National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG121 Nivolumab in combination with ipilimumab | Advice Document v1.0 | April 2025

Nivolumab in combination with ipilimumab for the neoadjuvant treatment of resectable stage III melanoma [A]

NCMAG Decision | this off-label use 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 Scottish Medicines Consortium 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 plus ipilimumab 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	NHSScotland oncologists treating malignant melanoma
Medicine Name	Nivolumab plus ipilimumab
Cancer type	Skin cancer
Proposed off-label[B] use	Neoadjuvant treatment of resectable stage III melanoma with at least one pathologically proven lymph-node metastasis and a maximum of three in-transit metastases

Medicine Details	Form: concentrate for solution for infusion Dose: Nivolumab 240mg plus ipilimumab 80mg intravenous infusion every three weeks for a total of 2 cycles. Patients not achieving a major pathological response receive adjuvant nivolumab 480mg every 4 weeks or adjuvant oral dabrafenib 150mg twice daily plus trametinib 2mg once daily (if BRAF V600 mutant) for a total of 46 weeks.
Advice eligibility criteria	Inclusion criteria: • At least 16 years of age • Performance Status 0 to 1 • Able to tolerate doublet immunotherapy • Stage III melanoma with at least one pathologically proven lymph-node metastasis and a maximum of 3 in-transit metastases Exclusion Criterion: • Uveal or ocular melanoma

[B] Nivolumab in combination with ipilimumab is indicated for:

1. the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.
2. See SPC for further licensed indications

Nivolumab as monotherapy is indicated for:

1. the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Adjuvant treatment is given after cancer surgery, while neoadjuvant treatment is given before surgery.
2. See SPC for further licensed indications

1. Current Management Context

Malignant cutaneous melanoma, incidence and prognosis

Malignant melanoma is a cancer that develops in melanocytes and accounts for 2% of all skin cancers but nearly all skin cancer deaths. Signs of cutaneous malignant melanoma include a new or changing mole. Stage III melanoma has spread into the skin, lymph vessels, or lymph glands close to the primary tumour. In-transit metastases occur when the melanoma is more than 2 cm away on the skin or subcutaneous tissue but has not reached a distant lymph node[1]. Stage IV melanoma is when it has spread to distant organs such as liver or brain and symptoms can include fatigue, weight loss or, in some cases, seizures. Approximately 40% of patients will harbour a BRAF V600E mutation[8].

Malignant melanoma is the most invasive type of skin cancer, and its incidence is increasing in Scotland. There were 112 new diagnoses of Stage III malignant melanoma of the skin in Scotland in 2021[2]. The use of postoperative adjuvant immunotherapy treatment in Scotland has increased each year since 2018 with a median age of 65 years in those patients treated [3]. Seventy-five percent of patients in England will survive five years after diagnosis with Stage III melanoma but recurrence rates are high, and approximately 40% to 50% of patients will recur within 5 years even with post-operative adjuvant treatments[4-7].

Malignant cutaneous melanoma treatment pathway in NHSScotland

Patients with localised melanoma undergo surgery, firstly to diagnose and remove the primary cancer and thereafter to remove clinically detectable lymph nodes or resectable metastases. After surgery, for Stage III melanoma in NHSScotland, adjuvant treatment options include pembrolizumab or nivolumab, with an alternative option of dabrafenib plus trametinib for patients with a BRAF V600E mutation. Treatment is given for 12 months. Treatment decisions are based on patient characteristics, preference for oral or intravenous therapy, and the side effect profiles of the different regimens. Outcomes between nivolumab, pembrolizumab, and dabrafenib plus trametinib are considered to be similar[9, 10].

International context for proposed use

The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the European Association of Dermato-Oncology (EADO), and the European Society for Medical Oncology (ESMO) support the use of neoadjuvant nivolumab plus ipilimumab for patients with resectable Stage III melanoma, with neoadjuvant therapy preferable to adjuvant therapy.

Pharmacology of nivolumab and ipilimumab

Both nivolumab and ipilimumab are immunotherapies that enable the immune system to recognise and kill cancer cells. Nivolumab binds to the PD-1 receptor on immune cells, allowing the immune system to target cancer cells, while ipilimumab is a CTLA-4 inhibitor that increases T-cell activity, enhancing the immune system's ability to recognise and kill cancer cells.

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were nivolumab, ipilimumab, melanoma and resectable. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key studies were critically appraised using the Cochrane risk of bias version 2.0 tool.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The key evidence supporting this proposal is the NADINA study[11]. The NADINA study was a phase III multicentre randomised open-label trial comparing neoadjuvant nivolumab in combination with ipilimumab to adjuvant nivolumab in patients with resectable, macroscopic stage III cutaneous or acral melanoma, which aligns with the submitted proposal[11]. Patients aged 16 years and older, with a World Health Organisation Performance Status (PS) of 0 to 1, with at least one pathologically proven lymph node metastasis and a maximum of three additional in-transit metastases were included. Staging was confirmed using the eighth edition of the cancer staging manual of the American Joint Committee on Cancer. In the study, 423 patients were randomly assigned to receive either neoadjuvant (n=212) or adjuvant (n=211) therapy; stratified by continent (Australia, Europe and North America); presence of a BRAF V600E (yes or no) or V600K (yes or no) and the presence of in-transit metastases (yes or no)[11]. Patients in the neoadjuvant arm received two cycles of intravenous nivolumab (240mg) in combination with ipilimumab (80mg) every three weeks followed by surgery. After pathological evaluation of response, those patients with >10% viable tumour remaining received either adjuvant dabrafenib (150mg orally twice daily) plus trametinib (2mg orally once daily) if the melanoma had a BRAF V600E or V600K mutation, or they received 11 cycles of adjuvant intravenous nivolumab (480mg every four weeks). In those with a locally assessed major pathological response, defined as ≤10% viable tumour remaining, patients did not receive adjuvant therapy. In the control arm of adjuvant treatment following surgery patients received 12 cycles of intravenous nivolumab (480mg) every 4 weeks, commencing between weeks 6 and 12 following surgery. The primary outcome was investigator assessed event-free survival (EFS), defined as the time from randomisation to the occurrence of progression to unresectable melanoma before surgery, disease recurrence or death due to melanoma or due to treatment. In the case of an early event (within 12 weeks) EFS was assessed centrally. Secondary outcomes include overall survival, response (investigator and central review), which was measured via CT scan at baseline, week 6 (prior to surgery in neoadjuvant and prior to commencing adjuvant), week 12 (start of adjuvant treatment in the neoadjuvant group) and 12 weekly thereafter, safety and quality of life.

Results from the NADINA study

At the interim data cut of 12 January 2024, the median duration of follow up was 10.6 months (interquartile range [IQR] 5.2 to 16.8) in the neoadjuvant group and 9.9 months (IQR 4.6 to 17) in the adjuvant group. Baseline characteristics were well matched across the two groups: the majority of patients were WHO performance score 0 (91%), the median time from commencing neoadjuvant treatment to surgery was 45 days (IQR 42 to 49), and 93% of patients in the neoadjuvant group received surgery. Nine patients in the neoadjuvant group did not receive surgery due to toxic effects (n=3), progression (n=5) and unknown (n=1). Investigator-assessed EFS at 12 months in the intention to treat population was higher in the patient group receiving neoadjuvant treatment. A major pathological response (≤10% viable cancer cells) was reported in 59% of patients with 47% achieving a complete response (0% viable cancer cells) and 12% a near complete response[11]. Overall survival was not included as part of this analysis due to the immaturity of the data.

Table 1| Results from NADINA for primary and secondary outcomes[11]

	Neoadjuvant nivolumab plus ipilimumab (n=212)	**Adjuvant nivolumab (n=211)**
Primary outcome: Investigator[a] assessed EFS		
Events, %	28	72
EFS, at 12 months (99.9% CI)	84% (74 to 95)	57% (45 to 73)
Adjusted HR (99.9% CI)	0.32 (0.15 to 0.66)	
Adjusted difference in restricted mean survival time[b], months (99.9% CI)	8.0 (4.94 to 11.05); p<0.001	
Response[c]		
Major[d] pathological response rate (%)	125 (59%)	NA
Partial[e] pathological response rate (%)	17 (8%)	NA
Pathological non-response rate (%)	53 (25%)	NA
Estimated 12-month recurrence free survival according to pathological response		
Major[d] pathological response	95.1% (99.9% CI, 87.4 to 99.9)	NA
Partial[e] pathological response	76.1% (99.9% CI, 44.4 to 99.9)	NA
Pathological non-response	57.0% (99.9% CI, 33.3 to 97.6)	NA

[a] if an event occurred within 12 weeks confirmation was required by central review
[b] the restricted mean survival time point had a restriction timepoint of 27.8 months
[c] confirmed by central review as per international neoadjuvant consortium criteria
[d] 0-10% residual viable tumour; 47% of patients had pathological complete response: 0% residual viable tumour
[e] 11-50% residual viable tumour
Key: EFS: event free survival; CI: confidence interval; HR: hazard ratio; NA: not applicable

Patient Reported Outcomes

Quality of life was included as a secondary outcome in the NADINA study; however, the results have not been published yet.

Safety evidence

Based on data from the NADINA trial, in the neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab groups respectively the proportion of patients reporting a treatment related grade 3 or higher adverse event (AE) was 30% versus 15%. The most frequently reported treatment related grade 3 AEs were diarrhoea (3.8% versus 0.6%), alanine aminotransferase increased (4.7% versus 2.4%), aspartate aminotransferase increased (4.2% versus 2.4%) and colitis (3.3% versus 0). Treatment discontinuation due to an AE occurred in 9% of the neoadjuvant group and 14% in the adjuvant group. Serious adverse events (SAEs) were reported in 36% of the neoadjuvant group versus 24% in the adjuvant group. Surgery-related adverse events of grade 3 or higher occurred in 14.1% and 14.4% of the neoadjuvant and adjuvant patients, respectively. Surgery was not performed in three patients in the neoadjuvant group because of toxic events. Patient deaths due to SAEs were reported in one patient in the adjuvant setting, due to pneumonitis caused by nivolumab, with no deaths reported in the neoadjuvant arm.

Quality appraisal

The NADINA study is a phase III open label randomised, multi-centre study. Overall, the study was assessed to have a low risk of bias. Randomisation was conducted online using the ALEA randomisation software package, thus limiting the risk of selection bias.

The study used an open label design and for the primary outcome, investigator assessment was employed, which could increase the risk of outcome detection bias and reporting of subjective outcomes. However, for events within 12 weeks, assessment was conducted centrally. All response outcomes were completed by both investigator and central assessment, with minimal differences noted between the results. This consistency may increase confidence in the assessment of the primary outcome.

Clinical effectiveness considerations

Neoadjuvant nivolumab plus ipilimumab improved EFS

The NADINA study met its primary outcome, demonstrating that neoadjuvant nivolumab plus ipilimumab, surgery, then tailored adjuvant therapy depending on pathology, improved EFS compared to surgery then adjuvant nivolumab. At 12 months, EFS was 84% (99.9% CI 74 to 95) for nivolumab and ipilimumab, compared to 57% (99.9% CI 45 to 73) for adjuvant treatment, with a statistically significant hazard ratio improvement of 0.32 (0.15 to 0.66). Median follow-up was short at approximately 10 months. Although the proportional hazard assumption was violated, a sensitivity analysis based on piece-wise hazard functions provides reassurance with a consistent overall hazard ratio. This improvement was consistent across subgroups, including those with BRAF mutant disease[11].

Overall survival data are immature

Due to the short follow-up at the time of the interim analysis and the likelihood of prolonged overall survival, overall survival data have not been reported, but the marked improvement in EFS may be an appropriate surrogate[12]. Mature data may take longer than 10 years of follow-up and it may be confounded by subsequent treatments and other factors. However, in another study of adjuvant immunotherapy early improvements in relapse-free survival and distant metastasis-free survival were maintained at 7 years follow-up[13]. Major pathological response has also been associated with an overall survival benefit[14]. The statistically significant improvement in EFS and approximate 60% major pathological response rate is encouraging in the interim.

Neoadjuvant therapy with tailored adjuvant therapy may allow patients to have shorter treatment durations or make treatment response informed decisions.

Approximately 60% of patients achieved a major pathological response and did not require adjuvant treatment. This approach is supported by an estimated 12-month recurrence-free survival of 95% for patients achieving a major pathological response and more mature data from other neoadjuvant nivolumab plus ipilimumab trials[15]. Awareness of tumour response to neoadjuvant immunotherapy supports more informed decisions about post-surgery adjuvant treatment for those who do not achieve a major pathological response, particularly for those with BRAF V600 mutations. Response based treatment may reduce toxicity from unnecessary post operative treatments and improve outcomes by ensuring the most appropriate therapy is chosen post-surgery to minimise the risk of future recurrence.

The control arm in the NADINA study is relevant to NHSScotland practice

Adjuvant nivolumab is a relevant comparator for this proposal. In NHSScotland, patients with BRAF V600E/K mutations would also have the option of adjuvant dabrafenib plus trametinib. In the NADINA study, the adjuvant control arm did not include dabrafenib and trametinib as a treatment option. This should not significantly affect the generalisability of the results, as immunotherapy and dabrafenib plus trametinib are considered to have similar efficacy in the population with a BRAF V600 mutation[9, 10].

The results are likely generalisable to NHSScotland

A Public Health Scotland report on adjuvant immunotherapy use in stage III melanoma patients in NHSScotland was published in December 2024 and included a broader population than the proposed patient population, but it is sufficiently similar to understand the generalisability of the NADINA study. It reported a median age of 65 years, with 79% of patients having a WHO PS of 0 and 17% having a PS of 1. In the NADINA study, the median age was 60 years, with 91% having a WHO PS of 0[3]. This suggests the results of NADINA are likely generalisable to the NHSScotland population. Additionally, as a doublet immunotherapy, this regimen is likely to be used in fitter and younger patients compared to those currently offered single-agent immunotherapy.

There is some uncertainty regarding the generalisability of the results to patients with rarer forms of melanoma, such as acral and mucosal melanoma, which were excluded from the NADINA study.

The license for adjuvant nivolumab includes rarer subtypes, although patient numbers were very small in the registration trial[16].

The safety profile is similar to on-label nivolumab plus ipilimumab in patients with advanced melanoma

Rates of grade 3 or worse adverse events were higher with the neoadjuvant doublet combination compared to adjuvant nivolumab, which is expected with combination therapy. Three patients in the neoadjuvant group did not undergo surgery due to toxic effects. The types of adverse events were similar to the on-label combination for advanced melanoma, which used higher dosing for ipilimumab. The rates of adverse events were lower than the on-label combination, which may be expected when giving only two cycles of neoadjuvant treatment, with lower ipilimumab dosing, for stage III melanoma. Nonetheless, some of the adverse events, such as hypothyroidism or adrenal insufficiency, may require long term management.

4. Patient Group Summary

We received a statement from Melanoma Focus, who are a registered charity. Melanoma Focus reported that pharmaceutical industry funding accounted for 24% of total funding received in 2023/24. A representative from Melanoma Focus attended the NCMAG council meeting. The key points from the submission are documented below:

When diagnosed early, melanoma is a highly curable cancer. In the event of an advanced diagnosis or progression to stage 4, with the likely spread to the lungs, liver, bone or brain, patients may experience distressing symptoms. Around a quarter of patients who are diagnosed with melanoma are under 50 years, and the symptoms and management of the cancer may place a significant burden on their ability to work and contribute to their family's finances and everyday life.

The current standard of care adjuvant treatments for melanoma reduces the likelihood of melanoma recurrence, however patients may progress despite treatment. Patients and their families have increased anxiety about the cancer spreading or recurring.

The evidence supporting this proposal is promising with around 60% of patients not requiring further adjuvant treatment. This will allow these patients to continue with their lives without the need for a year of adjuvant treatment and the risk of further side effects.

5. Benefit-Risk Balance

The proposal is for the off-label use of neoadjuvant nivolumab plus ipilimumab for stage III melanoma. In the NADINA study, neoadjuvant nivolumab plus ipilimumab (followed by adjuvant treatment for patients without a major pathological response) was associated with a statistically significant improvement in EFS compared to adjuvant treatment with nivolumab. The results are likely generalisable to the NHSScotland population. The substantial clinical benefit based on EFS

provides reassurances in the absence of overall survival data. There were no unexpected safety signals compared to the on-label use of nivolumab plus ipilimumab in advanced melanoma.

6. Council Review |Clinical Benefit-Risk Balance Evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were satisfied that the case had been made for the clinical effectiveness of nivolumab plus ipilimumab.

7. Economic Evidence Review Summary

Economic Overview

Type of economic evaluation

The literature search for economic evidence on this topic returned no cost-effectiveness analysis which evaluated nivolumab in combination with ipilimumab for the neoadjuvant treatment of resectable stage III melanoma in the proposed population. Therefore, a de-novo cost-comparison was performed.

Population, intervention, comparator and outcomes

The patient population was resectable stage III melanoma with at least one pathologically proven lymph-node metastasis and a maximum of three in-transit metastases. The intervention was nivolumab in combination with ipilimumab as neoadjuvant treatment followed by tailored adjuvant treatment where appropriate, hereafter referred to as neoadjuvant nivolumab plus ipilimumab regimen. The current standard of care for adjuvant treatment in NHSScotland depends on BRAF mutation status. Approximately 40% of patients harbour a BRAF mutation[8], these receive either dabrafenib plus trametinib, or immunotherapy with nivolumab or pembrolizumab. The remaining 60% receive nivolumab or pembrolizumab in the adjuvant setting. Therefore, for the purpose of this cost-comparison, NHSScotland standard of care (SOC) was assumed to be a basket of comparator medicines used in the adjuvant setting, weighted by proportion of patients who receive each comparator treatment, details of which are summarised in Table 2. As a cost-comparison analysis was performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Costs

The cost comparison included medicine acquisition costs, administration, healthcare resource use and adverse event management costs. Medicine acquisition costs were calculated based on available formulations, pack sizes and unit costs for each treatment regimen in Table 2. The price of 240mg/24ml solution for infusion vials of nivolumab and 50mg/10ml solution for infusion vials of ipilimumab were used to calculate medicine acquisition cost in the treatment arm. The calculation included wastage for intravenous (IV) medicines. The duration of treatment was informed by median number of cycles from the NADINA study, summary of product characteristics (SPC) and

validated with clinical expert opinion[11]. The confidential NHSScotland Patient Access Scheme (PAS) price of medicines was used (accessed February 2025).

The administration cost for IV medicines was based on delivery of simple parenteral chemotherapy which accounts for 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of one cycle (NHS National Reference costs 2022-23, corrected for inflation).

The healthcare resource use costs were calculated in alignment with clinical expert feedback, which determined that an additional Computerised Tomography (CT) scan and pathological assessment would be required for patients in the neoadjuvant arm. In addition, the cost for one phlebotomy appointment (including test for lactate dehydrogenase, complete blood count and complete metabolic panel) and one specialist consultant appointment were included for all cycles in the NHSScotland SOC and neoadjuvant nivolumab plus ipilimumab treatment arms in proportion to the patient distribution of each arm, as summarised in Table 2. The resource use unit costs were sourced from NHS National Reference costs 2017-18 and 2022-23 and corrected for inflation.

The adverse event (AE) costs included in the model comprised the following grade 3 or higher AEs: transaminitis, adrenal insufficiency, colitis and diarrhoea. They were applied as fixed one-off costs based on proportion of AEs reported in the NADINA study[11]. The unit costs corresponding to non-elective hospital inpatient stay of an average of five days were considered appropriate for calculation (NHS National Reference costs 2022-23, corrected for inflation).

Table 2 | Dosing schedule and duration summary

Regimen	Regimen component	Dosing schedule description	Cycles (one year treatment)
NHSScotland SOC adjuvant treatment basket (proportion of patients based on clinical expert opinion)			
Dabrafenib plus trametinib[a] (30%)	Dabrafenib	150mg orally twice daily	13
	Trametinib	2mg orally once daily	
Nivolumab monotherapy (3%)	Nivolumab	480mg IV every four weeks	13
Pembrolizumab monotherapy (67%)	Pembrolizumab	400mg IV every six weeks	9
Neoadjuvant nivolumab plus ipilimumab regimen (proportion of patients based on NADINA study[11])			
Neoadjuvant (100%)	Nivolumab	240mg IV every three weeks	2
	Ipilimumab	80mg IV every three weeks	2

Regimen	Regimen component	Dosing schedule description	Cycles (one year treatment)
Tailored adjuvant (41% pPR and pNR)	Nivolumab monotherapy (38%)	480mg IV every four weeks	11
	Dabrafenib plus trametinib[a] (62%)	Dabrafenib 150mg orally twice daily and trametinib 2mg orally once daily	11

[a] BRAF V600E/K mutation-positive receive dabrafenib plus trametinib.
Key: Adjuvant: post-surgery; neoadjuvant: before surgery; IV = intravenous; pPR = Partial pathologic response; pNR = No pathologic response; SOC = standard of care

Results

All figures in the cost-comparison exclude VAT.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues. Based on NHSScotland PAS price of medicines (accessed February 2025), the cost-comparison results suggested that treatment with neoadjuvant nivolumab plus ipilimumab regimen would result in lesser total costs than the NHSScotland SOC comparator treatment. The main source of cost-saving was avoidance of adjuvant treatment in approximately 60% of patients in the treatment arm and the higher treatment acquisition cost of the NHSScotland SOC arm.

Table 3 | Summary of cost-comparison results (confidential price, excluding VAT)

Cost category / Treatment	Medicine acquisition (£)	Medicine administration (£)	Healthcare resource use (£)	Adverse event (£)	Total costs per-patient (£)
Neoadjuvant nivolumab plus ipilimumab regimen	CIC	1,538	1,419	146	CIC
NHSScotland SOC[a]	CIC	1,209	1,388	59	CIC
Cost difference	CIC	329	32	86	CIC (cost-saving)

[a] NHSScotland SOC refers to basket of comparators listed in Table 2.
Key: SOC = standard of care; CIC = commercial in confidence

Cost-effectiveness considerations

Generalisability of the cost comparison

The dosing schedule of neoadjuvant nivolumab plus ipilimumab regimen reflects the NADINA study, consistent with the proposed dosing in NHSScotland[11].

The NHSScotland PAS prices for medicines were considered in confidence to increase the generalisability of the net costs.

Limitations of the cost comparison

There was no published cost-effectiveness analysis for the proposed use and cost-effectiveness is not known.

Due to an absence of cost-effectiveness analysis, the analysis only compared costs. Given the favourable NADINA study results, the neoadjuvant treatment regimen with nivolumab in combination with ipilimumab may offer clinical benefit in the proposed patient population with resectable stage III melanoma[11]. An estimate of cost-effectiveness can be made by modelling the benefits over a longer period and comparing with costs. However, due to absence of a QALY estimate, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

The choice of immunotherapy medicine used in the adjuvant setting could vary by clinical practice across regions in NHSScotland.

The base-case proportion of patients receiving NHSScotland SOC was based on clinical expert opinion. However, regional variations can be expected in immunotherapy use across NHSScotland cancer networks as published in the Immunotherapy Report (2018 – 2022) by Cancer Medicines Outcomes Programme (CMOP). It was noted that nivolumab is prescribed at a higher proportion in the south-east of Scotland, whereas pembrolizumab is prescribed at a higher proportion in the west of Scotland[3]. Different proportions of immunotherapy would create variation in the NHSScotland SOC costs. However, this would have a minor impact on the conclusion, as the overall cost-saving benefit of the neoadjuvant nivolumab plus ipilimumab regimen remains significant despite variations in the proportion receiving different adjuvant immunotherapy as SOC.

Cost-comparison did not include dosing adjustments.

Duration and dose may vary in the real-world setting due to multiple factors. Due to issues of data paucity, adjusting for these factors would likely increase the uncertainty of estimated medicine acquisition costs and were therefore not considered in the calculation. The dosing was not adjusted to account for dose reductions or treatment interruptions. Including these aspects would reduce the dose or duration of treatment, reducing the treatment cost. This is likely to be applicable to both arms, with the overall cost impact remaining uncertain.

Costs incurred in one year of treatment are considered.

A simplistic assumption was made to compare treatment costs incurred in one year of treatment. It is known that recurrence rates are high in patients surviving treatment for stage III melanoma; approximately 40% to 50% of patients may recur within 5 years even with post-operative adjuvant

treatments[4-7]. Costs associated with future recurrences were not included in the analysis. Based on published evidence, the neoadjuvant nivolumab plus ipilimumab regimen has been shown to provide an estimated 12-month recurrence-free survival of 95% for patients achieving a major pathological response, which could potentially lower overall healthcare costs in the neoadjuvant group.[11, 15]

Summary

The cost-comparison indicated that the neoadjuvant treatment regimen with nivolumab in combination with ipilimumab is a cost-saving intervention compared to NHSScotland SOC for patients with resectable stage III melanoma. However, in the absence of a lifetime cost-effectiveness analysis, it is difficult to quantify treatment benefits in relation to costs and the actual cost-effectiveness remains unknown.

8. Council review | Cost-Effectiveness Evaluation

After considering all the available evidence, the Council accepted that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider additional relevant information including service impact and estimated net medicines budget impact under the Decision-making Framework for Value Judgements.

9. Service Impact

Neoadjuvant nivolumab plus ipilimumab, given as two cycles over 6 weeks, is likely to be service sparing. Approximately 60% of patients did not require adjuvant treatment, which is usually 9 to 12 cycles of single agent intravenous nivolumab or pembrolizumab, or oral dabrafenib and trametinib, over one year. There will be a need for additional reporting by pathology services after surgery, to assess response to neoadjuvant treatment. Increased rates of grade 3 or worse adverse events, compared to adjuvant therapy, may result in increased hospital admissions or need for specialist services, for example gastroenterology or endocrinology. Patients will also require an additional CT scan prior to surgery.

10. Budget Impact

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

Patient uptake

The potential number of patients to be treated with the nivolumab plus ipilimumab regimen for the neoadjuvant treatment of resectable stage III melanoma with at least one pathologically proven lymph-node metastasis and a maximum of three in-transit metastases was estimated to range from 70 to 90 patients per year in Scotland. The estimates were based on local prescribing data extrapolated to provide a national estimate and were validated with clinical expert opinion. Discontinuation and mortality rates were not included. The base case is presented using the upper

estimate of annual patient uptake of 90 and additional scenario is presented to explore a lower uptake of 70 patients per year.

Per patient medicine cost and treatment duration

These prices include VAT.

The medicine acquisition cost was used to determine net medicine budget impact. The confidential NHSScotland Patient Access Scheme (PAS) price of medicines was used (accessed February 2025). The price of 240mg/24ml solution for infusion vials of nivolumab and 50mg/10ml solution for infusion vials of ipilimumab were used to calculate medicine acquisition cost in the treatment arm. The acquisition costs for medicines in the NHSScotland SOC basket was based on weighted average methodology using proportion of patients for each regimen. The duration of treatment was informed by median number of cycles from the NADINA study, SPC and validated with clinical expert opinion[11]. The estimated proportion and duration of various treatment regimens is summarised in Table 2.

Comparator displacement

Based on feedback from clinical experts, the following adjuvant regimens are likely to be displaced by the neoadjuvant nivolumab plus ipilimumab regimen: dabrafenib plus trametinib (BRAF V600E/K mutation-positive), nivolumab and pembrolizumab, which together comprise the NHSScotland SOC (outlined in Table 2). The base case assumed that neoadjuvant nivolumab plus ipilimumab regimen would displace 100% of NHSScotland SOC in the proposed patient population.

Results

All figures in the budget impact include VAT.

The Council considered results using NHSScotland PAS price in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. The results suggested that use of the neoadjuvant nivolumab plus ipilimumab regimen would decrease the net medicines budget for this patient group when compared to NHSScotland SOC.

Table 4 | Budget impact analysis base case results (confidential price, including VAT)

	Year 1[a]
Acquisition cost[b]	
Neoadjuvant nivolumab plus ipilimumab regimen	CIC
NHSScotland SOC	CIC
Displacement	
Percentage of NHSScotland SOC displaced by neoadjuvant nivolumab plus ipilimumab regimen	100%

Number of patients treated	90
Budget Impact	
Budget impact – Net medicine costs	CIC (budget decrease)

SOC = standard of care; VAT = value added tax; CIC = commercial in confidence
[a] Year 1 results would represent subsequent years as it was assumed that patients or treatment duration would not continue to subsequent years.
[b] Refer to Table 2 for details of dosing and duration.

Scenario considerations

The following table presents budget impact scenarios, exploring lower annual patient uptake and alternate proportion of medicine use in NHSScotland SOC basket.

Table 5 | Scenario analyses (confidential prices, including VAT)

#	Scenario	Base case	Neoadjuvant nivolumab plus ipilimumab regimen acquisition cost	NHSScotland SOC acquisition cost per patient	Annual patient uptake	Budget impact – Net medicine costs
					Year 1[a]	
	-	Base case	CIC	CIC	90	CIC (budget decrease)
Annual uptake						
1	70 patients	90 patients	CIC	CIC	70	CIC (budget decrease)
NHSScotland SOC proportion of patients						
2	Based on CMOP Immunotherapy report (2018-2022)[b]	Based on clinical expert opinion[c]	CIC	CIC	90	CIC (budget decrease)
Analysis exploring point where budget impact changes from budget decreasing to increasing, through adjusting proportion of patients requiring adjuvant therapy, due to not achieving a major pathological response with neoadjuvant therapy. Please note that the cost increase calculation is not based on clinical evidence of expected outcomes.						
3	77%	41%	CIC	CIC	90	CIC (budget increase)

SOC = standard of care; VAT = value added tax; CIC = commercial in confidence
[a] Year 1 results would represent subsequent years as it was assumed that patients or treatment duration would not continue to subsequent years.

[b] Based on baseline distribution of immune checkpoint inhibitor use across NHSScotland from the CMOP report (nivolumab 43% and pembrolizumab 57%)[3]. Proportional adjustment resulted in dabrafenib plus trametinib (30%), nivolumab (30%), pembrolizumab (40%) in the adjuvant setting.
[c] Refer to Table 2 for base-case patient distribution.

Limitations

As discussed in the limitations of the cost-comparison (section 7), factors including no dosage adjustments for dose reductions or treatment interruptions could contribute to uncertainty of the overall estimate of budget impact. However, real-world variability could affect the budget impact in either direction. The base case represents the upper estimate of annual patient uptake. Patient uptake is likely an overestimate as not all the eligible population will be suitable for, or choose, neoadjuvant nivolumab plus ipilimumab regimen. Scenario 1 explored lower annual patient uptake (Table 5). In addition, Scenario 2 explored the proportion of patients on adjuvant immunotherapy medicine in the NHSScotland SOC arm based on CMOP Immunotherapy report (2018-2022)[3]. To assess the budget impact of an increase in proportion of patients requiring neoadjuvant nivolumab plus ipilimumab and going on to receive adjuvant treatment, due to not achieving a major pathological response with neoadjuvant therapy, an exploratory scenario 3 was conducted. Results showed this would need to increase from 41% to 77% or more for the overall budget impact result to change from a decrease to an increase in the net medicines budget impact.

Summary

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 PAS contract pricing. Based on the NHSScotland PAS price of medicines (accessed February 2025, including VAT), the use of neoadjuvant nivolumab plus ipilimumab regimen is estimated to decrease the net medicines budget for this patient group when compared to NHSScotland SOC.

Separate information will be supplied to 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

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13. References

1. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N*, et al.* European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2024. Eur J Cancer. 2025;215:115153.

2. Public health scotland: Cancer Incidence and Prevalence in Scotland: https://publichealthscotland.scot/media/20142/2023-03-28-cancer-incidence-report_revised.pdf.

3. Public Health Scotland: Cancer Medicines Outcomes Programme Public Health Scotland (CMOP-PHS) report: Skin Cancer (Melanoma; Merkel cell carcinoma; Squamous cell carcinoma) 2018-2022; https://publichealthscotland.scot/publications/cancer-medicines-outcomes-programme-public-health-scotland-cmop-phs-report/cancer-medicines-outcomes-programme-public-health-scotland-cmop-immunotherapy-report/.

4. Eggermont AMM, Kicinski M, Blank CU, Mandala M, Long GV, Atkinson V*, et al.* Five-Year Analysis of Adjuvant Pembrolizumab or Placebo in Stage III Melanoma. NEJM Evidence. 2022;1(11):EVIDoa2200214.

5. Hauschild A, Dummer R, Santinami M, Atkinson V, Mandalà M, Kirkwood JM*, et al.* Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III BRAF V600–mutant melanoma: Five-year analysis of COMBI-AD. J Clin Oncol. 2020;38(15_suppl):10001-.

6. Weber JS, Middleton MR, Yates G, Sharpe DJ, Kurt M, Lobo M*, et al.* Estimating Long-Term Survivorship Rates Among Patients With Resected Stage III/IV Melanoma: Analyses From CheckMate 238 and European Organization for Research and Treatment of Cancer 18071 Trials. J Clin Oncol.0(0):JCO.24.00237.

7. Cancer research UK: Survival for melanoma skin cancer: https://www.cancerresearchuk.org/about-cancer/melanoma/survival.

8. Charakidis M, Backen A, Wallace AJ, Blackhall FH, Wang X, Lorigan P. 1134P BRAF codon 600 mutations in patients diagnosed with melanoma in the UK; An audit to assess variation in mutation frequency & methods between clinical testing centres. Ann Oncol. 2020;31:S760.

9. Bloem M, Meza MMd, Aarts MJB, Berkmortel FVD, Blank CU, Blokx W*, et al.* Adjuvant BRAF/MEK versus anti-PD-1 in BRAF-mutant melanoma: Propensity score–matched recurrence-free, distant metastasis-free, and overall survival analysis. J Clin Oncol. 2024;42(16_suppl):9573-.

10. Longo C, Pampena R, Lallas A, Kyrgidis A, Stratigos A, Peris K*, et al.* Adjuvant therapy for cutaneous melanoma: a systematic review and network meta-analysis of new therapies. Journal of the European Academy of Dermatology and Venereology. 2020;34(5):956-66.

11. Blank CU, Lucas MW, Scolyer RA, van de Wiel BA, Menzies AM, Lopez-Yurda M*, et al.* Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma. N Engl J Med. 2024;391(18):1696-708.

12. Suciu S, Eggermont AMM, Lorigan P, Kirkwood JM, Markovic SN, Garbe C*, et al.* Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II–III Melanoma Adjuvant Therapy. JNCI: Journal of the National Cancer Institute. 2017;110(1):87-96.

13. Eggermont AMM, Kicinski M, Blank CU, Mandala M, Long GV, Atkinson V*, et al.* Seven-year analysis of adjuvant pembrolizumab versus placebo in stage III melanoma in the EORTC1325 / KEYNOTE-054 trial. Eur J Cancer. 2024;211:114327.

14. Menzies AM, Amaria RN, Rozeman EA, Huang AC, Tetzlaff MT, van de Wiel BA*, et al.* Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2021;27(2):301-9.

15. Rozeman EA, Hoefsmit EP, Reijers ILM, Saw RPM, Versluis JM, Krijgsman O*, et al.* Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med. 2021;27(2):256-63.

16. European Medicines Agency, variation assessment report, nivolumab https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0041-epar-assessment-report-variation_en.pdf.

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