD-L1 ≥1% population) (n=282). The efficacy of nivolumab in the ITT population is driven by the efficacy in the PD-L1 ≥1% population and as such, the marketing authorisation and consequently this appraisal are restricted to the PD-L1 ≥1% population . The primary endpoint was investigator-assessed disease-free survival (DFS), with OS measured as a key secondary endpoint. The immature OS results have not been released. Final results are anticipated in April 2026.

Results from several data-cuts are available: August 2020 (minimum follow-up 6.3 months), February 2021 (minimum follow-up 11 months) and October 2022 (minimum follow-up 31.6 months). At the most recent data-cut (October 2022), median DFS was 52.6 months with nivolumab versus 8.4 months with placebo (hazard ratio of 0.52; 95% confidence interval 0.37 to 0.72), for the PD-L1 ≥1% population. This data-cut was used to inform the cost-effectiveness analysis. The Review Group's main concern regarding the clinical evidence is the absence of available OS data.

2. Safety of nivolumab (Opdivo®)

Overall, the safety data from CheckMate 274 were consistent with the known safety profile of nivolumab with no new safety concerns observed. Safety data are reported for the ITT population, with a comparable safety profile observed for the PD-L1 ≥1% population. Treatment-related adverse events (TRAEs) that occurred in greater than 5% of the CheckMate 274 ITT population and immune-related adverse events (IMAEs) were considered in the cost-effectiveness analysis, with grade three or above events modelled.

Any grade TRAEs were reported in 77.5% of individuals receiving nivolumab and 55.5% receiving placebo. Grade three or above TRAEs were more common with nivolumab (17.9%) compared to placebo (7.2%). TRAEs of grade three or above reported with nivolumab

included lipase increased, amylase increased, diarrhoea, rash (including maculo-papular), asthenia, decreased appetite, fatigue and blood creatinine increased. IMAEs occurred more frequently with nivolumab compared to placebo, with most grade one or two in severity. The most common IMAEs experienced with nivolumab were rash, hypothyroidism, hyperthyroidism and pneumonitis.

3. Cost effectiveness of nivolumab (Opdivo®)

Methods

The cost-effectiveness evaluation was informed by direct evidence from CheckMate 274; placebo was considered a proxy for BSC (i.e. routine surveillance). A de novo semi-Markov model contained four health states: 'initial disease-free', 'long-term disease-free', 'recurred disease', and an absorbing 'death' state. Health state occupancy in the 'initial disease-free' health state was estimated based on extrapolated DFS patient-level data from CheckMate 274 and background mortality derived from Irish life tables. Individuals without recurrence after five-years switched to the 'long-term disease-free' state where they were assumed to no longer be at risk of recurrence with mortality rates considered equivalent to the general population in Ireland. Individuals who experienced recurrence before five-years entered the 'recurred disease' health-state. Survival in the 'recurred disease' health state was informed by the published literature, and was assumed to be independent of treatment received. As such the effect of nivolumab on survival was captured indirectly via the increased time spent in the 'initial disease-free' and larger proportion of individuals entering the 'long-term disease-free' health state. Individuals could progress to 'death' from any other health state and transitions back to a previous health state were not permitted. The Review Group considered the approach to modelling DFS to be reasonable. The Review Group had concerns regarding assumptions surrounding the modelling of OS and the lack of available OS data from the CheckMate 274 trial. An OS benefit for nivolumab versus BSC, for this indication, has not been demonstrated.

Utility estimates were based on the ITT population from CheckMate 274, at the October 2022 data-cut. Time of clinical recurrence was recorded in the trial and as such separate data-sets were available for patients who were disease-free and those who experienced disease recurrence. Utility values estimated for the disease-free health states were higher

than general population values, as such the Applicant assumed the use of general population utility values (from an age- and sex-matched cohort) for the 'initial disease-free' and 'long-term disease-free' health states. For 'recurred disease' the absolute difference in utility between disease-free and recurred disease observed in CheckMate 274 was applied as a decrement to the age-dependent value. Utility decrements were also included for TRAEs.

Direct medical costs were included for drug acquisition (including administration), PD-L1 testing, routine care and monitoring, subsequent treatment, end-of-life care and the management of TRAEs. Irish costs were used where possible. Due to the rapidly evolving treatment landscape, in the progressed disease setting, the most relevant subsequent treatments are uncertain. The cost-effectiveness analysis was sensitive to the inclusion of further ICIs as subsequent treatments.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group made several changes to the Applicant base case based on plausible alternative assumptions. These included:

- direct use of the CheckMate 274 DFS Kaplan Meier curve up to five-years i.e., with no extrapolation (after which individuals are assumed to enter the long-term disease-free health state),
- changes to assumptions about subsequent treatments,
- an increased mortality rate (compared to that of the general population) in the 'long-term disease-free' health state,
- application of utility decrements for MIUC and for radical bladder resection, and
- stratifying the 'recurred disease' health state by local and distant recurrence.

The results of the Applicant's base case, and NCPE-adjusted, deterministic cost-effectiveness analyses are presented in Table 1.

Table 1: Incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis					
Nivolumab	101,209	5.97	38,335	1.88	20,412
Best supportive care	62,873	4.10	-	-	-
NCPE-adjusted analysis					
Nivolumab	91,378	5.43	46,237	1.36	34,103
Best supportive care	45,141	4.07	-	-	-

ICER: incremental cost-effectiveness ratio; **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

The Review Group highlights that, under the NCPE-adjusted base case, the cost-effectiveness model predicts an incremental life year gain of approximately two years. OS data from CheckMate 274 have not been released, and thus an OS benefit of nivolumab, versus BSC, has not been demonstrated. It was not feasible to implement a scenario where nivolumab is not associated with a survival benefit. The Review Group emphasizes that this prediction is subject to considerable uncertainty.

Sensitivity analysis

In the Applicant's base case, the mean probabilistic sensitivity outputs were consistent with the deterministic analyses. For the NCPE-adjusted base case the outputs of the probabilistic analysis were consistently skewed downwards. As such, the resultant probabilities of cost-effectiveness are likely overestimated and are not reported here.

A price ICER analysis on the NCPE-adjusted deterministic base case demonstrated that a price reduction of 45.85% on the price to wholesaler is required to achieve an ICER of €20,000 per QALY.

4. Budget impact of nivolumab (Opdivo®)

The price-to-wholesaler of a 240mg vial of nivolumab is €2,987.97. VAT is applicable. The total cost per treatment course is €56,876.70 (€45,476.58 excluding VAT). This estimate included all relevant fees, mark ups and rebates. Time on treatment was based on the mean duration in the CheckMate 274 trial (August 2020 data-cut).

The Applicant used several sources to inform eligible patient estimates. These included National Cancer Registry Ireland (NCRI) and Marie Keating Foundation data, data from the published literature and clinical opinion. The Applicant estimated an initial market share for nivolumab, in the current indication, of 43% in year one increasing to 85% for subsequent years. Overall, the Applicant estimated 18 individuals would be treated with nivolumab in year one, rising to 37 in year five. Based on the Applicant's assumptions, the five-year cumulative gross drug budget impact was estimated to be €9.2 million (€7.4 million excluding VAT). The cost-effectiveness analysis used the October 2022 data-cut to estimate mean time on treatment. Using this data-cut the five-year cumulative gross budget impact was €9.5 million (€7.6 million excluding VAT). Reimbursement of nivolumab for this indication is not expected to result in the displacement of other drugs. Therefore, the net drug budget impact is the same as the gross drug budget impact.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that nivolumab (Opdivo®) 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.*