SMC2645

nivolumab, relatlimab concentrate for solution for infusion (Opdualag®)

Bristol Myers Squibb

07 June 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

nivolumab, relatlimab (Opdualag®) is accepted for use within NHSScotland.

Indication under review: first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

In a randomised, double-blind, phase II/III study of adults with previously untreated advanced melanoma, nivolumab-relatlimab fixed-dose combination was associated with a statistically significant improvement in progression-free survival when compared with a single-agent immunotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

This treatment is a fixed-dose combination of nivolumab, a programmed death 1 (PD-1) inhibitor, with relatlimab, an inhibitor of lymphocyte activation gene 3 (LAG-3). Nivolumab blocks PD-1 receptor interaction with PD-1 ligands, PD-L1 and PD-L2, enhancing the anti-tumour immune response. Relatlimab blocks LAG-3 receptor interaction, promoting T cell activation. Together, they increase T cell activation more than either alone. In mouse models, combining these antibodies inhibits tumour growth and promotes regression.[1]

The recommended dose for adults and adolescents ≥ 12 years of age is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous (IV) infusion over 30 minutes. This dose is established for adolescent patients weighing at least 30 kg. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[1]

1.2. Disease background

Melanoma is a heterogeneous type of skin cancer with a range of clinical factors and molecular abnormalities which significantly influence its prognosis. It ranks sixth in cancer prevalence in Europe and its incidence steadily increased over the past 40 years. While it typically occurs around age 65, it can affect individuals of any age. Most melanomas start as superficial tumours in the skin before progressing deeper, probably because of genetic abnormalities. Cutaneous melanoma, the most common subtype, accounts for over 90% of cases and frequently bears the BRAF mutation (in about 50% of cases), which is linked to poorer outcomes. Metastatic melanoma can spread to various organs, causing pain and neurological issues, among other symptoms. Clinical factors like raised lactose dehydrogenase (LDH) levels and visceral metastases (notably liver and brain), multiple metastatic sites, and poor performance status are predictive of poor responses to targeted and immunotherapies.[2]

1.3. Treatment pathway and relevant comparators

The primary goal of treatment in unresectable or metastatic melanoma is to extend progression-free survival (PFS) and to enhance overall survival (OS). In patients with advanced melanoma, immunotherapy using immune checkpoint inhibitors is recommended as the initial treatment, regardless of BRAF status. Nivolumab combined with ipilimumab should be considered for eligible patients in this category (SMC 1187/16). If nivolumab plus ipilimumab is not suitable or acceptable due to factors such as potential toxicity or patient preference, pembrolizumab(SMC 1086/15) or nivolumab alone (SMC 1120/16) should be considered.[2, 3]

For patients with a BRAF mutation, targeted therapies such as BRAF- or MEK-inhibitor-containing regimens such as encorafenib plus binimetinib (SMC2238) or dabrafenib plus trametinib (SMC1161/16, SMC2328) should be considered for the subsequent lines if nivolumab plus ipilimumab, pembrolizumab, or nivolumab monotherapy are not suitable or if there is insufficient time for an adequate immune response due to factors such as extensive disease burden or rapid disease progression.[3]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of nivolumab-relatlimab for this indication comes from the ongoing study, RELATIVITY-047. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[2, 4]

Criteria	RELATIVITY-047
Study design	Ongoing, international, randomised, double-blind controlled, phase II/III study.
Eligible patients	• Age ≥ 12 years • ECOG PS of ≤ 1 or Lansky PS ≥ 80% for minors • Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the AJCC staging system (8th edition) • No prior systemic anticancer therapy for unresectable or metastatic melanoma. • Measurable disease by CT or MRI per RECIST v1.1 criteria • Tumour tissue from an unresectable or metastatic site provided for biomarker analyses • Known BRAF V600 mutation status or consent to BRAF V600 mutation testing
Treatments	Administered as an IV infusion every 4 weeks: • 160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination • or 480 mg of nivolumab For adolescent patients < 40 kg, dosing was planned to be weight-based (relatlimab 2 mg/kg, nivolumab 6 mg/kg). Treatment continued until the occurrence of disease progression, unacceptable adverse effects, or withdrawal of consent. Treatment beyond initial progression (as defined by investigators) was permitted if the investigators assessed that the patient had clinical benefit and if the patient did not have unacceptable side effects.
Randomisation	Equal randomisation stratified according to LAG-3 expression (≥1% or <1%), PD-L1 expression (≥1% or <1%), BRAF V600 mutation status, and metastasis stage (M0 or M1 with normal LDH levels vs M1 with elevated LDH levels) as defined in the Cancer Staging Manual of the AJCC, 8th edition.
Phase 3 primary outcome	PFS assessed according to RECIST, version 1.1, by BICR and defined as the time between the date of randomisation and the earliest date of documented disease progression or the date of death from any cause, whichever occurred first.
Phase 3 secondary outcomes	• OS, defined as the time between the date of randomisation and the date of death due to any cause. • ORR assessed by BICR, defined as the proportion of subjects who achieved a best overall response of complete response or partial response based on RECIST 1.1. Confirmation of response is required at least 4 weeks after the initial response.
Statistical analysis	A hierarchical statistical testing strategy was applied in the phase 3 of the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. PFS by BICR was tested first then OS, followed by ORR by BICR. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported). Other outcomes were not to be tested formally. Efficacy analyses were performed in the ITT population, which included all patients who underwent randomisation.

Abbreviations: AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; BRAF = v-raf murine sarcoma viral oncogene homolog B1; CT = computerised tomography; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; LAG-3 = lymphocyte activation gene-3; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PS = performance status RECIST: Response Evaluation Criteria in Solid Tumours; V600 = amino acid substitution at position 600 in BRAF.

At the final PFS analysis (09 March 2021 data cut off), a statistically significant improvement in PFS was demonstrated with nivolumab-relatlimab compared with nivolumab alone. Updated descriptive data (October 2022 data cut off) were presented by the submitting company. Results are summarised in Table 2.2.[2, 5, 6]

Table 2.2: Primary and secondary outcomes' results from RELATIVITY-047 phase 3 [2, 5, 6]

	Nivolumab-relatlimab (N=355)	**Nivolumab (N=359)**	**Nivolumab-relatlimab (N=355)**	**Nivolumab (N=359)**
Data cut off	**Final PFS analysis - 9 March 2021**		**Updated descriptive analysis - October 2022**	
Mean follow-up duration	13.2 months		25.3 months	
Primary outcome – PFS by BICR				
Event, n (%)	180 (51%)	211 (59%)	*	*
Median PFS (95% CI), months	10.1 (6.4 to 15.7)	4.6 (3.4 to 5.6)	10.2 (6.5 to 14.8)	4.6 (3.5 to 6.5)
HR (95% CI), p value	0.75 (0.62 to 0.92), 0.0055		0.81 (0.67 to 0.97)	
KM-estimated 1-year PFS, %	48	36	48	37
KM-estimated 3-year PFS, %	-	-	31	27
KM-estimated 4-year PFS, %	-	-	*	*
Data cut off	**Final OS analysis –28 October 2021**		**Updated descriptive analysis – October 2022**	
Mean follow-up duration	19.3 months		25.3 months	
Secondary outcome – OS				
Deaths, n (%)	137 (39%)	160 (45%)	*	*
Median OS, months (95% CI)	NR (34.2 to NR)	34.1 (25.2 to NR)	NR (31.5 to NR)	33.2 (25.2 to 45.8)
HR (95 % CI)	0.80 (0.64 to 1.01)		0.82 (0.67 to 1.02)	
P value	0.0593 (NS; p value <0.04302 needed for statistical significance)		-	
KM-estimated 2-year OS rate, %	-	-	62	58
KM-estimated 4-year OS rate, %	-	-	52	42
Secondary outcome – ORR by BICR				
ORR, %	43	33	44	34
Difference in ORR, %	10		9.8	
Odds ratio (95% CI)	1.58 (1.16 to 2.15)		*	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; KM = Kaplan-Meier; NR = not reached; NS = not significant; ORR = objective response rate; OS = overall survival, PFS = progression-free survival; HR = hazard ratio; * = other data were assessed but remain confidential

Exploratory outcomes included PFS assessed by investigator. At the final PFS analysis (09 March 2021 data cut off), the median PFS with nivolumab-relatlimab was 10.15 months compared with 6.51 months with nivolumab alone HR = 0.85 (95% CI: 0.69 to 1.03).[2] At the latest descriptive analysis (data cut off October 2022), results were similar. [5]

*Other data were also assessed but remain confidential.**

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the functional assessment of cancer therapy-melanoma (FACT-M), which assesses the effects of melanoma symptoms on functioning and well-being and includes 27 items from FACT-G domains, a 16-item melanoma subscale, and an 8-item melanoma surgery scale; each item is rated on a 5-point scale, with the minimally important change estimated of 2 to 4 points. The EuroQol 5-dimension, 3-level (EQ-5D-3L) visual analogue scale (VAS) and utility index scores were also used to assess overall health status. Changes of 0.08 for utility index score and 7 for VAS considered minimally important differences.[2, 4]

Overall, there were no significant changes in the HRQoL for participants in either treatment group; and any differences noted did not reach the minimal important difference thresholds. While there were slightly higher scores for nivolumab monotherapy in some domains these differences did not translate into meaningful differences in HRQoL between the two treatment groups.[2]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing nivolumab-relatlimab with nivolumab plus ipilimumab, and with pembrolizumab for untreated unresectable or metastatic melanoma, a propensity score adjusted analysis (hereinafter termed the adjusted indirect treatment comparison [ITC]) and a network meta-analysis (NMA) were conducted. The results from these have been used to inform the economic model. See Table 2.3 for details.

Table 2.3 Summary of indirect treatment comparison

Criteria	Overview
Design	**1.** Adjusted ITC using patient level data and a propensity score adjusted analysis to address imbalances in the distribution of baseline characteristics. **2.** Bayesian NMA using fixed effects model.
Population	Adult patients with untreated unresectable or metastatic melanoma.
Comparators	**1.** ITC: Nivolumab plus ipilimumab. **2.** NMA: Nivolumab plus ipilimumab and pembrolizumab.
Studies included	**1.** ITC: Two randomised controlled trials (RCTs); RELATIVITY-047 and CheckMate-067.[4, 7] **2.** NMA: Four RCTs; CheckMate 067, CheckMate 069, KEYNOTE-006 and RELATIVITY-047.[4, 7-9]
Outcomes	**1.** ITC: OS, investigator-assessed PFS, BICR-assessed PFS and safety outcomes including all-cause AEs, AEs (grades 3 to 4), TRAEs (grades 3 to 4), discontinuation due to AEs and discontinuation due to TRAEs. **2.** NMA: OS, PFS (using combined investigator-assessed and BICR-assessed data) and safety outcomes including AEs (grades 3 to 4), TRAEs (grades 3 to 4), discontinuation due to AEs and discontinuation due to TRAEs. Time-varying and constant HRs were estimated and both were used to inform the economic model.
Results	**1.** ITC: Results indicated that for PFS (both investigator-assessed PFS and BICR-assessed PFS) and OS there was no evidence of a difference between nivolumab-relatlimab and nivolumab plus ipilimumab. Safety results suggest that nivolumab-relatlimab had a more favourable safety profile than nivolumab plus ipilimumab, with lower rates of grade 3 or 4 AEs and TRAEs, and TRAEs leading to discontinuation. **2.** NMA: o Comparisons against nivolumab plus ipilimumab: Results for the time-varying HRs indicated that for PFS and OS there was no evidence of a difference at all timepoints with the 95% CrIs including 1 from 3 to 48 months between nivolumab-relatlimab and nivolumab plus ipilimumab. The constant HR estimates were similar to the time-varying

	HRs with all the CrI including 1. When comparing nivolumab-relatlimab with nivolumab plus ipilimumab there was a lower risk of grades 3 or 4 AEs, grades 3 or 4 TRAEs and discontinuations due to AEs and TRAEs; the 95% CrI did not include 1 for all safety outcomes indicating there is some evidence of a difference between the two medicines. ○ Comparisons against pembrolizumab: Time-varying HRs suggest that nivolumab-relatlimab is likely to be superior to pembrolizumab for PFS (with HR < 1 and CrI not crossing 1) from 3 months onwards; however, for OS there is no evidence of difference over time between these treatments with CrIs including 1. The constant HR estimates were similar to the time-varying HRs (all < 1); however for both PFS and OS comparisons the 95% CrI included 1 suggesting no evidence of difference between these treatments. When comparing nivolumab-relatlimab with pembrolizumab, there was a higher risk of grade 3 or 4 AEs, discontinuations due to AEs and discontinuations due to TRAEs. The 95% CrI included 1 for discontinuations due to AEs and TRAEs indicating there was no evidence of a difference between the two medicines for these safety outcomes.
Abbreviations: AE: adverse events; BICR: blinded independent central review; CI: confidence intervals; CrI: credible intervals; ITC: indirect treatment comparison; NMA: network meta-analysis; PFS: progression-free survival; OS: overall survival; TRAEs: treatment-related adverse events	

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

As expected for a combination therapy, nivolumab-relatlimab exhibited higher toxicity compared to nivolumab alone, including a higher incidence of severe adverse events related to the drug. However, most adverse events were mild to moderate (grades 1 to 2), and the safety of the combination treatment was considered manageable using established guidelines for adverse event (AE) management and no new safety concerns identified compared to nivolumab alone. [2]

In the RELATIVITY-047 study at data cut off 27 October 2022, any treatment-emergent AE was reported by 99% (352/355) of patients in the nivolumab-relatlimab group and 96% (344/359) in the nivolumab group and these were considered treatment-related in 85% and 73% respectively. In the nivolumab-relatlimab and nivolumab groups respectively, patients reporting a grade 3 or 4 AE were 45% versus 39%, and patients discontinuing therapy due to an AE was 17% versus 8.6%. [6]

There were four treatment-related deaths in the nivolumab-relatlimab group (hemophagocytic lymphohistiocytosis, acute oedema of the lung, pneumonitis, and multi-organ failure) and two in the nivolumab group (sepsis and myocarditis, and worsening pneumonia).[6]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The combination of nivolumab and relatlimab demonstrated superiority over nivolumab alone in terms of PFS by BICR, with a median improvement of 5.5 months, which was considered clinically relevant by regulators, at the final PFS analysis.[2]
- Although median OS was not reached in the nivolumab and relatlimab group, there was a trend for OS benefit compared to nivolumab monotherapy, supported by Kaplan-Meier curves. No detrimental effect was observed. Additionally, confirmed objective response rate (ORR) per

BICR also numerically favoured the combination treatment.

4.2. Key uncertainties

- Direct comparative data against the other relevant comparators, nivolumab plus ipilimumab or pembrolizumab alone are lacking. To address this the submitting company conducted an adjusted ITC and an NMA. Both the adjusted ITC and NMA had limitations, however the company's conclusion from the ITC of no evidence of a difference between nivolumab-relatlimab and nivolumab plus ipilimumab for PFS and OS and a more favourable safety profile for nivolumab-relatlimab seems reasonable. Limitation within the NMA mean that the company's conclusions for the NMA are uncertain and the adjusted ITC analyses are likely to be the more reliable source of comparative data for nivolumab-relatlimab versus nivolumab plus ipilimumab.
- The final OS analysis did not achieve statistical significance. The study is ongoing, and the company submission is based on updated data from a descriptive analysis with a median follow-up of only 25.3 months at which point median OS in the nivolumab-relatlimab group was not reached. There is uncertainty about the longer-term treatment effect of this new treatment on OS. In addition, statistical testing of ORR was not performed due to the hierarchical testing strategy.
- No adolescents were enrolled in the key study, raising uncertainty about efficacy and safety in this population. However, extrapolation of efficacy and safety from adults to adolescents was considered acceptable. [2]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that nivolumab-relatlimab is a therapeutic advancement thanks to improved efficacy when compared with PD-1 inhibitor monotherapy and potential safety benefits compared with the currently available combination immunotherapy (nivolumab plus ipilimumab).

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Melanoma Focus and Melanoma Action and Support Scotland (MASScot). Melanoma Focus is a registered charity and MASScot is a Scottish charitable incorporated organisation.

- Melanoma Focus has received 20% pharmaceutical company funding in the past two years, including from the submitting company. MASScot has not received any pharmaceutical company funding in the past two years.

- Melanoma incidence is related to age, however, unlike most other cancer types, melanoma occurs relatively frequently in younger age groups. Patients are often young adults, frequently with dependent children and elderly relative responsibility. There is a growing population of melanoma patients who are younger in age with the majority of their life ahead of them, many

of them will be living with long-term side effects from their treatment.

- Ipilimumab + nivolumab is standard treatment for patients with no co-morbidities. Some patients suffer side effects from this treatment that can be irreversible and affect quality of life.

- An alternative treatment option with a more favourable toxicity profile, such as nivolumab-relatlimab, would be very much welcomed by the patient community.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (40 years, with an assumed starting age of 61.2)
Population	Adult and adolescent patients over the age of 12 years with previously untreated advanced (metastatic or unresectable) melanoma.
Comparators	Nivolumab-relatlimab was compared with nivolumab monotherapy, nivolumab plus ipilimumab and pembrolizumab monotherapy
Model description	A cohort-based partitioned survival model was used with three health states: progression-free (PF), progressed disease (PD) and death.
Clinical data	Progression-free survival (PFS), overall survival (OS), safety data for nivolumab-relatlimab and nivolumab and patient characteristics were from the RELATIVITY-047 study.[2, 5, 6] Relative clinical efficacy for nivolumab plus ipilimumab was estimated from an adjusted indirect treatment comparison (ITC), and for pembrolizumab this was from a network meta-analysis (NMA).
Extrapolation	Long-term OS and PFS for nivolumab-relatlimab and nivolumab were extrapolated using parametric survival modelling. Curve selection was based on goodness of fit statistics, visual fit, clinical plausibility and external validation of long-term survivorship for patients with advanced melanoma treated with immunotherapies from the CheckMate-067 study.[4, 7] This resulted in the selection of the Gompertz distribution in both the nivolumab-relatlimab and nivolumab arms of the model for OS. The Gompertz distribution was also selected for both treatments for PFS from 3-months; for the first 3-months Kaplan-Meier data was used directly. The respective constant hazard ratios (HRs) from the adjusted ITC were applied to the nivolumab-relatlimab PFS and OS curves for nivolumab plus ipilimumab. The respective constant HRs from the NMA were applied to the nivolumab-relatlimab PFS and OS curves for pembrolizumab. Mortality hazards in the model were restricted to be greater than or equal to the general population mortality hazards at all times.
Quality of life	Utility values were based on EQ-5D-3L data that were collected in the RELATIVITY study, which were age adjusted. Disutilities due to adverse events were taken from published literature.
Costs and resource use	Costs included medicine acquisition and administration, management of adverse events, monitoring and disease management, palliative and end-of-life care costs. Costs of subsequent treatments were included derived from the proportions receiving subsequent treatment observed in RELATIVITY-047 and CheckMate-067. The distribution of each subsequent therapy was informed by clinical expert opinion.

PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for nivolumab, nivolumab plus ipilimumab and pembrolizumab and these were included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The base case analysis, using list prices for all medicines, estimated incremental cost-effectiveness ratios of £89,942, £197,845 and £45,331 for the comparison against nivolumab, nivolumab plus ipilimumab and pembrolizumab respectively.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

To explore areas of uncertainty the company conducted deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analysis. These analyses suggested that economic results were sensitive to alternative survival projection assumptions and choice of treatment in subsequent lines of therapy.

Results cannot be presented here, as the company marked these as commercial in confidence.

6.4. Key strengths

- The model structure was appropriate and consistent with the approach used in the assessment of other oncology treatments.
- Availability of randomised evidence from the RELATIVITY-047 to estimate the relative efficacy of nivolumab-relatlimab compared with nivolumab, which was a relevant comparator.
- Availability of individual patient level data from CheckMate-067 to facilitate an adjusted ITC to estimate the relative efficacy of nivolumab plus ipilimumab with nivolumab-relatlimab.

6.5. Key uncertainties

- Although a trend for OS benefit was observed in the Kaplan-Meier (KM) data from RELATIVITY-047 for nivolumab-relatlimab, median OS was not reached, and the final OS analysis did not achieve statistical significance. Despite this, the company's projections of OS in the economic model assumes a long-term OS benefit over the modelled time horizon. The SMC Committee viewed an OS gain for nivolumab-relatlimab as highly plausible, although the scale of that advantage was uncertain.
- The base case analysis applied the point estimate constant HRs for OS and PFS from the NMA to estimate the relative efficacy of pembrolizumab compared to nivolumab-relatlimab despite the credible intervals from this analysis crossing 1. An alternative approach assuming equal efficacy between nivolumab and pembrolizumab for PFS and OS, and nivolumab and nivolumab-relatlimab for OS, resulted in a much higher cost-effectiveness estimate.

- The distribution of subsequent treatments following first-line nivolumab-relatlimab in routine Scottish clinical practice was uncertain and the estimates of cost-effectiveness were sensitive to alternative assumptions. The company assumed that patients receiving first-line nivolumab-relatlimab were less likely to receive second line ipilimumab monotherapy than patients who received nivolumab or pembrolizumab first-line. The company based this on nivolumab-relatlimab sharing a toxicity profile with nivolumab plus ipilimumab, however this seemed uncertain.

7. Conclusion

After considering all the available evidence, the Committee accepted nivolumab-relatlimab for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published in August 2023 a revised version of the SIGN146 Cutaneous melanoma national clinical guideline first published in January 2017.[10]

The National Institute for Health and Care Excellence published in August 2022 and updated version of its guideline Melanoma: assessment and management [NG14] first in July 2015.[11]

The European Society for Medical Oncology published in 2019: Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up.[12]

9. Additional Information

9.1. Product availability date

27 December 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 4-week cycle (£)
nivolumab, relatlimab	**480 mg nivolumab and 160 mg relatlimab fixed-dose combination every 4 weeks administered as an intravenous infusion**	**12,270**

Costs from Dictionary of Medicines and Devices Browser on 4 June 2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimated there would be 122 patients eligible for treatment with nivolumab-relatlimab in Year 1 rising to 618 patients in Year 5. The uptake rate was estimated to be 15% with 18 patients eligible in Year 1 and 37 patients eligible in Year 5 assuming a discontinuation rate of 33% in Year 3 rising to 60% in Year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 April 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are

therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.