Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2385

nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)

Bristol-Myers Squibb

14 January 2022

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 assessed under the end of life process

nivolumab (Opdivo®) is accepted for use within NHSScotland.

Indication under review: in combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM).

In a phase III study of patients with previously untreated, unresectable MPM, overall survival was significantly longer in the nivolumab plus ipilimumab group compared with standard chemotherapy.

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

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Nivolumab in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM.[1, 2]

Dosing Information

The recommended dose is 360mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is continued for up to 24 months in patients without disease progression.

Atypical responses (an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose adjustment is not recommended. Adverse effects should be managed through dosing delay or discontinuation. Please see individual Summary of Product Characteristics (SPCs) for further information.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[1, 2]

Product availability date

26 July 2021
Nivolumab meets SMC end of life criteria for this indication.
Nivolumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 27 January 2021. The indication was in combination with ipilimumab in the first-line treatment of adult patients with unresectable MPM.

Summary of evidence on comparative efficacy

Nivolumab potentiates T-cell responses, including anti-tumour responses, by binding to programmed death-1 (PD1) receptor and blocking its interaction with programmed cell death ligand 1 (PD-L1) and PD-L2 ligands. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is also a key regulator of T-cell activity. Ipilimumab is a CTLA-4 inhibitor that blocks T-cell inhibitory signals and increases the number of reactive T-effector cells which mobilise to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Nivolumab and ipilimumab have been shown to have synergistic anti-tumour activity (in metastatic melanoma).[1, 2]

Evidence to support the efficacy and safety of nivolumab in combination with ipilimumab for this indication comes from CheckMate 743, a multicentre, randomised, open-label, phase III study that recruited adult patients with untreated histologically confirmed unresectable MPM that was not amenable to treatment with curative intent. Eligible patients had measurable disease in accordance with the modified Response Evaluation Criteria in Solid Tumours (mRECIST) for pleural mesothelioma or RECIST version 1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Prior palliative radiotherapy was permitted provided the course was completed at least 14 days before initiating study treatment with no residual signs of toxicity.[3, 4]

Patients were randomised equally to receive nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks (n=303), or standard of care chemotherapy (n=302) with cisplatin 75mg/m^2 or carboplatin area under the curve (AUC) 5mg/mL/min plus pemetrexed 500mg/m^2 on day 1 of each 21 day cycle, all treatments were administered intravenously. Treatment continued until disease progression or unacceptable toxicity, or for 2 years in the immunotherapy group and six 21-day cycles in the chemotherapy group. Treatment with nivolumab plus ipilimumab was permitted to continue beyond disease progression if the patient had investigator-assessed clinical benefit and was tolerating treatment. Randomisation was stratified according to sex and histology (epithelial or non-epithelial [including sarcomatoid and mixed subtypes]).[3, 4] The primary outcome was overall survival, defined as the time between the date of randomisation and death due to any cause.[3, 4]

At an interim analysis (data cut-off 3 April 2020), after a median follow-up of 29.7 months, the study was stopped for superiority of overall survival and this was considered the final primary analysis. There was a statistically significant improvement in overall survival associated with nivolumab and ipilimumab compared with chemotherapy. However, this was not supported by significant benefits in secondary outcomes including progression-free survival (PFS) and objective response rate (ORR). For patients that responded, a more durable response was observed in the nivolumab plus ipilimumab group. There was no hierarchy in the testing of secondary outcomes and no adjustment for multiplicity therefore outcomes were not formally tested and results are descriptive. Primary and secondary outcome results are presented in Table 1 below.[3, 4]

Table 1: Primary and secondary outcomes from CheckMate 743 in the ITT population (data cut-off 3 April 2020)[3, 4]

	Nivolumab plus ipilimumab (n=303)	**Chemotherapy (n=302)**
Primary outcome: overall survival		
Median follow-up for overall survival	17.4 months	13.3 months
Deaths (n)	200	219
Median overall survival	18.1 months	14.1 months
Hazard ratio (96.6% CI)	0.74 (0.60 to 0.91) p=0.002	
KM estimated overall survival at 12 months	68%	58%
KM estimated overall survival at 24 months	41%	27%
Secondary outcome: PFS by blinded independent central review per RECIST criteria[A, B]		
PFS Events (n)	218	209
Median PFS	6.8 months	7.2 months

Hazard ratio (95% CI)	1.0 (0.82 to 1.21)	
KM estimated PFS at 12 months	30%	24%
KM estimated PFS at 24 months	16%	7.2%
Secondary outcome: ORR by blinded independent central review per RECIST criteria[A, B]		
ORR, %(n/N)	40% (120/303)	43% (129/302)
Complete response	1.7%	0%
Partial response	38%	43%

CI=confidence interval, ITT=intention to treat, KM=Kaplan-Meier, ORR=objective response rate, , PFS=progression-free survival, RECIST=Response Evaluation Criteria in Solid Tumours. [A] Radiographic tumour assessments per mRECIST for pleural lesions and RECIST (version 1.1) for the other lesions. [B] Descriptive results as no control for multiplicity.

Analysis of pre-specified subgroups for overall survival were generally consistent with the primary analysis with the exception of some small subgroups; age ≥75 years, stage I disease, and stage II disease which favoured the chemotherapy group.[3, 4]

Results from a more recent data cut-off (May 2021) with a minimum follow-up of 35.5months were consistent with the previous analysis.[5]

Health Related Quality of Life (HRQoL) was assessed using the Lung Cancer Symptom Scale–Mesothelioma (LCSS-Meso) Average Symptom Burden Index (ASBI), LCSS-Meso 3-Item Global Index (3-IGI) and EQ-5D-3L utility index and visual analogue scale (VAS). These instruments were used at baseline, every six weeks for 12 months, then every 12 weeks until study discontinuation. A post treatment assessment was also conducted. In general, patients in the nivolumab plus ipilimumab group experienced stable or improved scores compared with patients in the chemotherapy group whose scores remained stable or deteriorated.[6]

Summary of evidence on comparative safety

Overall, the safety profile of nivolumab plus ipilimumab was consistent with that previously observed for other indications and in line with the already known safety profile of each component. Compared with previous studies in different tumour types, a higher frequency of hypersensitivity and infusion reactions were reported in CheckMate 743. The immunotherapy combination appears less well tolerated than chemotherapy due to the high incidence of adverse events.[4]

Safety data to support this indication is from CheckMate 743, the posology of nivolumab used in this study (3mg/kg every 2 weeks) is different to the fixed dosing regimen that is detailed in the SPC (360mg every 3 weeks). In CheckMate 743, the median duration of treatment in the nivolumab plus ipilimumab group was 5.6 months and in the chemotherapy group was 3.5 months. Any treatment-emergent adverse event (AE) was reported by 99.7% (299/300) of patients in the nivolumab plus ipilimumab group and 98% (277/284) in the chemotherapy group and these were considered treatment-related in 80% and 82% respectively. In each group respectively, patients reporting a grade 3 or higher AE were 53% versus 43%, patients with a reported serious AE were 55% versus 25% and patients discontinuing therapy due to an AE were 29% versus 20%.[4]

Immunotherapies such as nivolumab and ipilimumab have characteristically high incidences of immune-related AEs compared with chemotherapy whose safety profile is characterised by bone marrow suppression. The most frequently reported immune-related AEs were rash (13%), hypothyroidism or thyroiditis (12%), diarrhoea or colitis (8.7%) and pneumonitis (6.7%) in the nivolumab plus ipilimumab group. Most were considered manageable and resolved with immune-modulating medications (mainly systemic corticosteroids). However, some patients with endocrine immune-related AEs required ongoing hormone replacement treatment. Other events of special interest were reported by 4.7% in the immunotherapy group and over half were considered grade 3 or 4 in severity, these included pancreatitis, encephalitis, myositis, myasthenic syndrome, uveitis and myocarditis. There were three treatment-related deaths in the immunotherapy group caused by pneumonitis, encephalitis and heart failure. There was one treatment-related death in the chemotherapy group due to myelosuppression.[3, 4]

Summary of clinical effectiveness issues

Malignant pleural mesothelioma is a highly aggressive cancer of the pleural membrane with the primary risk factor being occupational exposure to asbestos. Diagnosis usually occurs at an advanced stage as symptoms are non-specific and can include shortness of breath, pain and weight loss. Patients generally have a poor prognosis and less than 10% live beyond 5 years. There are three main histological subtypes: epithelioid, sarcomatoid and mixed-type; the poorest prognosis is in non-epithelioid subtypes. The recommended first-line systemic treatment is chemotherapy with cisplatin in combination with pemetrexed; carboplatin may be used as an alternative for patients unable to tolerate cisplatin. Clinical trials should be considered for patients with a good performance status and are recommended above second-line treatments. Surgery is generally limited to patients with stage I to III disease and most are not suitable for surgical cure. Radiotherapy may be used for palliative symptom relief.[4, 7, 8] Nivolumab in combination with ipilimumab is the first immunotherapy licensed for the treatment of MPM. Clinical experts consulted by SMC considered that nivolumab plus ipilimumab fills an unmet need for the first-line treatment of patients with unresectable MPM. Nivolumab plus ipilimumab meets SMC end of life criteria for this indication.

In CheckMate 743, treatment with nivolumab plus ipilimumab demonstrated a statistically significant improvement in overall survival of 4 months compared with chemotherapy in patients with unresectable MPM; this was considered clinically relevant by the EMA. The overall survival benefit was not supported by benefits in secondary outcomes including PFS and ORR. Subgroup analyses of the primary outcome were generally consistent with the primary analysis, a survival benefit was observed in the immunotherapy group regardless of histology and the treatment effect was larger in the non-epithelioid subtype, which is usually associated with poorer responses to chemotherapy. [3, 4]

The dose of nivolumab received by patients in CheckMate743 (3mg/kg every 2 weeks) is different from the licensed dose for MPM in the SPC (360mg every 3 weeks). The EMA considered this acceptable based on pharmacokinetic and pharmacodynamic data provided by the submitting

company. CheckMate 743 had an open label study design because of differences between immunotherapy and chemotherapy infusion regimens and toxicity profiles; this could potentially introduce assessment bias for subjective efficacy, HRQoL and safety outcomes. This risk was mitigated for subjective efficacy outcomes as assessment was conducted by blinded independent central review. Following a change to the study protocol, PFS was removed as a co-primary outcome as the extensive nature of MPM makes tumour measurements challenging and is imprecise for the measurement of clinical benefit; the hierarchical testing strategy of secondary outcomes was also removed and therefore results are descriptive only.[3, 4]

There are limited data for patients aged ≥75 years and no information for patients with an ECOG performance status of 2. CheckMate 743 did not compare dual immunotherapy with nivolumab or ipilimumab monotherapy; evidence for the additive efficacy is based on cross study comparisons in patients with previously treated MPM. Chemotherapy with cisplatin or carboplatin in combination with pemetrexed is an appropriate comparator as this is first-line standard of care in Scottish clinical practice and is recommended by clinical guidelines. In Checkmate 743, the majority (about two thirds) of patients in the chemotherapy group received carboplatin and the rest received cisplatin. Cisplatin is generally more toxic than carboplatin and, in contrast to carboplatin, is licensed for this disease.[3, 4]

Clinical experts consulted by SMC considered that combination immunotherapy with nivolumab and ipilimumab represented a therapeutic advancement due to significant improvements in overall survival demonstrated in CheckMate 743. They considered it would be used according to the licensed indication and is likely to replace chemotherapy for suitable patients as first-line treatment in unresectable MPM. The introduction of nivolumab plus ipilimumab for this indication would have an impact on the service and patient, as the duration of treatment with immunotherapy is longer compared with standard chemotherapy. Additional oncology clinics, chemotherapy day-unit capacity, and pharmacy input will be required. Close monitoring and management of immune-mediated AEs will be necessary. Patients would also be required to attend regular hospital appointments for administration, monitoring and follow-up.

Patient and Clinician Engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of nivolumab, as an end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Malignant pleural mesothelioma (MPM) is a highly aggressive cancer caused by occupational or environmental exposure to asbestos. Due to the historic use of asbestos in heavy industry and building, areas of Scotland currently have the highest incidence of mesothelioma in the world.

- Most patients with MPM currently die within 1 year. The disease is characterised by a high symptom burden, particularly intractable pain and breathlessness. A diagnosis of mesothelioma is devastating for patients and their family.
- The physical and psychosocial impact of living with MPM includes significant fatigue, pain, breathlessness, cough, anxiety, grief, anger, antagonism and /or feelings of helplessness.
- The benefits of standard chemotherapy with platinum plus pemetrexed are modest and approximately half of eligible patients choose not to proceed with treatment suggesting a great unmet need for alternative effective therapies.
- Nivolumab plus ipilimumab is the first immunotherapy licensed for the treatment of MPM. Results from the CheckMate 743 study demonstrated that nivolumab plus ipilumumab extended overall survival compared with chemotherapy. This survival benefit was observed regardless of histology and the treatment effect was larger in the non-epithelioid subtype, which is usually associated with poorer responses to chemotherapy.
- The study indicated that when a response is achieved the duration of response with immunotherapy is longer. By having a prolonged response to treatment the pain associated with advanced disease may be diminished. These favourable effects may improve quality of life by allowing patients to focus on post cancer wellbeing and fitness, spend more time with family and friends, maintain independence and participate in social events. Some patients may be able to continue a normal life and in particular, younger patients may be able to go back to work.
- MPM affects a diverse range of patients. This is the first drug therapy for over 10 years that has demonstrated an improvement in survival over standard chemotherapy.

Additional Patient and Carer Involvement

We received patient group submissions from Action on Asbestos, June Hancock Mesothelioma Research Fund (JHMRF) and Mesothelioma UK. Action on Asbestos is a Scottish charitable incorporated organisation, JHMRF is a registered charity and Mesothelioma UK is a charitable incorporated organisation. Action on Asbestos has not received any pharmaceutical company funding in the past two years. JHMRF has not received any pharmaceutical company funding in the past two years. Mesothelioma UK has received 1.11% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

A cost-utility analysis was presented evaluating the combination of nivolumab and ipilimumab for the first-line treatment of adult patients with unresectable MPM. Comparison was made against pemetrexed and cisplatin or carboplatin (PDC). Based upon clinical expert input received by SMC, PDC appears to be the appropriate comparator.

A standard three-state portioned survival model was used to represent the progression free (PF), progressed disease and dead health states. The model structure allowed for the separate modelling of treatment duration in the PF health state, as well as representing one subsequent treatment line upon progression. A twenty-year time horizon was used and a one-week cycle length applied.

Clinical effectiveness data, in terms of progression-free and overall survival, were derived from the CheckMate-743 study.[3] As the proportional hazards assumption did not appear to hold, a range of standard and spline-based parametric models were independently fitted to the data for the separate study arms. The submitting company assessed each model in terms of visual and statistical fit with the observed data, as well as clinical plausibility in terms of alignment with a previous randomised study of pemetrexed and cisplatin, and consideration of the hazard profiles.[9] Based upon these considerations, the submitting company selected a piecewise log-logistic function for nivolumab plus ipilimumab, and a piecewise exponential model for PDC (using Kaplan-Meier data to month 22 in both cases). A similar approach was used for the extrapolation of PFS, albeit only fitting standard parametric functions, which required limited extrapolation due to the maturity of these data. A lifetime treatment effect was assumed for nivolumab and ipilimumab, which the submitting company states is justified based upon more mature data from other tumour types.

EQ-5D data were collected in the CheckMate-743 study and valued according to UK societal preferences. Regression analysis was used to derive pooled and treatment-specific utility weights for the PF and PD health states; the submitting company reported that there was a statistically significant difference in utility values between treatments. Therefore, utilities of 0.74 (nivolumab plus ipilimumab) and 0.73 (PDC) were used in the PF health state, and 0.65 and 0.58 in the PD state, for the respective treatment regimens. Disutilities due to common grade 3 and 4 adverse events were also applied.

Medicines costs included the acquisition costs of the two treatment regimens, as well as subsequent treatment comprising immunotherapies, anti-VEGF treatment and chemotherapies (based upon the distribution of treatments within the CheckMate-743 study). Mean number of doses of each first-line treatment was calculated from the study data, while treatment duration with subsequent treatments was assumed to be 1.7 months based upon a median value reported from a US observational study.[10] Treatment-specific administration and monitoring costs were included, as were routine healthcare requirements such as outpatient consultations, biochemistry and palliative care.

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 scheme, a PAS was applied to the nivolumab list price, in addition to a simple discount on the ipilimumab list price.

The base case results with both PAS applied resulted in incremental costs per QALY gained (ICER) of 71,408 £/QALY. The majority of QALY gains were derived from the estimated extension to life, alongside a small gain from the treatment-specific utilities and delay in disease progression. Incremental costs were largely driven by the additional medicine acquisition costs, although the extended duration of routine healthcare requirements also contributed to a lesser extent.

A number of scenario and sensitivity analyses were presented, with the key analyses shown in the table below.

Table 2: Key scenario analyses, with PAS

#	Category	Scenario setting	Base case setting	Incremental costs (£/QALY)
Base case				71,408
1.	OS extrapolation (PDC)	Spline on odds (1 knot)	Piecewise extrapolation (Kaplan-Meier and exponential)	77,878
2.	OS extrapolation (nivolumab plus ipilimumab)	Spline on probit link of survival (1 knot)	Log-logistic	100,163
3.	PFS (nivolumab plus ipilimumab)	Log-normal	Generalised gamma	75,130
4.	Utilities	Treatment-independent utilities	Treatment-dependent utilities	79,278
5.	Utilities	Standard age-adjustment performed	No age-adjustment performed	75,087
6.	Treatment duration	Time to treatment discontinuation data (by treatment)	Use of mean observed doses	74,632
7.	Medicines acquisition	Lowest cost formulation from BNF	Higher-priced generic formulations used	73,602
8.	Outpatient consultation costs	Outpatient costs using NHS reference costs	Outpatient costs using Scottish Costs Book (includes pharmacy dispensing costs)	55,242

9.	Combined analysis A (company-preferred survival estimates)	Combined use of scenarios 4, 5, 6, 7, 8	As base case	71,035
10.	Combined analysis B (alternative plausible survival estimates)	Combined use of scenario 9, plus alternative plausible OS distributions (scenarios 1 and 2)	As base case	131,703

Abbreviations: QALY: quality-adjusted life year, PDC: pemetrexed plus cisplatin or carboplatin, OS: overall survival, PFS: progression-free survival.

The analysis was associated with a number of limitations:

- As acknowledged by the submitting company, there is inherent uncertainty associated with the long-term extrapolation of survival estimates. The selected base case estimates, although representing one plausible combination of outcomes, appear to be at the more optimistic end of the scale when compared with other equally plausible combinations. While the PDC arm is only moderately sensitive to the use of alternative plausible distributions, the nivolumab plus ipilimumab arm is more sensitive to the use of alternative plausible models (Table 2, Scenarios 1 & 2).
- The use of treatment-specific utilities for the duration of the PD state implies an ongoing and indefinite treatment effect despite discontinuation of nivolumab + ipilimumab. It may be more appropriate to assume that this effect will wane, particularly for patients who receive subsequent treatment with chemotherapy and associated adverse events. This would likely result in a reduced QALY gain overall and lead to an increase in the ICER, although potentially to a lesser extent than if utilities were assumed equivalent in the PD health state (as shown in Table 2, Scenario 4).
- Age-adjustment of utilities has not been performed in the base case, despite extensive extrapolation beyond the trial data collection phase. It is more appropriate to include age-adjustment in this case, which leads to an increase in the ICER (Table 2, Scenario 5).
- The use of mean number of doses received in the CheckMate-743 study may not be appropriate. This assumes that this will apply to the Scottish healthcare setting, which may not be the case. In addition, this approach does not account for the likely causes of missed doses, which might relate to discontinuation due to adverse events or disease progression. Therefore the use of treatment discontinuation data as observed within the CheckMate-743 study provides a more reliable source for estimating total costs of treatment. As a result of the approach used in the base case, the total costs of treatment with nivolumab and ipilimumab have potentially been underestimated (Table 2, Scenario 6).
- The selection of unit costs for many generic medicines, including those in the PDC regimen, appears to use the highest cost versions available. It is more likely that the cheapest generic formulation will be used in practice, and therefore the base case approach is overestimates the costs of the comparator, with use of the lowest cost alternatives leading to a slightly increased ICER (Table 2, Scenario 7).

- The costs of treatment-related monitoring visits and general disease-state related outpatient consultations was overestimated in the original base case analyses, by including pharmacy dispensing costs. In this case, this error led the base case ICER to be overestimated as patients treated with nivolumab and ipilimumab will attend more routine outpatient consultations over the course of their lifetimes. The use of an equivalent cost of outpatient consultations from NHS Reference costs resulted in a significantly lower ICER (Table 2, Scenario 8).
- The combination of scenarios accounting for the above limitations results in an ICER consistent with the base case (Table 2, Scenario 9), until alternative OS extrapolations are considered (Table 2, Scenario 10). Therefore the cost-effectiveness of nivolumab + ipilimumab in this indication is predominantly influenced by the extrapolation of survival over the longer-term.

The Committee also considered the benefits of nivolumab plus ipilimumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted nivolumab plus ipilimumab for use in NHSScotland.

Additional information: guidelines and protocols

In 2018 the British Thoracic Society published 'British Thoracic Society Guideline for the investigation and management of Malignant Pleural Mesothelioma'. The following recommendations were made:

- Offer patients with malignant pleural mesothelioma with good performance status (WHO 0–1) first line therapy with cisplatin and pemetrexed.
- Where licensed (not presently in the UK), bevacizumab should be added to this regime. Raltitrexed is an alternative to pemetrexed.
- Where cisplatin is contraindicated, or has adverse risk, offer carboplatin in combination with pemetrexed.
- First-line clinical trials are an appropriate option for patients with good performance status and are recommended above any other option for second-line treatment, provided the patient is of adequate PS.[8]

In 2015 the European Society for Medical Oncology (ESMO) published guidelines: MPM: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. The following recommendations were made:

- Front-line chemotherapy improves survival of patients with unresectable MPM.
- Combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed, has shown a longer survival compared with cisplatin alone in randomised phase III trials,

- Carboplatin is an acceptable alternative to cisplatin and may be better tolerated in the elderly population.
- There is currently no second-line standard of care.
- In the absence of standard second-line or further line therapy, it is recommended that patients are enrolled into clinical trials.[7]

Additional information: comparators

Cisplatin or carboplatin in combination with pemetrexed.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 6-week cycle (£)
Nivolumab Ipilimumab	360mg administered IV every 3 weeks 1mg/kg administered IV every 6 weeks Maximum duration for both treatments is 24 months	15, 838

Costs from BNF online on 4 August 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Dosing based on a 70kg patient. Costs do not take patient access schemes into consideration.

Additional information: budget impact

With PAS

The submitting company estimated there would be 56 patients eligible for treatment with nivolumab and ipilimumab in each year. The estimated uptake rate was 90% assumed each year. This resulted in 50 patients treated each year in years 1 – 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.

*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 17 October 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.