NCPE Assessment Summary

Nivolumab-relatlimab (Opdualag®)

HTA ID: 24009

20 July 2026

Applicant: Bristol Myers Squibb

Nivolumab-relatlimab for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of nivolumab-relatlimab (Opdualag®).

Following assessment of the Applicant's submission, the NCPE recommends that nivolumab-relatlimab (Opdualag®) 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) Health Technology Assessment of nivolumab-relatlimab (Opdualag®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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 December 2025, Bristol Myers Squibb submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of nivolumab-relatlimab (Opdualag®) for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell programmed cell-death ligand 1 (PD-L1) expression < 1%. Bristol Myers Squibb is seeking reimbursement of nivolumab-relatlimab on the Oncology Drugs Management System.

Nivolumab-relatlimab is a single-vial, fixed-dose, dual-mechanism combination immunotherapy treatment. Nivolumab inhibits PD-1 receptors expressed by activated T-cells and B-cells, promoting tumour antigen-specific T-cell responses. Relatlimab inhibits lymphocyte-activation gene 3 (LAG-3) on T-cells and acts to restore their effector functions in the presence of invasive cancers while promoting cytokine secretion. One vial of nivolumab-relatlimab contains 240mg of nivolumab and 80mg of relatlimab. The licence recommends two vials (i.e., 480mg nivolumab, 160mg relatlimab) once, every four weeks via intravenous infusion. The SmPC states that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The current standard of care for patients with advanced (metastatic or unresectable) melanoma in the first line, in Ireland, is nivolumab in combination with ipilimumab (nivolumab + ipilimumab) where tolerated. Clinical opinion indicated that nivolumab + ipilimumab may be administered at the licensed dose (i.e., nivolumab 1mg/kg + ipilimumab 3mg/kg) [otherwise known as the 'full dose'] or an unlicenced dose (i.e., nivolumab 3mg/kg + ipilimumab 1mg/kg) [otherwise known as the 'flip dose']. Monotherapy immunotherapy treatment (nivolumab or pembrolizumab) is considered when a patient cannot tolerate combination immunotherapy (e.g., in the cases of frailty or if toxicity concerns arise). In Ireland, PD-L1 expression status testing is not routinely carried out in patients with melanoma.

1. Comparative effectiveness of nivolumab-relatlimab

The efficacy and safety of nivolumab-relatlimab versus nivolumab monotherapy is being assessed in an ongoing phase II/III, double-blind, randomised controlled trial (RELATIVITY-047). Nivolumab-relatlimab was administered as per the SmPC dosing and nivolumab

monotherapy was administered intravenously at 480mg, once every four weeks. The primary endpoint of RELATIVITY-047 is progression-free survival (PFS) as assessed by blinded independent committee review (BICR). Key secondary endpoints include overall survival (OS) rates, objective response rates, and health-related quality of life (HRQoL) changes. The interim analysis (October 2024) included four years of follow-up data. Median PFS in the nivolumab-relatlimab arm was 6.67 months (95% confidence interval [95% CI] 4.67 to 12.02 months) versus 2.96 months (95% CI 2.79 to 4.50 months) in the nivolumab monotherapy arm. A statistically significant improvement in PFS was observed (hazard ratio [HR] 0.68, 95% CI 0.54 to 0.85). Median OS in the nivolumab-relatlimab arm was 38.28 months (95% CI 24.31 to 58.64 months) versus 25.82 months (95% CI 18.73 to 42.41 months) in the nivolumab monotherapy arm. No statistically significant improvement in OS was observed (HR 0.79, 95% CI 0.62 to 1.01). In the updated data cut (October 2025, five-year follow-up), the statistically significant improvement in PFS was maintained (HR 0.67; 95% CI 0.53 to 0.86). A statistically significant OS benefit was observed in participants randomised to nivolumab-relatlimab compared to nivolumab monotherapy (HR 0.76; 95% CI 0.60 to 0.98). Clinical efficacy and safety inputs in the cost-effectiveness model (CEM) are based on the October 2024 data cut (4-year follow-up) from RELATIVITY-047.

2. Indirect Treatment Comparison

The Applicant performed a fractional polynomial (FP) network meta-analysis (NMA) to inform comparisons of nivolumab-relatlimab versus nivolumab + ipilimumab (flip- and full-dose) and pembrolizumab monotherapy, for the outcomes of OS, investigator-assessed (IA) PFS, and BICR-PFS, estimating time-dependent HRs. The Applicant also provided results from NMAs estimating constant, time-invariant HRs for OS and BICR-PFS outcomes, as well as published adjusted indirect treatment comparison (ITC) results for comparisons against full dose nivolumab + ipilimumab for OS and IA-PFS. Additionally, an independent published NMA from Boutros *et al.* was available and considered in this appraisal. The Review Group noted strong limitations with the Applicant's provided NMA, particularly due to heterogeneity which arose due to differing populations and inappropriate comparative analyses with respect to PFS.

The Applicant provided FP NMA results comparing IA PFS in the *whole trial population* of RELATIVITY-047 (regardless of tumour PD-L1 expression status) and the PD-L1 < 1%

subpopulations of CheckMate-067, CheckMate-069 and CheckMate-511 (nivolumab + ipilimumab). Furthermore, the FP NMA and constant HR NMA results presented for BICR-PFS included the BICR-PFS outcome from RELATIVITY-047, but IA-PFS from the CheckMate trials.

Results from the FP NMAs demonstrated no statistically significant differences in OS or IA-PFS between any of the treatments after six months. Results for BICR-PFS against pembrolizumab monotherapy were statistically significant and favourable towards nivolumab-relatlimab. However, these were based on a shorter follow-up of KEYNOTE-006 and a smaller dataset due to the PD-L1 < 1% cut-off, therefore containing large uncertainty. The NMA estimating constant HRs showed similar results for OS against all comparators and BICR-PFS for comparisons against full and flip dose nivolumab + ipilimumab. The only statistically significant results were for BICR-PFS between nivolumab-relatlimab and nivolumab monotherapy (HR 0.68; 95% credible interval [95% CrI] 0.54 to 0.85) and pembrolizumab monotherapy (HR 0.46; 95% CrI 0.27 to 0.78). From the adjusted ITC, results for OS were similar to those estimated from the FP and constant HR NMAs, while results for IA-PFS were similar to those from the FP NMA, but none of the results were statistically significant. The results from Boutros *et al.* were similar to the Applicant's for PFS, but results were not available for OS. There was no evidence to support a difference in OS compared to nivolumab + ipilimumab, and results from the NMAs and adjusted ITC implied more favourable PFS for nivolumab + ipilimumab, however, results were not statistically significant.

3. Safety of nivolumab-relatlimab

The safety analysis set was sourced from the population of RELATIVITY-047 with PD-L1 expression status < 1%. Overall, participants randomised to nivolumab-relatlimab had more frequent, severe and prolonged adverse events (AEs), serious AEs (SAEs), treatment related AEs (TRAEs) and AEs leading to discontinuation than those randomised to nivolumab monotherapy. Almost 100% of participants in the nivolumab-relatlimab arm experienced AEs, compared with 96.2% in the nivolumab monotherapy arm. The most common AEs (of any grade) in the nivolumab-relatlimab arm and nivolumab monotherapy arm, respectively, included: fatigue (31.6% versus 18.8%); diarrhoea (27.3% versus 24.0%); arthralgia (26.8% versus 17.5%) and anaemia (23.9% versus 18.0%). SAEs grade ≥ 3 were also more common in participants randomised to nivolumab-relatlimab (30.6% versus 26.9%) versus nivolumab

monotherapy. TRAEs were recorded at higher rates in the nivolumab-relatlimab arm (grade 1 to 2: 15.3% versus 8.0%; grade ≥ 3: 10.0% versus 5.2%). TRAEs led to discontinuation in 15.3% of participants treated with nivolumab-relatlimab and 8.0% of participants treated with nivolumab monotherapy. The SmPC for nivolumab-relatlimab contains a special warning to monitor for immune-related side effect manifestations (including but not limited to pneumonitis, colitis, hepatitis, nephritis, diabetes mellitus and endocrinopathies). Patients in receipt of immunosuppressive therapies (including corticosteroids) should not receive nivolumab-relatlimab, and all patients should be monitored from treatment initiation up until five months following discontinuation for the drug.

4. Cost effectiveness of nivolumab-relatlimab

The Applicant compared the cost-effectiveness of nivolumab-relatlimab to nivolumab + ipilimumab, nivolumab monotherapy and pembrolizumab monotherapy in the base case.

Methods

The Applicant submitted a partitioned-survival model including three mutually exclusive health states: progression-free (PF); progressed disease (PD) and; death. These health states captured PFS and OS. The model included a half-cycle correction, had a 40-year time horizon and had a cycle length of 30 days. In each cycle, patients accrued quality-adjusted life years (QALYs), and incurred costs based on the utility (HRQoL) values and costs specified for the health state occupied, the relevant treatment arm, and the time on treatment. The Applicant base case included a two-year stopping rule for nivolumab-relatlimab and all comparators. All participants enter the CEM in the PF health state and receive treatment with nivolumab-relatlimab, nivolumab + ipilimumab (100% of participants assumed to receive unlicensed 'flip-dose', with scenarios conducted assuming 'flip' and 'full' dose use), nivolumab monotherapy or pembrolizumab monotherapy. In each model cycle, patients either remained in their current health state, transitioned to the PD health state, or transitioned from the PF or PD health states to the death state. Transitioning to improved health states was not permitted. Treatment effects for the outcomes of PFS, OS and time to treatment discontinuation (TTD) for nivolumab-relatlimab and nivolumab monotherapy were informed by individual patient data from RELATIVITY-047. For nivolumab + ipilimumab, OS and PFS estimates were obtained by applying the time-varying HRs for OS and IA-PFS,

respectively, from the FP NMAs, using the nivolumab monotherapy curves as reference. TTD was informed by Kaplan Meier data from CheckMate-067. For pembrolizumab monotherapy, OS was estimated by applying the FP NMA HRs to the nivolumab monotherapy curve, while PFS and TTD were assumed equal to those of nivolumab monotherapy.

Results

An incremental analysis of the costs and benefits of nivolumab-relatlimab versus all comparators was presented by the Applicant. Results are presented in Table 1. The probabilistic results, which were estimated for 1,000 simulations, are stable and similar to the deterministic results for comparisons against nivolumab monotherapy and pembrolizumab monotherapy. For comparisons against nivolumab + ipilimumab, discrepancies are seen between the probabilistic and deterministic ICERs, likely caused by varying parameters for the parametric OS survival curves.

Table 1: Applicant base case incremental cost-effectiveness results[a,b,c]

	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab-relatlimab	221,918	4.58	-	-	-
Versus nivolumab + ipilimumab[d]	188,646	4.38	33,272	0.20	170,567
Versus nivolumab monotherapy	141,334	3.52	80,584	1.06	76,044
Versus pembrolizumab monotherapy	157,641	3.58	64,278	1.00	64,076

QALY: Quality adjusted life year; **ICER:** Incremental cost-effectiveness ratio

[a] The Review Group identified an error in the Applicant's CEM which incorrectly omitted the mandatory 9% Framework Agreement rebate for all treatments except pembrolizumab. Results shown here and throughout this section are inclusive of the rebate.

[b] Corresponding probabilistic ICER using 1,000 iterations =€203,686/QALY (versus nivolumab + ipilimumab); =€77,894/QALY (versus nivolumab monotherapy); =€65,633/QALY (versus pembrolizumab monotherapy). Figures in the table are rounded.
Discount rate of 4% is applied to costs and outcomes.

[c] A commercial-in-confidence Patient Access Scheme has been proposed for nivolumab-relatlimab and is in place for nivolumab + ipilimumab, nivolumab monotherapy and pembrolizumab monotherapy, not included here.

[d] The Applicant base case assumed 100% of patients receive flip dose nivolumab (3mg/kg) + ipilimumab (1mg/kg). This is considered a conservative approach in terms of costs in comparison to using the full dose. A scenario was explored assuming use of both the flip and full dose of nivolumab + ipilimumab by the Review Group.

The NCPE Review Group identified several limitations in the Applicant's base case and have made changes in the NCPE-adjusted base case. These included: introducing a cost for PD-L1 testing in line with the product licence for nivolumab-relatlimab; using health-state specific healthcare resource use costs (instead of time-dependent costs); applying the FP-NMA results based on BICR-PFS as opposed to IA-PFS using nivolumab-relatlimab as reference; removing the two-year stopping rule for all treatments (excluding pembrolizumab, for which the SmPC outlines the decision to continue treatment should be assessed at two years);

removing the TTD cap by PFS for all treatments; updating the TTD parametric curve for nivolumab-relatlimab and; updating TTD for nivolumab + ipilimumab such that TTD gradually declines to zero. The NCPE adjusted base case is presented in Table 2.

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

	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Nivolumab-relatlimab	611,012	4.58	-	-	-
Nivolumab + ipilimumab[c]	435,776	4.39	175,236	0.19	936,879
Nivolumab monotherapy	428,925	3.52	182,087	1.06	171,871
Pembrolizumab monotherapy	432,898	3.58	178,114	1.00	177,867

QALY: Quality adjusted life year; **ICER:** Incremental cost-effectiveness ratio

[a] Corresponding probabilistic ICER using 1,000 iterations =€1,131,770/QALY (versus nivolumab + ipilimumab); =€177,174/QALY (versus nivolumab monotherapy); =€187,144/QALY (versus pembrolizumab monotherapy). Figures in the table are rounded, and so calculations may not be directly replicable.

[b] A CIC PAS has been proposed for nivolumab-relatlimab and is in place for nivolumab + ipilimumab, nivolumab monotherapy and pembrolizumab monotherapy, not included here.

[c] The NCPE adjusted base case assumed 100% of patients receive flip dose nivolumab (3mg/kg) + ipilimumab (1mg/kg). This is considered a conservative approach in terms of costs in comparison to using the full dose. A scenario was explored assuming use of both the flip and full dose of nivolumab + ipilimumab by the Review Group.

Sensitivity analysis

Under NCPE adjusted base case assumptions, the probability of cost-effectiveness of nivolumab-relatlimab was 0.4% and 0.3% at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus nivolumab + ipilimumab). The probability of cost-effectiveness of nivolumab-relatlimab was 0.8% and 0.4% at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus nivolumab monotherapy). The probability of cost-effectiveness of nivolumab-relatlimab was 0.6% and 0.3% at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus pembrolizumab monotherapy).

A price-ICER analysis, using NCPE adjusted base case assumptions, indicated that a 70% and 72% reduction to the nivolumab-relatlimab PtW would be required for nivolumab-relatlimab to be cost-effective at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus nivolumab + ipilimumab). A 58% and 68% reduction to the PtW of nivolumab-relatlimab would be required for nivolumab-relatlimab to be cost-effective at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus nivolumab monotherapy). A 58% and 67% reduction to the PtW of nivolumab-relatlimab would be required for nivolumab-relatlimab to be cost-effective at the €45,000/QALY and the €20,000/QALY thresholds respectively (versus pembrolizumab monotherapy).

5. Budget impact of nivolumab-relatlimab

The PtW for one vial of nivolumab-relatlimab (240mg nivolumab, 80mg relatlimab) is €6,730 . Two vials are required per administration. The total cost, per patient, per treatment course was estimated to be €357,111 (including VAT) in the NCPE adjusted base case, based on a mean treatment duration of 21.95 months. The Applicant used population estimates from the Central Statistics Office and sex-specific incidence and mortality rates from the National Cancer Registry Ireland to the population living with melanoma in Ireland. Of these, 5% were assumed to have advanced (metastatic or unresectable) melanoma based on a study by Porter *et al.* Of those with advanced melanoma, the Applicant assumed 59% would screen positive for PD-L1 expression < 1%. The Applicant predicted that nine patients will be treated with nivolumab-relatlimab in Year one rising to 49 patients in Year five; a total of 146 patients over five years. The estimated five-year cumulative gross drug-budget impact for nivolumab-relatlimab is €19.76 million (including VAT) and the five-year cumulative net drug-budget impact is €9.29 million (including VAT). When PD-L1 costing was considered, the five-year cumulative net health-budget impact is €9.31 million (including VAT).

Many of the BIM inputs are uncertain and there is considerable uncertainty associated with the budget impact estimates. An NCPE adjusted budget impact analysis is presented where: PD-L1 testing positivity rates have been updated to 59.21%, in line with the CEM; the costs of PD-L1 testing have been updated to €199.53 from estimates provided by HSE vendors and; mean TTD for all treatments have been updated without PFS caps, as sourced from the CEM. The two-year stopping rule is not applied. The NCPE adjusted five-year cumulative gross drug budget impact for nivolumab-relatlimab is €53.39 million (including VAT), and the five-year cumulative net drug-budget impact is €36.90 million (including VAT). With the updated PD-L1 cost considered, the five-year cumulative net health-budget impact is €36.95 million (including VAT). The Review Group explored a number of scenarios including one where all patients with advanced melanoma, irrespective of PD-L1 expression status receive nivolumab-relatlimab (based on clinical opinion): 5-year net drug-budget impact €62.54 million.

6. Patient Organisation Submission

A patient organisation submission was received from Melanoma Support Ireland. This submission will form part of the information that the HSE considers when making their drug

funding decision.

7. Conclusion

The NCPE recommends that nivolumab-relatlimab (Opdualag®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatment*.

*Next steps: The NCPE Assessment Report and recommendation and Patient Organisation submission, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

Further information on this process may be found here.