Cost-effectiveness of nivolumab (Opdivo®) for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing chemotherapy

The 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®) not be considered for reimbursement. 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (BMS) economic dossier on the cost effectiveness 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 2018, Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd submitted a dossier of clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of nivolumab (Opdivo®) for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing chemotherapy. Final data was submitted by the Applicant in August 2018. BMS are seeking reimbursement for nivolumab (Opdivo®) in the hospital setting.

Nivolumab (Opdivo®)

Nivolumab is a human, monoclonal immunoglobulin G4 (IgG4) antibody that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Through this action, nivolumab prevents inactivation of T-cells, restoring T-cell activity against tumour cells, resulting in destruction of the tumour.

The recommended dose of nivolumab for this indication is 240 mg by IV infusion every two weeks. This is a modification to the original licensed dose of nivolumab which was 3 mg/kg every two weeks. Treatment should be continued for as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. No specific dose reductions are recommended. Nivolumab is formulated as a 10 mg/mL concentrate for solution for infusion.

Paclitaxel and best supportive care (BSC) were considered by the Applicant to be the main comparators of interest. Cisplatin+gemcitabine (cis+gem) and docetaxel were also included. This was considered appropriate by the NCPE and in line with the current standard of care in Ireland. It is anticipated that nivolumab will be used in either first or second-line locally advanced unresectable or metastatic urothelial carcinoma. This is in line with the licensed indication.

1. Comparative effectiveness of nivolumab

The efficacy of nivolumab in patients with urothelial carcinoma was assessed in two trials- CheckMate 275 and CheckMate 032.

CheckMate 275 is a multicentre, Phase II, single-arm study in which patients aged 18 years or older with metastatic or surgically unresectable locally advanced urothelial carcinoma received nivolumab 3 mg/kg intravenously every two weeks until disease progression and clinical deterioration, unacceptable toxicity or other protocol-defined reasons. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted if the subject had an investigator-assessed clinical benefit, did not have rapid disease progression, and was tolerating the study drug. No dose modifications were allowed, but predefined dose delays were permitted for adverse events. The primary endpoint was overall objective response confirmed by blinded independent review committee (BIRC) in all treated patients and by tumour PD-L1 expression (≥ 5% and ≥ 1%). Secondary endpoints included progression-free survival, overall survival, and investigator-assessed objective response.

At the first interim analysis, confirmed objective response was achieved in 52 (19.6%, 95% CI 15.0-24.9) of 265 patients. Confirmed objective response was achieved in 23 (28.4%, 95% CI 18.9-39.5) of the 81 patients with PD-L1 expression ≥ 5%, and 29 (23.8%, 95% CI 16.5-32.3) of the 122 patients with PD-L1 expression ≥ 1%. At a median follow up of 7 months (IQR 2.96-8.77), median overall survival was 8.74 months (95% CI 6.05 to not reached). Median progression free survival was 2.00 months (95% CI 1.87-2.63).

CheckMate 032 is a multicentre, Phase I/II, open-label study investigating the efficacy and safety of nivolumab or nivolumab combined with ipilimumab in patients with one of the following tumour types: urothelial carcinoma, triple-negative breast cancer, gastric cancer, pancreatic adenocarcinoma, small-cell lung cancer, and ovarian cancer. The Applicant presented data pertaining only to the nivolumab monotherapy urothelial carcinoma cohort of relevance to the submission. Patients received nivolumab 3 mg/kg intravenously every two weeks until disease progression and clinical deterioration, unacceptable toxicity or other protocol-defined reasons. Treatment beyond RECIST v1.1-defined progression was permitted if nivolumab was tolerated and clinical benefit was noted, on the basis of investigator assessment. No dose modifications were allowed, but predefined dose delays were permitted for adverse events. The primary endpoint was objective response by investigator assessment. Secondary endpoints included progression-free survival, overall survival, and duration of response.

At the first interim analysis, a confirmed investigator-assessed objective response was achieved in 19 (24.4%, 95% CI 15.3-35.4) of 78 patients. At a median follow up of 15.2 months (IQR 12.9-16.8), median overall survival was 9.7 months (95% CI 7.3-16.2). Median progression free survival was 2.8 months (95% CI 1.5-5.9).

In the absence of any direct comparative evidence of nivolumab versus a comparator of interest, the Applicant conducted a simulated treatment comparison (STC) and network meta-analysis (NMA) evaluating overall survival, progression free survival and objective response. The STC was an unanchored comparison due to the lack of any direct or indirect links between nivolumab and any of the comparators. The unanchored nature of the STC generated results that were subject to an unknown degree of bias and attempts by the Applicant to quantify systematic error generated results which were highly uncertain. Thus, the Review Group have significant concerns regarding the robustness of the STC and the results should be treated with caution. A fractional polynomial approach was employed for the NMA.

2. Safety of nivolumab

The safety and tolerability of nivolumab was evaluated as an exploratory endpoint in CheckMate 275 and as a secondary endpoint in CheckMate 032. In both trials, the safety population included all patients who had received at least one dose of nivolumab.

Similar numbers of adverse events (AEs) were reported in both trials, 98.9% in CheckMate 275 and 100% in CheckMate 032. AEs considered to be related to treatment were reported in 64.4% of patients in CheckMate 275 and 83.3% in CheckMate 032. There was a higher proportion of Grade 3-4 AEs in CheckMate 032 compared to CheckMate 275, 23.1% versus 17.8%. All-cause AEs leading to treatment discontinuation were reported in 20.7% and 7.7% of patients in CheckMate 275 and CheckMate 032, respectively. The proportion of deaths due to study drug was 1.1% in CheckMate 275 and 3% in CheckMate 032. The most commonly reported treatment related AEs were fatigue (32.2% and 53.8% in CheckMate 275 and CheckMate 032, respectively), nausea (22.2% and 29.5%, respectively), and decreased appetite (21.9% and 14.1%, respectively).

Overall, no new safety concerns pertaining to nivolumab were identified across the two trials and the demonstrated safety profile is consistent with the safety/tolerability profile observed with nivolumab in trials for multiple other tumour types.

3. Cost effectiveness of nivolumab

For the cost-effectiveness analysis, the effectiveness inputs in the model were PFS and OS. Clinical efficacy inputs were derived from the pooled CheckMate 275 and CheckMate 032 data and the STC NMA. Cost-effectiveness was investigated using a three state health model with a 32 year time horizon. The model simulates patients through three health states: 'Progression-free', 'Progressive disease' and 'Death'. All health states are mutually exclusive, and death is an absorbing state. All patients start in the progression-free state; transitions to the death state could occur from either the progression-free or progressive disease states.

Patient characteristics, dose intensity, and utility values used in the model are derived from CheckMate 275 and CheckMate 032. Adverse event disutilities are based on values obtained from the literature, whilst the frequency of each AE is derived from the trial informing each treatment arm. Resource use data was obtained from a systematic review of the literature and validated by clinical experts. Costs captured in the model include drug acquisition and administration, hospital resource use, monitoring and follow up, management of Grade 3-4 AEs and terminal care costs. Following treatment discontinuation, a proportion of patients are assumed to receive radiotherapy and/or surgery. The proportion of patients receiving each was derived from a weighted average of CheckMate 275 and CheckMate 032; costs were estimated based on the HSE Casemix Ready Reckoner. Future costs and health-related outcomes are discounted at 5% per annum, in line with national guidelines.

Survival outcomes from the pooled CheckMate 275 and CheckMate 032 data were extrapolated using two different methods: response-based and standard parametric analysis. The response-based analysis modelled survival using the pooled Kaplan-Meier data until a pre-defined landmark time point, after which survival was individually assessed according to response to treatment (responder vs. non-responder). Standard parametric distributions were then fitted to the responder and non-responder curves to model progression-free survival and overall survival. The NCPE Review Group did not believe that

sufficient justification was provided to support the response-based landmark analysis and so a standard parametric analysis was also presented by the Applicant.

Analyses presented in this summary document are based on the list prices of the interventions. The ICERs for nivolumab versus each comparator based on the Applicant base case scenario considered most relevant by the NCPE (standard parametric extrapolation) are presented below:

Table 1 Applicant ICERs based on standard parametric extrapolation

	ICER
Versus paclitaxel	€94,315/QALY (incremental costs €79,429, incremental QALYS 0.84)
Versus best supportive care	€91,553/QALY (incremental costs €86,421, incremental QALYs 0.94)
Versus docetaxel	€97,824/QALY (incremental costs €83,603, incremental QALYs 0.85)
Versus cis+gem	€106,107/QALY (incremental costs €76,438, incremental QALYs 0.72)

The ICERs for nivolumab versus each comparator based on the response-based landmark analysis are presented below:

Table 2 Applicant ICERs based on response-based landmark analysis

	ICER
Versus paclitaxel	€50,382/QALY (incremental costs €53,227, incremental QALYS 1.06)
Versus best supportive care	€51,411/QALY (incremental costs €60,506, incremental QALYs 1.18)
Versus docetaxel	€53,693/QALY (incremental costs €57,563, incremental QALYs 1.07)
Versus cis+gem	€56,488/QALY (incremental costs €50,231, incremental QALYs 0.89)

The NCPE implemented a number of changes to the Applicant's base-case (standard parametric extrapolation) model including assuming 100% dose intensity, assuming a GP visit in the PFS state, updating the number of oncologist visits per cycle, and implementation of alternative parametric distributions. The ICERs for nivolumab versus each comparator based on these alternative assumptions are presented below:

Table 3 ICERs based on NCPE preferred assumptions

	ICER
Versus paclitaxel	€108,403/QALY (incremental costs €89,904, incremental QALYS 0.83)
Versus best supportive care	€111,077/QALY (incremental costs €103,389, incremental QALYs 0.93)
Versus docetaxel	€115,808/QALY (incremental costs €97,399, incremental QALYs 0.84)

Versus cis+gem	€116,150/QALY (incremental costs €82,184, incremental QALYs 0.71)

The NCPE Review Group highlights the uncertainty surrounding these cost-effectiveness estimates, due to the unreliability of the STC estimates informing the economic model.

4. Budget impact of nivolumab

Nivolumab is submitted for reimbursement in the hospital setting. The price to wholesaler (PTW) of the nivolumab 240 mg vial is €3147.08. This price is further subject to VAT. Assuming 100% dose intensity, the annual cost of treatment per patient is €79,160.23 including VAT and rebate, assuming patients receive 9.85 cycles. The Review Group note that the flat dosing regimen of nivolumab may result in individuals receiving more than is therapeutically necessary at a greater cost.

Based on the Applicant's estimate of the current eligible population and market share assumptions, the projected gross budget impact over the first five years is approximately €18.1 million. Assuming a relative dose intensity of 100% increases this projected gross budget impact to €19.4 million. The net budget impact, based on the Applicant's base-case assumptions, is €17.5 million. Given the relatively low costs of the off-patent comparator treatments, the net budget impact of nivolumab is considerable.

5. Patient submissions

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

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that nivolumab (Opdivo®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.