National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG122 Pembrolizumab | Advice Document v1 | April 2025

Pembrolizumab for the neoadjuvant treatment of stage IIIB to IIID or oligometastatic resectable stage IV 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 pembrolizumab 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 melanoma
Medicine Name	Pembrolizumab
Cancer type	Skin cancer
Proposed off-label[B] indication	Neoadjuvant treatment of stage IIIB to IIID or oligometastatic resectable stage IV melanoma
Medicine Details	Form: Pembrolizumab 25mg/ml concentrate solution for infusion

	Dose: Intravenous infusion of 200mg pembrolizumab every three weeks for a total of 3 doses before surgery. Followed by 1 additional cycle of 200mg pembrolizumab at a 3 weekly interval and 7 cycles of 400mg pembrolizumab at 6 weekly intervals.
Advice eligibility criteria	**Inclusion Criteria**: • Stage IIIB to IIID or oligometastatic resectable stage IV melanoma • At least 18 years of age • Performance Status 0 to 2 **Exclusion Criterion**: • Uveal or ocular melanoma

[B] Pembrolizumab as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.

1. Current Management Context

Malignant cutaneous melanoma, incidence and prognosis

Malignant melanoma is a cancer that develops in melanocytes, it 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 is melanoma that has spread into the skin, lymph vessels, or lymph glands close to the melanoma[1]. Approximately 40% of patients will harbour a BRAF V600E mutation[2].

Stage IV melanoma is when melanoma has spread to distant organs such as the liver or brain and symptoms can include fatigue, weight loss or, in some cases, seizures. 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[3, 4].The use of post operative adjuvant immunotherapy treatment in Scotland has increased each year since 2018 with a median age of 65 years in those patients treated[5, 6]. 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[7-10].

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. For stage IV resected melanoma adjuvant nivolumab is an option. Treatment is given for 12 months. Treatment decisions are based on patient characteristics, preference for oral or intravenous therapy, presence of BRAF mutation, and the side effect profiles of the different regimens. Outcomes between nivolumab, pembrolizumab, and dabrafenib plus trametinib are considered to be similar[11, 12].

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 pembrolizumab for patients with resectable stage III and stage IV melanoma, with neoadjuvant preferable to adjuvant therapy.

Pharmacology of pembrolizumab

Pembrolizumab binds to PD-1 receptors on immune cells, allowing the immune system to target and kill cancer cells[13].

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 pembrolizumab, 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[14].

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The SWOG S1801 study was identified as supporting the use of neoadjuvant pembrolizumab followed by adjuvant pembrolizumab. The SWOG S1801 study was a phase II randomised, open-label, multicentre study conducted in the US, which compared neoadjuvant pembrolizumab and adjuvant pembrolizumab (neoadjuvant-adjuvant group) with adjuvant pembrolizumab only (adjuvant-only group). The study included patients who were 18 years of age and older, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2, had clinically detectable and measurable stage IIIB to IIID melanoma or oligometastatic resectable stage IV (M1a, M1b, and M1c) melanoma (as defined in the eighth edition of the Cancer Staging Manual of the American Joint Committee on Cancer). The patients had to be suitable for surgical resection and neoadjuvant-adjuvant therapy or adjuvant-only treatment. Patients could have received previous adjuvant therapy, provided it was not immunotherapy or radiotherapy[15].

Patients were randomised equally (1:1) to the neoadjuvant-adjuvant group (n=154) or the adjuvant-only group (n=159) and stratified according to the stage of melanoma (IIIB, IIIC, or IIID or IV) and whether the patient's serum lactate dehydrogenase was above or below the upper limit of normal[15].

The neoadjuvant-adjuvant group received an intravenous infusion of pembrolizumab 200mg every three weeks for three cycles prior to surgery, followed by an additional 15 cycles as adjuvant therapy. The adjuvant-only group had surgery followed by adjuvant therapy with an intravenous infusion of pembrolizumab 200mg every three weeks for a total of 18 cycles. The time between the last dose of neoadjuvant therapy and surgery was expected to be no longer than five weeks[15].

The primary outcome was investigator-assessed event free survival (EFS), measured from randomisation to the first of: disease progression or toxicity from treatment precluding surgery; the inability to resect all gross disease; disease progression, surgical complications or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Safety was also evaluated[15].

Under design assumptions outlined in the study protocol, it was estimated that 104 events would provide the trial with 81% power to detect a hazard ratio of 0.64 (one-sided alpha level of 0.15) with the use of a log-rank test for the comparison of the neoadjuvant-adjuvant group and the adjuvant-only group with respect to event-free survival[15].

Results

The median age was 64 years, range (19 to 90) in the neoadjuvant-adjuvant group and 62 years, range (22 to 88) in the adjuvant-only group. Thirty-five percent of the study population were female and all but one patient had an ECOG performance status of 0 or 1. Ninety-four percent of patients had a cutaneous or unknown melanoma subtype and 86% of patients had a disease stage of IIIB or IIIC with remaining patients being stage IIID or IV. All patients that were randomised were included in the analysis[15].

At analysis, the median duration of follow-up was 14.7 months in both groups. Event-free survival was significantly longer in the neoadjuvant–adjuvant group than in the adjuvant-only group (p=0.004 by the log-rank test)[15].

Reasons for not undergoing surgery following neoadjuvant treatment were withdrawal of consent after randomisation (two patients), toxic effects (one patient), disease progression (twelve patients), and coexisting conditions (one patient)[15].

Events that occurred prior to the initiation of adjuvant treatment were assigned an event at day 84; the rationale for this approach was to account for differences in time to receipt of adjuvant therapy across the two treatment groups. In the neoadjuvant-adjuvant group 28 events occurred prior to adjuvant treatment that were assigned an event day 84. In the adjuvant group 22 events were assigned event day 84[15]. A conclusion on overall survival cannot be drawn until data matures.

Table 1| Results from SWOG S1801 for primary and secondary outcomes in intention to treat population[15, 16]

	Neoadjuvant-adjuvant group (n=154)	**Adjuvant-only group (n=159)**
Primary outcome: EFS		
Median follow up, months	14.7 months (NR to NR)	
Median time to EFS	NR	NR
EFS, at unreported data cut	116 (75%)	92 (58%)
EFS, at unreported data cut Hazard ratio (95% CI)	0.59 (0.40 to 0.86), one sided log-rank p=0.0015	
Events at data cut	38 (25%)	67 (42%)
2-year survival		
EFS (95% CI)	72% (64 to 80)	49% (41 to 59)

	Neoadjuvant-adjuvant group (n=154)	Adjuvant-only group (n=159)
Secondary outcome: overall imaging-based response		
Complete response	9/142 (6%)	N/A
Partial response	58/142 (41%)	N/A
Overall survival		
Deaths	14/154	22/159
Hazard ratio (95% CI)	0.63 (0.32 to 1.24) one-sided p=0.091	

CI: confidence interval, EFS: event free survival, N/A: not applicable, NR: not reached

Patient reported outcomes

Patient reported outcomes were not assessed as part of the SWOG S1801 study[15].

Safety evidence

In the SWOG S1801 study, during the neoadjuvant phase there were 19 adverse events (AE) of grade 3 or 4 reported which included but were not limited to five cases of increased liver enzymes, two cases of hyperglycaemia and one case of myocarditis. One patient did not proceed to surgery due to 'toxic effects' but the time point at which this occurred or the specific causal adverse event was not reported[15].

In the neoadjuvant-adjuvant group, 127 patients (out of 154) went on to have surgery[15]. One patient did not proceed to surgery due to 'toxic effects' but the time point at which this occurred or the specific causal adverse event was not reported. Three patients in this group did not start adjuvant treatment due to toxic effects from neoadjuvant pembrolizumab (colitis, pneumonitis, and polymyalgia rheumatica in one patient each).

Of note, the original SWOG 1801 paper reports 11 grade 4 increases in ALT in the neoadjuvant-adjuvant arm attributed to surgery. However private communication with the authors (24th February 2025), has confirmed there was an error in the published manuscript, which should have stated one grade 4 ALT AE, rather than 11 grade 4 ALT AEs attributable to surgery[17]. A request for a printed correction to the original paper has been submitted by the authors.

In the adjuvant-only group 141 patients (out of 159) underwent surgery and there were five grade 3 AEs deemed to be surgery related, but there were no grade 4 or higher surgery related AEs in this group[15].

The rate of grade 3 or 4 AEs during adjuvant therapy in both the neoadjuvant-adjuvant and adjuvant-only groups were 22 versus 32 events. During the adjuvant phase of treatment increases in liver enzymes of grades 3 or 4 were similar across the neoadjuvant and adjuvant groups (5 events versus 4 events)[15].

No new toxic effects of pembrolizumab were observed in this study and no deaths were deemed attributable to pembrolizumab. At the time of the data cut there were 14 deaths (9%) of 154 in the neoadjuvant– adjuvant group and 22 deaths (14%) of 159 in the adjuvant-only group[15].

Quality assessment of clinical evidence

Overall, the study SWOG S1801 was judged to have low risk of bias though there were some concerns noted based on assessment with the Cochrane Risk of Bias version 2 tool[14]. Randomisation was performed centrally, limiting the risk of selection bias. The study used an open label design meaning treatment assignments were not masked for patients or investigator staff, which could introduce bias on subjective outcomes.

Concerns have been raised about the potential for bias in outcome analysis[18]. Firstly, assigning an event time of 84 days to events that occurred prior to starting adjuvant therapy, to account for differences in time to starting adjuvant therapy between the two groups, distorts the distribution of events over time. Secondly, it has been estimated that there may have been higher rates of early censoring in the neoadjuvant group[18]. The SWOG S1801 is a phase II study, and it is possible for spurious results to occur given the estimated 80.5% power of detection. For this reason, results will be interpreted cautiously and discussed within the wider research context below.

Clinical effectiveness considerations

Neoadjuvant-adjuvant pembrolizumab improved EFS compared to adjuvant pembrolizumab. The SWOG S1801 study met its primary outcome, demonstrating that neoadjuvant-adjuvant pembrolizumab improved EFS compared to adjuvant only pembrolizumab. The EFS hazard ratio was 0.59 (95% CI 0.40-0.86, p=0.0015)[16]. Two-year event-free survival was 72% (95% CI 64 to 80) in the neoadjuvant–adjuvant group compared to 49% (95% CI 41 to 59) in the adjuvant-only group. The improvement in EFS was consistent across all subgroups, including those with BRAF mutant disease. The median duration of follow-up was short at 14.7 months. As a phase II trial, with a lower power and higher risk of a finding due to chance there may be some uncertainty on the magnitude of the benefit of neoadjuvant-adjuvant treatment. Furthermore, the approach to assign all early events to day 84 post-surgery has an uncertain impact on Kaplan-Meier based outcome measures. However, the difference in number of events (38 in neoadjuvant-adjuvant group and 67 in adjuvant only group) and the significant difference of estimated 2-year EFS of 23% may provide some reassurance[15].

Overall survival data is immature

The overall survival data is immature, with 14 deaths in the neoadjuvant-adjuvant arm (n=154) and 22 deaths in the adjuvant arm (n=159). The improvement in EFS may be an appropriate surrogate[19].

Due to the short follow-up time, overall survival estimates have not been reported. Mature data may take longer than 10 years of follow-up and when mature data are reported it may be confounded by subsequent treatments and other factors. However, in another study of adjuvant immunotherapy in melanoma, early improvements in relapse-free survival and distant metastasis-free survival were maintained at 7 years follow-up[20]. The statistically significant improvement in EFS is encouraging in the interim.

The control arm in the SWOG 1801 study is relevant to NHSScotland practice

Adjuvant pembrolizumab, the control arm in SWOG 1801, is a treatment option in NHSScotland and is a relevant comparator for this proposal. Patients with BRAF V600E/K mutations would also have the option of adjuvant dabrafenib plus trametinib. The control arm of SWOG1801 study did not include dabrafenib plus trametinib as a treatment option[15]. However, this should not significantly affect the generalisability of the results, as immunotherapy and dabrafenib plus trametinib are considered to have similar efficacy[9, 11].

SWOG 1801 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 is sufficiently similar to understand the generalisability of the SWOG 1801 study findings. It reported a median age of 65 years, with 79% of patients having a ECOG PS of 0 and 17% having a PS of 1. The SWOG 1801 study reported a median patient age of 64 years in the neoadjuvant-adjuvant arm and 62 years in the adjuvant arm, with approximately 75% having a ECOG PS of 0 and 25% having a PS of 1[15]. The eligibility criteria for SWOG1801 included patients with a PS of 2. However, only one patient was PS 2, which may reduce the generalisability of neoadjuvant-adjuvant pembrolizumab to patients with a PS of 2 treated in NHS Scotland. Overall, the results of SWOG1801 are likely generalisable to the NHSScotland population, despite the SWOG 1801 study being conducted in the USA only.

For patients with rarer forms of melanoma, such as acral and mucosal melanoma, there is some uncertainty regarding the generalisability of the results as the patient numbers for these subtypes were small and no efficacy data were available. The licence for the adjuvant indication includes mucosal and acral melanoma, despite these subtypes not being included in the registration trial population[21].

The 6-weekly dosing regimen does not match the SWOG 1801 dosing regimen

The proposed dosing is pembrolizumab 400mg every 6 weeks during the adjuvant treatment phase, whereas the trial used 200mg every 3 weeks throughout. Pembrolizumab monotherapy is now licensed for 6-weekly administration across various tumour types and settings, including for

the adjuvant treatment of melanoma. The six-weekly dosing schedule is considered equivalent to the 3-weekly schedule; it is supported by pharmacokinetic and clinical data and is not expected to affect the efficacy or safety of pembrolizumab[13, 22, 23].

The safety profile of neoadjuvant-adjuvant pembrolizumab is similar to adjuvant pembrolizumab and did not significantly affect surgery

Rates and types of grade 3 or worse adverse events were similar between the neoadjuvant-adjuvant and adjuvant arms, with no unexpected safety signals. The published SWOG 1801 paper reported 11 grade 4 increases in ALT in the neoadjuvant-adjuvant arm; however, this was an error in reporting, and there was only 1 grade 4 ALT increase AE. Only one patient in the neoadjuvant-adjuvant arm was unable to have surgery due to neoadjuvant pembrolizumab side effects [15, 17].

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 2024. 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 reduce 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 a promising step in the management of this patient group. It was noted that there are reassurances that neoadjuvant treatment may not prevent or delay surgery.

5. Benefit-Risk Balance

The proposed neoadjuvant use of pembrolizumab is off-label. The SWOG 1801 study, met its primary outcome, showing a statistically significant increase in EFS for patients treated with neoadjuvant-adjuvant pembrolizumab compared to adjuvant pembrolizumab[15]. Two-year EFS was improved by 23%[15]. The results are likely generalisable to the NHSScotland population. The substantial clinical benefit based on EFS provides reassurances in the absence of mature overall survival data. There were no unexpected safety signals, and only one out of 152 patients was unable to undergo surgery due to side effects from neoadjuvant pembrolizumab.

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 pembrolizumab.

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 pembrolizumab for neoadjuvant treatment of stage IIIB to IIID or oligometastatic resectable stage IV melanoma. Therefore, a de-novo cost-comparison was performed.

Population, intervention, comparator and outcomes

The patient population was stage IIIB to IIID or oligometastatic resectable stage IV melanoma. The intervention was neoadjuvant pembrolizumab, followed by adjuvant pembrolizumab, hereafter referred to as neoadjuvant-adjuvant pembrolizumab. The current standard of care in NHSScotland for this patient population is adjuvant treatment and depends on BRAF mutation status. Patients can receive adjuvant nivolumab or pembrolizumab, with an alternative option of dabrafenib plus trametinib (for 40% patients who harbour a BRAF mutation[2]). 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 and healthcare resource use. Medicine acquisition costs were calculated based on available formulations, pack sizes and unit costs for each treatment regimen in Table 2. The price of 100mg/4ml concentrate for infusion vial of pembrolizumab was used to calculate medicine acquisition cost in the treatment arm. The duration of treatment was informed by median number of cycles from the SWOG S1801 study, summary of product characteristics (SPC) and validated with clinical expert opinion[15]. 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 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-adjuvant pembrolizumab 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 events were assumed similar across the neoadjuvant-adjuvant and adjuvant arms based on clinical expert opinion.

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-adjuvant pembrolizumab			
Pembrolizumab (100%)	Pembrolizumab (neoadjuvant)	200mg IV every three weeks	3
	Pembrolizumab (additional adjuvant cycles)	200mg IV every three weeks	1
		400mg IV every six weeks	7

[a] BRAF V600E/K mutation-positive receive dabrafenib plus trametinib.
Key: Adjuvant: post-surgery; neoadjuvant: before surgery; IV = intravenous; 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-adjuvant pembrolizumab would result in lesser total costs than the NHSScotland SOC comparator treatment. The main source of cost-saving was higher treatment acquisition cost of NHSScotland SOC arm.

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

Cost category / Treatment	Medicine acquisition (£)	Medicine administration (£)	Healthcare resource use (£)	Total costs per-patient (£)
Neoadjuvant-adjuvant pembrolizumab	CIC	2,072	1,632	CIC
NHSScotland SOC[a]	CIC	1,209	1,388	CIC
Cost difference	CIC	862	244	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-adjuvant pembrolizumab reflects the SWOG S1801 study, consistent with the proposed dosing in NHSScotland[15].

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 a cost-effectiveness analysis, the analysis only compared costs. Given the favourable SWOG S1801 study results, the neoadjuvant-adjuvant pembrolizumab may offer clinical benefit in the proposed patient population[15]. 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[5]. 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 neoadjuvant-adjuvant pembrolizumab 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[7-9]. Costs associated with future recurrences were not included in the analysis. The findings from the SWOG S1801 study showed that neoadjuvant-adjuvant pembrolizumab had lower recurrences after starting adjuvant therapy compared to the adjuvant arm (9 events versus 41 events)[15]. A lower recurrence rate could potentially lower overall healthcare costs in the neoadjuvant-adjuvant pembrolizumab arm.

Summary

The cost-comparison indicated that the neoadjuvant-adjuvant pembrolizumab is a cost-saving intervention compared to NHSScotland SOC for patients with stage IIIB to IIID or oligometastatic resectable stage IV 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

Overall, neoadjuvant-adjuvant pembrolizumab is not expected to have a significant service impact. Neoadjuvant-adjuvant pembrolizumab will involve two extra infusions if replacing adjuvant pembrolizumab but will involve two fewer infusions if replacing adjuvant nivolumab, due to the use of 3- and 6-weekly pembrolizumab within the overall regimen. There may be a service impact where 11 cycles of neoadjuvant-adjuvant intravenous pembrolizumab replaces 13 cycles of adjuvant oral dabrafenib and trametinib. There will also be an additional CT scan after neoadjuvant pembrolizumab.

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 eligible for neoadjuvant-adjuvant pembrolizumab for stage IIIB to IIID or oligometastatic resectable stage IV melanoma was estimated to be around 130 patients per year in Scotland. The estimate is based on local prescribing data extrapolated to provide a national estimate and was 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 130 and an additional scenario is presented to explore a lower uptake of 70 patients per year to represent patients who are not suitable, or choose other treatment options (Table 5).

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 PAS price of medicines was used (accessed February 2025). The price of 100mg/4ml concentrate for infusion vial of pembrolizumab was 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 the proportion of patients receiving each regimen according to clinical expert opinion. The duration of treatment was informed by the median number of cycles from the SWOG S1801 study, SPC and validated with clinical expert opinion[13, 15]. 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 neoadjuvant-adjuvant pembrolizumab: dabrafenib plus trametinib (BRAF V600E/K mutation-positive), nivolumab and pembrolizumab, which together comprise the NHSScotland SOC. The base case assumed that neoadjuvant-adjuvant pembrolizumab 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 neoadjuvant-adjuvant pembrolizumab 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-adjuvant pembrolizumab	CIC
NHSScotland SOC	CIC
Displacement	
Percentage of NHSScotland SOC displaced by neoadjuvant-adjuvant pembrolizumab	100%
Number of patients treated	130
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-adjuvant pembrolizumab acquisition cost	NHSScotland SOC acquisition cost per patient	Number of patients treated	Budget impact – Net medicine costs
					Year 1[a]	
	-	Base case	CIC	CIC	130	CIC (budget decrease)
Annual uptake						
1	70 patients	130 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	130	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] Based on baseline distribution of immune checkpoint inhibitor use across NHSScotland from the CMOP report (nivolumab 43% and pembrolizumab 57%)[5]. 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 as 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-adjuvant pembrolizumab which is explored in Scenario 1 (Table 5). In addition, Scenario 2 explored the proportion of patients on immunotherapy in the NHSScotland SOC arm based on CMOP Immunotherapy report (2018-2022)[5].

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-adjuvant pembrolizumab 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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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