National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG106 Nivolumab | Advice Document v1.0 | October 2023

Pleural or peritoneal mesothelioma; second or subsequent line in patients whose disease has progressed on or after platinum-based chemotherapy [A]

NCMAG Decision | This off-label use of nivolumab is supported

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for nivolumab in the proposed population. After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	Clinicians treating mesothelioma tumour groups from across NHSScotland regional cancer networks
Medicine Name	Nivolumab
Cancer type	Malignant pleural and peritoneal mesothelioma
Proposed off-label[B] use	Pleural or peritoneal mesothelioma; second or subsequent line in patients whose disease has progressed on or after platinum-based chemotherapy
Medicine Details	Form: Concentrate for solution for infusion

	Dose: Intravenous infusion, 240mg every 2 weeks, 360mg every 3 weeks or 480mg every 4 weeks. Treatment should continue for one year or until unacceptable toxicity.
Proposed advice eligibility criteria	• progression on or after platinum-based chemotherapy • no prior immunotherapy treatment • no limit to number of lines of prior therapy • Performance status 0 to 1 and expected survival at least 12 weeks. • exclusions: uncontrolled CNS metastases and active autoimmune disease

[B] Nivolumab currently has 14 on-label indications either as monotherapy or in combination ipilumumab or with chemotherapy.[1]

1. Current Management Context

Malignant mesothelioma incidence, prognosis and symptoms

Malignant mesothelioma is a cancer that primarily originates in the pleura (95% of cases) and peritoneum (4% of cases) but can also affect the heart, vagina and testes. It is associated with asbestos exposure, which causes chronic inflammation and DNA damage, leading to cancer, often decades later. In England and Wales, the mean age at the time of diagnosis for malignant pleural mesothelioma (MPM) and for malignant peritoneal mesothelioma (MPeM) is approximately 76 and 71 years of age, respectively.[2] In 2017, Scotland recorded 194 pleural mesothelioma diagnoses, with around 50 patients receiving first-line anti-cancer treatment annually.[3] MPeM incidence is lower, no specific data for Scotland is readily available, there were 105 UK cases between 2016 and 2018.[4]

Prognosis is poor, with 40% of MPM patients in England and Wales alive at one year after diagnosis and only 10% alive at three years.[3] Peritoneal mesothelioma patients have better long term survival rates with 40% alive at one year and 18% alive at three years. Furthermore, peritoneal mesothelioma patients who undergo cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have a longer median overall survival from initial diagnosis, ranging from 34 to 92 months.[5] The benefit of surgery in pleural mesothelioma is less certain.[6] Of the three main histological subtypes of MPM (epithelioid, sarcomatoid, and biphasic), the epithelioid subtype is associated with the best prognosis.

Symptoms of pleural mesothelioma, include breathlessness, haemoptysis, chest pain, fatigue, cough and weight loss. Symptoms of peritoneal mesothelioma include abdominal pain and swelling, nausea, poor appetite, fatigue, weight loss and diarrhoea or constipation.

National and international context for the proposed off-label use

The first-line treatment options for MPM include nivolumab and ipilimumab or cisplatin and pemetrexed. Nivolumab and ipilimumab were accepted for use by the SMC in February 2022.[7] Nivolumab and ipilimumab is the preferred first-line treatment, particularly for non-epithelioid histology. Patients who receive nivolumab and ipilimumab as first-line treatment for MPM would not normally receive further immunotherapy in the second-line or beyond setting. As a result, the number of patients eligible for nivolumab in the relapsed setting is likely to decrease.

There are no standard, routinely available second-line treatment options for pleural mesothelioma, with variation in what is accessible in Scotland and different chemotherapy regimens being chosen. Re-treatment with a pemetrexed-platinum doublet, if a patient has had good disease control from first line use, is also an option. European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) support the use of off-label immunotherapy, including nivolumab, if chemotherapy was used in the first line setting .[8, 9 10] Best supportive care should be offered to patients with a poor performance status.

Japan has licensed nivolumab for the treatment of MPM that has progressed after chemotherapy.[11] Nivolumab is available via The Cancer Drug Fund in England to the cohort of patients who received chemotherapy prior to first line nivolumab and ipilimumab becoming available in June 2022.[12]

Pharmacology of nivolumab

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor on T-cells. When PD-1 binds to the PD-L1 receptor on cancer cells, it inhibits immune T-cell function. By preventing this binding, nivolumab activates the immune system's ability to detect and destroy cancer cells.[13]

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including Medline and Embase. The main search concepts were nivolumab and mesothelioma. No filters were applied to limit the retrieval by study type. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key research study was critically appraised using the Cochrane risk of bias version 2.0 tool.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Evidence comparing nivolumab with placebo

The key trial supporting this proposal of using nivolumab in patients with relapsed malignant mesothelioma is the CONFIRM study.[14] The CONFIRM study was a phase lll double-blind, multicentre, randomised controlled trial which compared nivolumab with placebo in patients with malignant pleural or peritoneal mesothelioma who had radiological evidence of disease progression after at least one course of platinum-based chemotherapy. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and measurable disease according to modified Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST version 1.1 were included. In the study, 332 patients were randomly assigned to receive either nivolumab (n=221) or placebo (n=111); stratified by epithelioid versus non-epithelioid histology. The co-primary outcomes were investigator assessed progression-free survival (PFS) (defined as the time from randomisation to disease progression or death, whichever occurred first) and overall survival (defined as the time from randomisation to death of any cause). The co-primary endpoints were monitored every 3 months following discontinuation of treatment. Secondary outcomes included the following - overall response to treatment (defined as either complete or partial response as assessed by a blinded investigator), stable disease or progressive disease, 1-year overall survival and 1-year PFS, and safety. Efficacy according to tumour PD-L1 tumour proportion score was also investigated.

Results from the CONFIRM study

At the preliminary data cut-off, January 2021, the median duration of follow-up was 11.6 months (Interquartile range [IQR] 7.2 to 16.8 months). The median age of patients was 70 years with the majority male (76%), previously exposed to asbestos (69%), an epithelioid subtype (88%) and 34% of patients had a tumour PDL-1 proportion score of at least >1% (a predictive biomarker). Nearly one third of patients received nivolumab as their second-line treatment and more than half of the patients received nivolumab as their third-line treatment. The median time since mesothelioma diagnosis in the nivolumab group was 17.8 months (IQR 11.7 to 27.4 months) and 17.7 months (IQR 10.9 to 25.7 months) in the placebo group. Progression-free survival data were mature after 299 events; overall survival data were immature, as 210 events had occurred out of a planned 291. Investigator-assessed PFS and median overall survival improved with nivolumab compared with placebo (see Table 1).

Table 1 | Results for CONFIRM primary and secondary outcomes[14]

	Nivolumab (n=221)	Placebo group (n=111)
Co-primary outcome: Overall survival		
Overall deaths, %	134 (61)	76 (68)
Median overall survival, months (95%CI)	10.2 (8.5-12.1)	6.9 (5.0-8.0)
Adjusted hazard ratio (95%CI)	0.69 (0.52-0.91)	
Co-primary outcome: Investigator-assessed PFS		
PFS events, %	198 (90)	101 (91)
Median PFS, months (95%CI)	3.0 (2.8-4.1)	1.8 (1.4-2.6)
Adjusted hazard ratio (95%CI)	0.67 (0.53-0.85)	
Secondary outcomes		
Progression-free survival at 1 year, % (95%CI)	14.2 (9.9-19.3)	7.2 (3.1-13.8)
Overall survival at 1 year, % (95%CI)	43.4 (36.3-50.4)	30.1 (21.0-39.6)
Progressive disease (%)	51 (23)	46 (41)
Stable disease (%)	117 (53)	54 (49)
Overall response (%)	25 (11)	1 (1)

PFS: progression-free survival; CI: confidence interval

Tumour PD-L1 expression

The prespecified sensitivity analyses to assess the predictive ability of PD-L1 expression, using the patient group who had quantifiable PD-L1 expression tissue samples (n=252 [76%]), revealed no evidence of PD-L1 expression being predictive of response to treatment for either PFS or overall survival.

Other evidence sources

Five non-comparative studies were identified which had the aim to evaluate the efficacy of nivolumab in patients with MPM. Two were retrospective cohort studies,[15, 16] two were phase II single-arm trials[17, 18] and one was a prospective cohort study.[19] The number of patients included ranged from 34 to 109 and the majority of patients included in each of the studies were administered nivolumab as a second line therapy (range: 51% to 97%). An overview of the results of these studies are in Table 2.

Table 2 | Summary of non-comparative studies and results[15-20]

Study name, year Country (design)	2nd line (%)	ECOG PS (%)[a*]	Follow-up (months)	Objective response rate[a] n (%)	Median PFS, months (95%CI)	Median overall survival, months (95%CI)
Assie et al 2022[15] France (n=109) Prospective cohort	51	0/1 (83%)	21.1	15.6	3.8 (3.2 to 5.9)	12.8 (9.2 to 16.4)
Cantini et al 2020[16] The Netherland (n=107) Retrospective cohort	97	0 (19%) 1 (64%)	10.1	10	2.3 (1.6 to 2.9)	6.7 (6.2 to 10.0)
Fujimoto et al 2021 (MERIT)[17] Japan (n=34) Phase II trial	71	0 (38%) 1 (62%)	16.8	29.4	5.9 (not reported)	17.3 (11.5 to 26.6)
Nakamura et al 2020[19] Japan (n=35) Prospective cohort	40	0 (31%) 1 (60%)	6	20	4.4 (not reported)	13.1 (not reported)
Quispel-Janssen et al 2018 (NIVOMES)[18] The Netherlands (n=34) Phase II trial	97	0 (53%) 1 (47%)[b]	27.5	26	2.6 (2.2 to 5.5)	11.8 (9.7 to 15.7)

ECOG PS - Eastern Cooperative Oncology Group Performance Status
[a]Response to treatment was evaluated according to the modified RECIST criteria.
[b]PS was measured using the WHO classification system.
*PS in Assie et al and Cantini et al studies is unknown in 4% and 12% of patients, respectively. A PS of 2 was reported for 13%, 5% and 9% of patients in the Assie, Cantini and Nakamura studies.

In addition, a systematic review and network meta-analysis (NMA) was identified which compared the benefits of various second line treatments in patients with relapsed MPM in terms of PFS and overall survival.[21] However, on full review the study was not considered relevant in terms of the comparisons used in the analysis so has not been presented here.

Patient-reported outcomes

Quality of life (QoL) was included as a secondary outcome in the CONFIRM study, however, results have not been reported separately. Quality of life data were collected using the EuroQOL visual analog scale and the Lung Cancer Symptom Scale Meso symptom burden scale in the MERIT study. Although results indicated that there were no changes in QoL over time this needs to be interpreted with caution given the open-label and single-arm design of this study.

Safety evidence

Based on data from the CONFIRM trial, in the nivolumab and placebo groups respectively, the proportion of patients reporting a grade 3 or higher adverse event (AE) was 19% versus 6.3%; no grade 5 AEs were reported. The most frequently reported grade 3 treatment-related AEs were diarrhoea (3% versus 2% in the nivolumab and placebo groups, respectively) and infusion-related reaction (3% versus none). Serious adverse events (SAEs) were reported for 41% patients in the nivolumab group and 44% of patients in the placebo group. A SAE is any untoward medical occurrence that results in death or is considered life-threatening.[22] The most common SAEs for the

nivolumab and placebo groups respectively were: dyspnoea (8% versus 9%); pneumonia (6% versus 5%); and lower respiratory tract infection (4% versus 7%). In the nivolumab and placebo groups respectively, patients' treatment was discontinued due to toxicity in 14% versus 3% and delayed at least once in 44% versus 33%. Patient deaths due to SAEs were 5% versus 6% for nivolumab and placebo respectively, with respiratory disorders being the most common cause of death in both groups.

Quality assessment of clinical evidence

The CONFIRM trial was considered to be well-designed and, overall, was assessed as low risk of bias. Randomisation was conducted using a web-based system with patients and investigators blind to treatment allocation. Progression-free survival was added as a co-primary outcome during the study due to concerns that immunotherapy may be used following progression in the placebo group, posing risk of bias to the overall survival outcome. After study unblinding, 12 patients (11%) in the placebo group were reported to receive nivolumab on progression. The use of investigator-reported PFS was considered by the study team to be a relevant measure of PFS and forms the basis of the early PFS results in the absence of independent centrally assessed outcome data. It is acknowledged that assessment of PFS in mesothelioma is challenging and central validation of findings using mRECIST criteria is optimal. Quality of life data and cost per quality-adjusted life year (QALY) data are expected to be reported separately so is not considered as an outcome selection bias.

Clinical effectiveness considerations

The use of nivolumab significantly improved overall survival with a modest benefit in PFS

Based on the preliminary analysis, the CONFIRM study showed a 3.3 month improvement in median overall survival compared to placebo in a heavily pre-treated population. The overall survival data were immature at the time of the preliminary analysis. Overall survival is a robust marker of efficacy which is particularly the case for immunotherapy regimens.[23] Thirty-five per cent of patients received subsequent therapy in both the placebo and nivolumab arms, with 11% of patients in the placebo arm receiving nivolumab. It is uncertain if this confounded overall survival.

Improvement in PFS was modest at 1.2 months. As a double-blind trial with two weekly investigator assessed CT scans, the PFS outcome is robust. However, it is recognised that objective assessment of response and progression is challenging in malignant mesothelioma.

Non-comparative evidence from the phase II trials, MERIT and NIVOMES, suggests similar nivolumab efficacy to the CONFIRM trial.

Retrospective, real-world studies mostly found similar response and overall survival rates. Cantini's studies reported lower PFS and overall survival rates, which may be due to the inclusion of patients with an ECOG performance status (PS) of 2 and poor survival in patients who did not achieve at least a partial response.[16]

CONFIRM results are likely generalisable to the NHS Scotland population who have not received first line doublet immunotherapy

The CONFIRM study was a UK based multi-centre trial, with patients recruited between May 2017 and March 2020. Median age and ECOG PS were similar between the CONFIRM study and the NHS Scotland population (included from January 2014 to December 2020), based on data obtained from the Scottish Cancer Medicines Outcomes Programme (CMOP); 70 years old versus 71 years and 20% with a ECOG PS of 0 versus 22% with a ECOG PS of 0, respectively. The first-line chemotherapy regimens used before patients entered the CONFIRM trial were similar to those used in NHS Scotland. In the CONFIRM trial, there was an approximately even split between the use of carboplatin and cisplatin, both in combination with pemetrexed. The CMOP data showed there was an approximate 60/40% split between carboplatin and cisplatin, respectively, when used in combination with pemetrexed in the NHS Scotland population. [14, 24]

There is some uncertainty regarding efficacy of therapies in the second-line and beyond setting

There is no standard second-line treatment, however chemotherapy may be used in some cases based on individual requests. As the COMFIRM study compared nivolumab to placebo, it is uncertain how nivolumab compares to chemotherapy. There is limited evidence of second line and beyond therapies providing overall survival benefit in MPM including chemotherapy, targeted therapies and immunotherapies.[25]

Patients with peritoneal mesothelioma represented 5% of the CONFIRM population and relative outcomes in this group alone are uncertain.

Immunotherapy is not routinely available in either the first line or subsequent line for MPeM. The CONFIRM study enrolled patients with MPeM, who are recognised to have better prognosis and treatment options compared to patients with MPM. The study was balanced between the two arms for MPeM. However, the CONFIRM trial did not provide specific efficacy or safety data for the MPeM group. No real-world data were identified for patients treated with nivolumab for MPeM.

Nivolumab was administered every 2 weeks until disease progression, no longer tolerated or for a maximum of 12 months in CONFIRM.

The licensed duration for nivolumab in combination with ipilimumab for the first line treatment of MPM is two years. Treatment duration in the CONFIRM study was up to one year, with 6% of patients completing treatment. The efficacy and safety of extending treatment beyond one year for patients experiencing clinical benefit remains unclear in this group of patients.

The proposal is for either 2-weekly, 3-weekly, or 4-weekly administration of nivolumab. While nivolumab was administered 2-weekly in the CONFIRM trial, data from other tumour types suggests there are no clinically significant differences between these treatment schedules. From a service capacity perspective, 4 weekly administration would be the preferred regimen. [1]

Nivolumab was well tolerated with low rates of grade 3 or worse immune mediated adverse reactions.

There were no treatment-related deaths in the nivolumab arm. The most frequently reported immune-related treatment-related adverse events of any grade were gastrointestinal (34% of patients in the nivolumab group compared to 26%) and skin (23% in the nivolumab group compared to 13% in the placebo group). Grade 3 or worse immune-mediated adverse events in the nivolumab arm included cardiac dysfunction, hypothyroidism, colitis, diarrhoea, hepatitis, myositis, and pneumonitis. These adverse reactions occurred at a low frequency of around 1-3 %.

4. Patient Group Statement Summary

We received one statement from Mesothelioma UK. In summary, the patient group partner outlined that mesothelioma is a rare and aggressive cancer with poor prognosis and a current overall median survival of around 12 months. The group highlighted that prior to the CONFIRM study no phase III trial had shown overall survival improvement at this stage in therapy. The patient group believed that nivolumab would offer evidence-based life extending treatment and hope to those affected by mesothelioma. In relation to the potential harms of nivolumab it was acknowledged that while the majority of CONFIRM study participants had at least one side effect these were considered mild.

5. Benefit-Risk Balance

A phase III trial comparing nivolumab to placebo showed a statistically significant improvement in overall survival by 3.3 months and progression-free survival by 1.2 months. Overall survival at 1 year was 43·4% (95% CI 36·3 to50·4) in the nivolumab group versus 30·1% (95% CI 21·039·6) in the placebo group. There are no standard treatment options for MPM and MPeM in the second line or later settings. There were no unexpected rates of side effects, including pneumonitis, in the nivolumab arm, and there were no treatment-related deaths. The evidence is likely generalisable to the proposed Scottish population. See below for comparative efficacy and safety of nivolumab from the CONFIRM trial.

Table 3 | Comparative effects table

Effect	Description	Unit	Nivolumab	Placebo	Uncertainties/ Strength of Evidence
Median OS	Time from randomisation to the date of death of any course	months (95% CI)	10.2 (8.5-12.1)	6.9 (5.0-8.0)	0.69 (95% CI 0.52-0.91)
Median PFS	Time from randomisation to the date of death of any course PFS measured by mRECIST	months (95% CI)	3.0 (2.8-4.1)	1.8 (1.4-2.6)	0.67 (95% CI 0.53-0.85)

Effect	Description	Unit	Nivolumab	Placebo	Uncertainties/ Strength of Evidence
Treatment related adverse events	Grade 3 or above	%	19	6.3	Double-blind design
Adverse Events leading to discontinuations	All causality - Discontinuations due to adverse events	%	14	3	Double-blind design
Fatigue	Treatment related common adverse event	%	G1/2*: 27 G3/4: 1	G1/2: 18 G3/4: 1	Double-blind design
Diarrhoea	Treatment related common adverse event	%	G1/2: 13 G3/4: 3	G1/2: 7 G3/4: 2	Double-blind design
Nausea	Treatment related common adverse event	%	G1/2: 15 G3/4: 0	G1/2: 8 G3/4: 0	Double-blind design

*'G' refers to grade and the number refers to the level of grade assigned to the adverse event.

6. Council Review | Clinical Benefit-Risk Balance Evaluation

After consideration of all the evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for this off-label use of nivolumab. Under the decision-making framework for value judgements, Council considered the clinical case to be compelling.

7. Economic Evidence Review Summary

Economic Overview

Type of economic evaluation

No relevant published cost-utility analysis was identified in the literature search. A cost-utility analysis remained in progress (as of September 2023) and was not available for this review.[26] Therefore, a de-novo cost-comparison was performed.

Population, intervention, comparator and outcomes

The population was patients with pleural or peritoneal mesothelioma, whose disease has progressed on or after platinum-based chemotherapy, requiring treatment in 2nd or subsequent lines. The intervention was intravenous nivolumab. As the intervention provides access to a new treatment line which has not been uniform throughout Scotland, no comparator was considered. As a cost-comparison was performed, only costs were included.

Costs

Medicine acquisition, intravenous administration and monitoring costs were included. Nivolumab was costed at 480mg every 4 weeks. The number of treatment cycles used was 3. This was based on the median number of doses reported in the CONFIRM study. The CONFIRM study reported a

median of six doses of 240mg nivolumab every 2 weeks. This was converted to three doses of 480mg nivolumab every 4 weeks in the cost comparison.

Results

These exclude VAT.

The medicine acquisition cost of nivolumab per patient was £15,798 (BNF list prices). When including administration and monitoring this figure was £17,179 (BNF list prices).

Cost-effectiveness considerations

Generalisability of the cost comparison

NHSScotland PAS prices were used to obtain results of greater relevance.

Limitations of the cost comparison

Due to an absence of a published cost-utility analysis, the cost comparison only compares costs. Nivolumab is a cost-increasing intervention. Given the evidence supporting the clinical benefit of this intervention, it is likely to offer an increased quality-adjusted life year (QALY) gain compared to its comparator. However, given the absence of a QALY estimate, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

Treatment related adverse events were not included in the cost comparison. These were omitted for simplicity. If including these, the cost of nivolumab treatment- would likely increase. However, given the low rate of treatment related grade 3 adverse events for nivolumab in CONFIRM, the additional cost is not expected to be significant.

The dosing schedule used for nivolumab (480mg every 4 weeks) was different to that of CONFIRM (240mg every 2 weeks). The SPC notes that there is no clinically significant difference between these doses in other tumour types. If considering reducing the dose frequency, medicine costs will be unaffected but the administration costs will increase.

Summary

The cost-comparison indicated that nivolumab is a cost increasing intervention. Given the evidence supporting the clinical benefit of this intervention, it is likely to offer an increased QALY gain compared to its comparator. However, in the absence of an analysis to quantify treatment benefits in relation to costs, an ICER was not available, and the cost-effectiveness remains unknown.

A detailed budget impact analysis, exploring the financial impact of medicine cost in the anticipated population is presented in Section 10.

8. Council Review | Cost-Effectiveness Evaluation

After consideration of the available evidence, the Council accepted that the proposed intervention was cost-increasing, and that, in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider other relevant

information including service impact and estimated net medicines budget impact under the decision-making framework for value judgements.

9. Service Impact

The number of patients eligible for nivolumab is expected to be approximately 10 patients per year and expected to drop to less than 5 per year in two years. Depending on first-line immunotherapy uptake, there may be minimal patients accessing nivolumab by year 5.

Nivolumab treatment requires clinic reviews, blood tests, and intravenous infusions every four weeks. The service impact of the proposed used is unlikely to be significant.

10.Budget Impact

In the absence of a cost-effectiveness analysis, a detailed budget impact analysis was conducted.

Patient uptake

The number of patients expected to be treated with nivolumab was estimated to be 10 in Year 1, with less than 5 receiving treatment in an annual steady state. This was based on prescribing data from a large NHSScotland health board and extrapolated based on population proportion to give a national figure, and clinician opinion of the eligibility for second line treatments. The uptake is expected to fall steadily as first line immunotherapy becomes the main standard of care for many patients, and within 5 years there may be minimal patient uptake.

Per patient medicine cost and treatment duration

These prices include VAT.

Nivolumab: Nivolumab was costed at 480mg in 4-weekly cycles (using 240mg/24ml, 1 vial, £3,160 BNF list prices, August 2023). These costs were applied for 3 treatment cycles, based on the median administered dosing in CONFIRM and consistent with the cost-comparison.

Comparator displacement

As there is no routinely accessible standard of care for this treatment line, and medicines accessed through individual request are not uniform throughout Scotland, no comparator was considered.

Results

In Year 1 the net medicines budget impact was estimated to be £190k (BNF list prices) based on an uptake of 10 patients. In subsequent years the net medicines budget impact was estimated to be £76k (BNF list prices) based on an uptake of 4 patients.

Table 4 | Budget impact analysis base case results (List prices; Including VAT)

	Year 1	Subsequent years
Nivolumab acquisition cost		
Acquisition cost	£18,958*	£18,958*
Number of patients treated	10	4
Budget Impact		
Budget Impact (new medicine and supportive medicine costs only)	£189,576	£75,830

*based on 3 treatment cycles of treatment, 480mg every 4 weeks.

Scenario considerations

The following table presents a budget impact (net medicines cost) scenario, exploring changes in treatment duration.

Table 5 | Scenario analyses (List prices; including VAT)

#	Base case	Scenario	Nivolumab acquisition cost per patient	Number of patients treated (Year 1)	Budget impact – Net medicine costs Year 1	Number of patients treated (Steady state)	Budget impact – Net medicine costs steady state
	Base case	-	£18,958	10	£189,576	4	£75,830
1	3 cycles of nivolumab	6 cycles of nivolumab *	£37,915	10	£379,152	4	£151,611

* Upper quartile of doses of nivolumab in CONFIRM was 12 (using 240mg every 2 weeks). This was converted to six cycles of 480mg every 4 weeks.

Limitations

Per patient treatment costs for nivolumab assumed 3 cycles of treatment. There was variation in the number of doses administered in CONFIRM. As a conservative scenario, the upper quartile for administered doses from CONFIRM was used. The results are shown in budget impact scenario 1.

Patient numbers were estimated and were subject to uncertainty. The base case budget impact results were based on an annual uptake of 10 in Year 1 and 4 in a steady state. This may overestimate budget impact in the steady state as it is expected, from clinical expert opinion, that less than 5 patients will receive nivolumab within two years, and within 5 years there may be minimal patient uptake as first line immunotherapy becomes the main standard of care.

The proposal form noted treatment being accessed through individual requests. Therefore, the Year 1 budget impact of the proposal may be overestimated as some patients may already be receiving nivolumab and these costs have not been accounted for.

Summary

The use of nivolumab will increase the budget impact for this patient group. For 3 cycles of nivolumab, the medicine acquisition cost was expected to be £19k (BNF list prices) per patient. Based on a Year 1 uptake of 10 patients, the estimated net medicines budget impact was £190k (BNF list prices) in Year 1. Based on a steady state uptake of 4 patients, the budget impact was £76k (BNF list prices) in the steady state. VAT is included in these figures.

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing 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 pricing.

Separate information will be supplied by the boards to facilitate local budget impact assessment.

11. Council review | Overall proposal evaluation

After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

12. Acknowledgements

NCMAG would like to acknowledge the patient group partner, Mesothelioma UK, for their valuable contribution.

We would also like to acknowledge the data provided by the Cancer Medicines Outcomes Programme, which provided very helpful context for this advice document.

NCMAG would like to acknowledge the Southampton Health Technology Assessments Group (SHTAC) at the University of Southampton for their communication and cooperation on the progress of the cost-utility analysis.

13. References

1. Electronic Medicines Compendium (EMC). Bristol Myers Squibb Pharmaceuticals limited. Nivolumab. OPDIVO 10 mg/mL concentrate for solution for infusion. Last accessed August 2023. https://www.medicines.org.uk/emc/product/6888/smpc#gref

2. Royal College of Physicians (RCP). National Mesothelioma Audit report 2020 (audit period 2016-18). https://www.rcplondon.ac.uk/projects/outputs/national-mesothelioma-audit-report-2020-audit-period-2016-18. Last accessed 23/03/23. 2020.

3. Public Health Scotland. Cancer statistics - Lung cancer and Mesothelioma. https://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Lung-Cancer-and-Mesothelioma/. Last accessed March 2023.

4. Cancer Research UK. Mesothelioma incidence statistics. Mesothelioma incidence by anatomical site.

5. Verma V, Sleightholm RL, Rusthoven CG, Koshy M, Sher DJ, Grover S*, et al.* Malignant Peritoneal Mesothelioma: National Practice Patterns, Outcomes, and Predictors of Survival. Ann Surg Oncol. 2018;25(7):2018-26. Epub 2018/05/04. 10.1245/s10434-018-6499-1.

6. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK*, et al.* Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(2):129-42. 10.1016/j.annonc.2021.11.005.

7. Scottish Medicines Consortium. Nivolumab (Opdivo®). Last accessed August 2023. https://www.scottishmedicines.org.uk/medicines-advice/nivolumab-opdivo-full-smc2385/.

8. Popat S. ES18.01 Immunotherapy - Current State of Play (Concentrating on Current Data for First Line and Salvage Strategies). Journal of Thoracic Oncology. 2021;16(3 Supplement):S84. https://dx.doi.org/10.1016/j.jtho.2021.01.042.

9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Mesothelioma: Pleural. Version 1.2023. December 2022.

10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Mesothelioma: Peritoneal. Version 2.2023. July 2023.

11. Nivolumab. Review Report. Pharmaceuticals and Medical Devices Agency. October 2021. https://www.pmda.go.jp/files/000246571.pdf. Last accessed 14th August 2023.

12. NHSEngland. National Cancer Drugs Fund List. Version 1.271. 8th August 2023.

13. Bristol Myers Squibb Pharmaceuticals limited (OPDIVO®). Summary of product characteristics. Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/6888 .Last accessed April 2023.

14. Fennell DA, Ewings S, Ottensmeier C, Califano R, Hanna GG, Hill K*, et al.* Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. The Lancet Oncology. 2021;22(11):1530-40. https://dx.doi.org/10.1016/S1470-2045%2821%2900471-X.

15. Assie JB, Crepin F, Grolleau E, Canellas A, Geier M, Grebert-Manuardi A*, et al.* Immune-Checkpoint Inhibitors for Malignant Pleural Mesothelioma: A French, Multicenter, Retrospective Real-World Study. Cancers (Basel). 2022;14(6):15. https://dx.doi.org/10.3390/cancers14061498.

16. Cantini L, Belderbos RA, Gooijer CJ, Dumoulin DW, Cornelissen R, Baart S*, et al.* Nivolumab in pre-treated malignant pleural mesothelioma: real-world data from the Dutch expanded access program. Transl. 2020;9(4):1169-79. https://dx.doi.org/10.21037/tlcr-19-686.

17. Fujimoto N, Okada M, Kijima T, Aoe K, Kato T, Nakagawa K*, et al.* Clinical Efficacy and Safety of Nivolumab in Japanese Patients With Malignant Pleural Mesothelioma: 3-Year Results of the MERIT Study. JTO Clin Res Rep. 2021;2(3):100135. https://dx.doi.org/10.1016/j.jtocrr.2020.100135.

18. Quispel-Janssen J, van der Noort V, de Vries JF, Zimmerman M, Lalezari F, Thunnissen E*, et al.* Programmed Death 1 Blockade With Nivolumab in Patients With Recurrent Malignant Pleural Mesothelioma. J Thorac Oncol. 2018;13(10):1569-76. https://dx.doi.org/10.1016/j.jtho.2018.05.038.

19. Nakamura A, Kondo N, Nakamichi T, Kuroda A, Hashimoto M, Matsumoto S*, et al.* Initial evaluation of nivolumab in patients with post-operative recurrence of malignant pleural mesothelioma. Jpn J Clin Oncol. 2020;50(8):920-5. https://dx.doi.org/10.1093/jjco/hyaa069.

20. Okada M, Kijima T, Aoe K, Kato T, Fujimoto N, Nakagawa K*, et al.* Clinical efficacy and safety of nivolumab: Results of a multicenter, open-label, single-arm, Japanese phase II study in malignant pleural mesothelioma (MERIT). Clin Cancer Res. 2019;25(18):5485-92. https://dx.doi.org/10.1158/1078-0432.CCR-19-0103.

21. Tsai YC, Chen HL, Lee TH, Chang HM, Wu KL, Chuang CH*, et al.* Salvage Therapy for Relapsed Malignant Pleural Mesothelioma: A Systematic Review and Network Meta-Analysis. Cancers (Basel). 2021;14(1):30. https://dx.doi.org/10.3390/cancers14010182.

22. International Conference on Harmonisation of Technical Requirments for Registration of Pharmaceuticals for human use. ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and standards for expedited reporting E2A. Last accessed 7th September 2023 at https://database.ich.org/sites/default/files/E2A_Guideline.pdf.

23. Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. Eur J Cancer. 2019;106:196-211. https://doi.org/10.1016/j.ejca.2018.11.012.

24. The Scottish Cancer Medicines Outcomes Programme (CMOP). Personal communication. September 2023.

25. Tai MH, Cai Q, Fu AZ, Khare V, Kaila S. Real-world patient characteristics and treatment outcomes among newly diagnosed multiple myeloma patients initiating daratumumab, lenalidomide, and dexamethasone as first-line therapy. Blood. 2021;138(SUPPL 1):1979. https://dx.doi.org/10.1182/blood-2021-149002.

26. Fennell DA, Ewings S, Ottensmeier C, et al. Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. Lancet Oncol 2021; published online Oct 14. Supplementary appendix. https://ars.els-cdn.com/content/image/1-s2.0-S147020452100471X-mmc1.pdf. Last accessed September 2023.

This advice represents the view of the NCMAG Council 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.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by