

National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG126 Nivolumab in combination with ipilimumab | Advice

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Nivolumab in combination with ipilimumab for the neoadjuvant treatment of adults with mismatch repair deficient or microsatellite instability-high locally advanced colon cancer classified as T4 or borderline resectable ^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 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 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 colorectal cancer
Medicine Name	Nivolumab plus ipilimumab
Cancer type	Colon cancer
Proposed off-label use ^B	Neoadjuvant treatment of mismatch repair deficient or microsatellite instability-high (dMMR or MSI-H) locally advanced colon cancer classified as T4 or borderline resectable

<p>Medicine Details</p>	<p><u>Form</u>: Concentrate for solution for infusion, intravenous (IV)</p> <p><u>Dose</u>: Nivolumab 3mg/kg of bodyweight IV day 1 and 15 (two doses total)</p> <p>Ipilimumab 1mg/kg of bodyweight IV day 1 (one dose total)</p> <p>Followed by surgery usually within 4 weeks of second nivolumab dose.</p>
<p>Advice eligibility criteria</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Radiologically classified T4 colon cancer or deemed by multidisciplinary team that tumour is borderline resectable. • Confirmed MSI-H/dMMR. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Clinical symptoms or radiological suspicion of obstruction (unless defunctioned). • Active autoimmune disease or requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of drug administration. • Prior immunotherapy for colon cancer.

^B Nivolumab in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings (dosing different to this proposal):

- first-line treatment of unresectable or metastatic colorectal cancer
- treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy
- See Summary of Product Characteristics for further licensed indications¹

1. Current Management Context

Locally advanced colon cancer symptoms, incidence and prognosis

Locally advanced nonmetastatic colon cancer has spread beyond the inner lining, muscle layers and potentially the outer serosal lining of the colon (T4a) and into adjacent organs (T4b). Symptoms are normally associated with larger tumours and/or advanced disease stages. Alterations in bowel habit, abdominal pain, weight loss without other specific causes, weakness, iron deficiency and anaemia are the most common symptoms². Genetic mutations can occur due to DNA mismatch repair deficiency (dMMR) and as a result cause microsatellite instability (MSI-H), either associated with Lynch syndrome, a genetic cancer pre-disposition syndrome, or as sporadic cancer usually associated with BRAF mutations³.

In Scotland, there were 3,039 colon cancer diagnoses in 2022, with the highest incidence in patients aged 70 to 74 years with 488 cases⁴. In 2022, 855 (22.3%) patients were diagnosed with stage II and 974 (25.4%) stage III colorectal cancer⁵. Five-year survival rates for those diagnosed between 2015-2019 were 46.4%⁶. Between 5% and 20% of colon cancers show dMMR/MSI-H⁷. The incidence of patients with stage II and III colorectal cancer with dMMR/MSI-H is fewer than 5 per 10,000 diagnosed per year in NHSScotland and meets orphan-equivalent criteria. The proposed population, with locally advanced colon cancer classified as T4 or borderline resectable is a subgroup of this population.

Colon cancer treatment pathway in NHSScotland

Within NHSScotland genetic testing is currently undertaken at diagnosis for all colorectal cancer patients prior to treatment. Those who are mismatch repair-proficient either have upfront surgery or receive neoadjuvant treatment with fluorouracil-based chemotherapy e.g. capecitabine plus oxaliplatin (CAPOX) or folinic acid plus fluorouracil and oxaliplatin (FOLFOX). Within NHSScotland there is no current recommended neoadjuvant treatment for dMMR/MSI-H colon cancer as CAPOX and FOLFOX treatment is not considered beneficial for this indication in the MSI-H population⁸. Patients with borderline resectable MSI-H disease can proceed directly to surgery, though this is typically an extensive procedure and may require resection of adjacent organs, with the possibility of residual disease. Following surgery, patients with stage II high-risk (including all patients with pathological T4 disease) and stage III (lymph nodes involved by cancer) low- or high-risk are considered for treatment with CAPOX, preferred, or FOLFOX for either 3 or 6 months. The choice is based on performance status, comorbidities, age, pathology, presence of stoma, and patient preference. For patients with residual disease after surgery, or whose cancer recurs and metastasises at a later stage, the combination of nivolumab plus ipilimumab (given for up to 2 years) is a first-line treatment option.

International Context for proposed use

The National Comprehensive Cancer Network (NCCN) support this treatment as the preferred option in cases that are T4b or bulky nodal disease⁹.

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 Programmed Cell Death 1 receptor on immune cells, allowing the immune system to target cancer cells, while ipilimumab is a Cytotoxic T-lymphocyte associated protein 4 inhibitor that increases T-cell activity, enhancing the immune system's ability to recognise and kill cancer cells^{1, 10}.

2. Evidence Review Approach

A literature search was conducted to identify clinical and economic evidence 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 search concepts included but were not limited to nivolumab, ipilimumab and colon cancer. 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 Risk of bias in non-randomised studies of interventions tool version 2¹¹.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The NICHE-2 study was a phase II single-arm, open-label, multicentre study conducted in the Netherlands, to evaluate the efficacy of neoadjuvant nivolumab plus ipilimumab in patients with nonmetastatic, locally advanced, previously untreated dMMR colon cancer¹². The initial study protocol included adults with clinical stage II or III colon cancer; an amendment to the protocol restricted the inclusion to patients with disease classified as T3 or higher, N+, or both by radiographic assessment, in order to enrich for high-risk disease, stage III disease, or both. Patients were required to have a resectable tumour with no distant metastases and a World Health Organisation performance status (WHO PS) score of 0 to 1¹². Staging was confirmed using the eighth edition of the cancer staging manual of the American Joint Committee on Cancer tumour-node-metastasis cancer staging system. Patients received two doses of nivolumab at a dose of 3mg per kilogram of bodyweight IV, on days one and day 15, and one dose of ipilimumab at a dose of 1 mg per kg bodyweight IV on day one, followed by surgery, which aligns with the proposed regimen. The study included two primary outcomes, one for efficacy and one for safety. The primary efficacy outcome was 3-year disease-free survival (DFS) defined as time from surgery to relapse or disease related death. The primary safety outcome was timely surgery, which was defined as the performance of planned surgery, with a delay of no more than 2 weeks beyond the prespecified 6 weeks following study enrolment, due to a treatment related adverse event. Key secondary outcomes included central assessment of pathological response; response was categorised as either a pathological response, a major pathological response or a complete

response when there were no more than 50%, 10% or no residual viable tumour in the resected specimens respectively. Only the primary outcomes were controlled for multiplicity¹².

Results

Efficacy results

The NICHE-2 study enrolled a total of 115 patients with locally advanced and previously untreated dMMR colon cancer. The median age was 60 years, range (20 to 82), 58% of patients were female and 87% had a WHO PS of 0. Sixty seven percent of patients had radiographically confirmed stage III disease and 64% of patients had a cT4 tumour. At an initial data-cut, median follow up was 26.2 months (range 9.1 to 65.3).

At the time of analysis, the primary endpoint of 3-year DFS data was not yet mature. No disease recurrences were reported at the 26.2 month follow up and all 37 patients who had a follow up greater than 36 months remained disease-free. Pathological response was found in 109 (98%) of patients in the study (95% confidence interval [CI] 94 to 100); of these patients 95% had a major pathological response (95% CI 89 to 98), and 68% had a pathological complete response (95% CI 58 to 78)¹². In the subgroup of patients with cT4a or cT4b (n=72), aligned with this proposal, 64% (95% CI 52 to 75) had a pathological complete response.

Other data were also assessed but remain confidential.

Safety results

All patients made it to surgery, with the median time from the first dose of immunotherapy to surgery being 5.4 weeks (range 4.0 to 33.6). The study met its primary outcome for safety, with 98% of patients undergoing cancer surgery within 6 weeks of study enrolment. A delay due to adverse events was noted in two patients, both due to grade 2 or 3 myositis, which resolved with immunosuppressive treatment, with delays to surgery of 10 and 27.8 weeks¹².

Grade three or four immune-related adverse events occurred in five patients (4% [95% CI 1 to 10]), this included rash (1 patient), asymptomatic increase in amylase and lipase levels (1 patient), myositis (1 patient), hepatitis (1 patient), and hyponatraemia (1 patient). Grade 3 surgery-related adverse events were reported in 12 patients (10% [95% CI 6 to 18])¹².

Supportive evidence for relative efficacy of current standard treatment to proposed treatment

Current management for the proposed population, of surgery followed by adjuvant oxaliplatin-fluoropyrimidine chemotherapy, is supported by evidence from multiple studies, including the SCOT trial comparing 3 with 6 months of adjuvant oxaliplatin-fluoropyrimidine chemotherapy and the recently published phase III FOXTROT study. The SCOT trial (n=6,088) confirmed that overall survival with 3 months of chemotherapy was non-inferior to 6 months of treatment^{8, 13}. The FOXTROT study (n = 1,053) compared perioperative chemotherapy (6-weeks pre-operative then surgery then 18-weeks post-operative) to surgery then 24 weeks of post-operative chemotherapy in patients with locally advanced colon cancer. Improved recurrence outcomes were reported in the peri-operative group (who received pre-operative chemotherapy), but this benefit was not seen in the subgroup with dMMR/MSI-H⁸.

The NICHE-2 and FOxTROT investigators conducted an indirect treatment comparison utilising individual patient level data from the NICHE-2 trial and comparing to aggregate patient data from a subgroup of the FOxTROT study with confirmed dMMR (n=185). This data was presented at European Society for Medical Oncology (ESMO) 2025, however has not yet been published in a peer-reviewed journal¹⁴.

The primary analysis of the indirect comparison was 3-year DFS, based on combined data for the perioperative and post-operative chemotherapy FOxTROT arms and an unweighted NICHE-2 population (n=111). The analysis highlights differences in baseline characteristics: NICHE-2 had a lower mean patient age (58 versus 63 years), higher proportion female (62% versus 47%) and a higher proportion with radiological T-stage 4 compared to the FOxTROT patients (77% versus 35%). Three-year DFS was estimated to be 100% for nivolumab plus ipilimumab treated patients and 80% for the chemotherapy treated patients¹⁴.

An analysis compared only the dMMR patients who had surgery followed by adjuvant chemotherapy in the FOxTROT trial, which aligns with current standard of care, with NICHE-2 trial patients, treated with pre-operative nivolumab plus ipilimumab (FOxTROT n=68, unweighted NICHE-2 population n=111). Three-year DFS was 81% for the adjuvant chemotherapy group compared to 100% with nivolumab plus ipilimumab. A separate analysis by T-stage in the dMMR subgroups of the FOxTROT trial estimated respective 3-year DFS of 84% and 70% for T3 and T4 cancers. For nivolumab plus ipilimumab patients, estimated 3-year DFS was 100% for both T3 and T4 subgroups¹⁴.

Other data were also assessed but remain confidential.

Patient Reported Outcomes

No patient reported outcomes on quality of life were identified for NICHE-2.

Risk Of Bias of Clinical Evidence

The risk of bias of the NICHE-2 study was assessed using the Risk of bias in non-randomised studies of interventions (ROBINS-I) tool. Overall, the study was judged to have a serious risk of bias; mainly due to the trial being a non-randomised, single-arm phase II trial with lack of adjustment for confounders. The remaining domains were scored as either moderate to low risk, with the main concerns coming from the lack of comparator arm, and immature DFS¹².

Clinical Effectiveness Considerations

NICHE-2 results demonstrate high levels of major and pathological complete response with neoadjuvant nivolumab plus ipilimumab.

The study included pathological response as a secondary efficacy outcome. Pathological response is determined post-surgery when analysing the removed mass for malignant cells. At the interim analysis, the NICHE-2 study demonstrated high levels of major pathological response (95%) and complete pathological response (68%)¹². In the absence of robust survival data, improvements in pathological response demonstrate treatment efficacy, however it is uncertain if this is an appropriate surrogate outcome for longer term outcomes¹⁵. While there is some evidence from

the FOxTROT trial that greater tumour regression on pathology after pre-operative chemotherapy correlated with improved recurrence outcomes, there is limited evidence to show an association between pathological response with neoadjuvant immunotherapy in locally advanced colon cancer and DFS or overall survival. Other tumour groups with better-established neoadjuvant treatment pathways have shown greater long-term survival in patients who achieved a pathological complete response; the CheckMate 816 study in resectable lung cancer compared neoadjuvant chemotherapy plus immunotherapy to neoadjuvant chemotherapy alone, the study noted higher 5-year overall survival in those patients who achieved a pathological complete response compared to those who did not¹⁶.

Disease-Free Survival data are immature

Data for 3-year DFS, the primary efficacy outcome for NICHE-2, were immature at the 18 July 2022 data-cut and there is uncertainty on the relative long-term benefits. Three-year DFS is a widely recognised surrogate for overall survival in colorectal cancer¹⁷. At the interim analysis the median follow up was 26 months, with no patients experiencing disease recurrence. The final 3-year DFS results are still to be published^{12, 18}.

The comparative efficacy of neoadjuvant nivolumab plus ipilimumab then surgery versus the current treatment of surgery then adjuvant chemotherapy is uncertain.

NICHE-2 is a single-arm study at high-risk of bias and the relative effects of neoadjuvant nivolumab plus ipilimumab are uncertain. No peer-reviewed evidence comparing the proposed treatment with the current standard of care was identified.

The abstract presented at the 2025 ESMO Conference, comparing nivolumab plus ipilimumab indirectly with chemotherapy in the dMMR subgroup of the FOxTROT study provides some insights into their relative efficacy¹⁴. Results from this analysis suggest a favourable effect for neoadjuvant nivolumab plus ipilimumab compared with current chemotherapy options for 3-year DFS. However, there are important clinical and methodological differences between the studies, including differences in the maturity of DFS data, that make cross trial comparisons uncertain, and results should be interpreted with caution¹⁴.

The indirect comparison is currently only available as an abstract and full methodological details are unavailable, so firm conclusions on this data remain highly uncertain.

The safety profile of neoadjuvant nivolumab plus ipilimumab

Treatment-related adverse events were reported for 63% of patients in NICHE-2 and of these 4% were grade three or higher, which may require additional treatment and monitoring¹⁹. The primary safety outcome of timely surgery was reached in 98% of patients. Some of the lower grade toxicities reported in the NICHE-2 study could potentially affect quality of life, such as fatigue (3%) or itch (3%), or would potentially require long-term treatment such as adrenal insufficiency (3%) and hypothyroidism (8%). Real-world data on the use of neoadjuvant nivolumab plus ipilimumab collated by NHSScotland, showed similar levels of adverse events compared to the NICHE-2 study²⁰.

A greater number of grade 3 or higher adverse events have been reported for the current standard of care, including in the SCOT trial which reported grade three and greater adverse events in 36% of patients including diarrhoea (11%), neutropenia (10%) and peripheral neuropathy (4%). Long-term side effects of grade 2 peripheral neuropathy can interfere with daily living which occurred in 25% of the 3-month cohort¹³.

The FOxTROT study reported grade three or higher adverse events in 21% of patients, including diarrhoea (5%), neutropenia (7%) and peripheral neuropathy (1.2%). Without head-to-head trials and indirect evidence, naive cross-study comparisons are very uncertain and should be interpreted with caution⁸.

There are some differences between the NICHE-2 and NHSScotland populations, however the results are likely generalisable to NHSScotland

The NICHE-2 study had a substantial proportion of patients with T4 disease (65%) which aligns with the proposed treatment population within NHSScotland. The NICHE-2 study was based in the Netherlands, however health systems and treatments are similar, as guided by ESMO advice. The NICHE-2 study included patients with a median age of 60 years and a WHO PS of 0 to 1, with 87% scoring 0. In NHSScotland, patients diagnosed with colon cancer are generally older and can include PS of up to 2, therefore representing an older and frailer population which may have lower tolerance for treatment.

4. Benefit-risk Balance

The proposal is for the off-label use and dosing of neoadjuvant nivolumab (two doses) plus ipilimumab (one dose) for dMMR or MSI-high locally advanced colon cancer classified as T4 or borderline resectable. In the single-arm NICHE-2 study, neoadjuvant nivolumab plus ipilimumab did not delay surgery in the majority of patients and was associated with high levels of major and complete pathological response in analysis of the removed tumour. In terms of DFS, no disease recurrences have been observed following a median follow up of 26.2 months (range, 9.1 to 65.3), however more mature data is required to consider 3-year DFS estimates. The effects of neoadjuvant nivolumab plus ipilimumab relative to adjuvant chemotherapy are uncertain, however the limited indirect data available is encouraging. There were no unexpected safety signals compared to the on-label use of nivolumab plus ipilimumab in colorectal cancer¹².

5. 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.

6. Economic Evidence Review Summary

Economic Overview

The literature search for economic evidence returned no cost-effectiveness publications which evaluated nivolumab plus ipilimumab for the treatment of locally advanced colon cancer in the proposed population.

Type of economic evaluation

- In the absence of a cost-effectiveness analysis, a de-novo cost-comparison analysis has been performed to support this assessment.
- The population used in the study were adult patients with dMMR or MSI-high locally advanced colon cancer, who have not received prior immunotherapy.
- The intervention consisted of two doses of nivolumab 3mg/kg of bodyweight and one dose of ipilimumab 1mg/kg of bodyweight, aligned with NICHE-2 study dosing. Based on feedback from clinical experts, the comparator included a split across post-operative (adjuvant) CAPOX and FOLFOX, where CAPOX consisted of capecitabine plus oxaliplatin, and FOLFOX consisted of folinic acid plus fluorouracil and oxaliplatin, both for a total duration of 3 months.
- It was assumed that 80% of patients in the comparator arm are administered CAPOX and 20% are administered FOLFOX, based on clinical expert estimates.
- As a cost-comparison analysis has been performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Costs

Costs included were medicine acquisition, administration and adverse event costs for time on treatment. Confidential NHSScotland National Framework prices for off-patent medicines were used and patient access scheme (PAS) prices for nivolumab plus ipilimumab (accessed January 2026). The lowest prices were used for each medicine according to doses calculated using standardised dose banding tables for Scotland.

The administration cost for intravenous medicines was based on delivery of either simple or complex parenteral chemotherapy depending on nurse and chair time for delivery of the required number of cycles (NHS National Reference costs 2024-25). The administration cost for nivolumab plus ipilimumab was based on delivery of simple parenteral chemotherapy. Based on clinical expert opinion, the medicine administration costs for all cycles of CAPOX and FOLFOX was assumed to involve administration of complex parenteral chemotherapy.

The costs associated with grade 3 or higher diarrhoea were calculated using adverse event rates from the SCOT study for CAPOX and FOLFOX, and NHS Reference costs 2024-25¹³. In the absence of a specific cost for chemotherapy-related diarrhoea, the cost code for non-elective inpatient, short-stay for inflammatory bowel disease with multiple interventions and low comorbidity score,

was considered to be the closest approximator for diarrhoea treatment. No adverse events were costed for nivolumab plus ipilimumab, as grade 3 or higher adverse events (AEs) were not found in greater than 5% of the NICHE-2 study population, or incurred negligible costs¹².

Monitoring costs such as blood tests, electrocardiograms and review appointments, were not included as these were considered to be similar between both treatments.

Costs were not discounted as the treatment duration did not exceed one year.

Results

All figures in the cost-comparison exclude VAT.

Based on medicine acquisition cost alone, nivolumab plus ipilimumab costs more per patient compared with CAPOX and FOLFOX combined (NHSScotland confidential prices, accessed January 2026). Overall, including medicine administration and adverse event costs, treatment with the nivolumab plus ipilimumab regimen is estimated to increase per patient costs compared to NHSScotland standard of care (SOC). The cost-comparison results are presented in Table 1.

Table 1 | Summary of cost-comparison results (confidential price, excluding VAT)

Cost category	Medicine acquisition (£)	Medicine administration^B (£)	Adverse event^C (£)	Total costs per patient (£)
Nivolumab plus ipilimumab^A	CIC	1,308	0	CIC
FOLFOX and CAPOX^A	CIC	2,512	96	CIC
Cost difference	CIC (cost increasing)	-1,204 (cost decreasing)	-96 (cost decreasing)	CIC (cost increasing)

CIC = commercial in confidence

^A The dosing schedule and regimen for one dose ipilimumab plus two doses nivolumab is described in the NICHE-2 study¹². The three-month duration for FOLFOX (six two-weekly cycles) and CAPOX (four three-weekly cycles) was based on practice in NHSScotland

^B Administration costs are based on the three doses total for nivolumab plus ipilimumab and the two-weekly cycle for FOLFOX and three-weekly cycle for CAPOX

^C Rates of grade 3 or higher diarrhoea from the SCOT study have been used to inform adverse event costs for FOLFOX and CAPOX¹³

Generalisability of the cost-comparison

The dosing schedule of nivolumab plus ipilimumab reflects the proposed dosing in NHSScotland. NHSScotland National Framework prices and PAS prices for medicines were considered in confidence to increase the generalisability of the net costs.

Limitations of the cost-comparison

Subsequent treatment costs are not considered in the cost-comparison

This cost comparison analysis only considers costs in the proposed setting and does not consider subsequent treatments. The indirect treatment comparison suggests that a greater number of patients treated with chemotherapy, rather than neoadjuvant nivolumab plus ipilimumab, will have disease recurrence¹⁴. In those that have disease recurrence and have unresectable or metastatic disease, nivolumab plus ipilimumab is the preferred first-line treatment and is continued until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression. This cost has not been accounted for and would be expected to increase the cost associated with the current standard of care approach.

Most adverse events associated with treatment were not costed in the analysis

Grade 3 adverse events in the NICHE-2 study did not affect a minimum of 5% of the patient population and were therefore not costed in the model. This includes adverse events such as rash and/or dermatitis, hepatitis and hyponatraemia, which were identified from clinical data and would have incurred hospitalisation and medication costs for treatment¹².

Many grade 3 adverse events were also identified in the SCOT study for CAPOX and FOLFOX but were not costed due to limited evidence on incurring significant management costs¹³.

The cost-comparison excluded adverse event related dosing adjustments for chemotherapies

The dosing was not adjusted to account for dose reductions or treatment interruptions. The duration and dosing may vary in real-world setting due to multiple factors like comorbidities and tolerability. 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.

Potential differences in complexity of surgery are not accounted for

Nivolumab plus ipilimumab has the potential to reduce NHS resource use, given that it may lead to less complex surgery compared to surgery before chemotherapy. However, there is no conclusive data to support this suggestion, and therefore any impact on surgery were not included in the cost analysis.

Summary

The cost-comparison indicated that the neoadjuvant treatment regimen with nivolumab plus ipilimumab is a more costly intervention compared to NHSScotland SOC for patients with dMMR or MSI-high locally advanced colon cancer. 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.

7. 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.

8. Service Impact

Compared with 3 months of CAPOX treatment, administrations would reduce from 4 down to 2 and with 3 months of FOLFOX treatment administrations would reduce from 6 down to 2. Neoadjuvant nivolumab plus ipilimumab would reduce the number of infusions required along with the associated clinical workload (prescribing, pharmacy, nursing time) and remove the need for central line placement which is required for FOLFOX treatment. For the predicted 26 patients eligible annually for this treatment the service impact is likely to be service sparing.

9. Budget Impact

The total estimated number of patients nationally expected to routinely access nivolumab plus ipilimumab for the proposed use on an annual basis is 26. This estimate is based on an extrapolation of unpublished NHS Scotland prescribing data between 1st July 2024 and 30th June 2025 across regional cancer networks.

Results

A budget impact was calculated using only medicine acquisition costs with value added tax (VAT) applied. This used the same dosing for nivolumab plus ipilimumab, CAPOX and FOLFOX as in the cost-comparison analysis.

The results for the estimated total annual patient uptake were presented as the base case in Table 2, which assumes that 26 patients will be eligible to receive nivolumab plus ipilimumab annually. The uptake is assumed to remain constant in subsequent years. A scenario where only 20 patients receive nivolumab plus ipilimumab was also explored in Table 2, this was considered due to the uncertainty in extrapolation of patient uptake numbers.

Budget impact costs were calculated over a 3-month period, as this was the time on treatment for the chemotherapy regimens. Discontinuation and mortality rates were not included.

Table 2 | Budget impact base case and scenario analysis results (confidential prices, including VAT)

#	Scenario	Base case	Nivolumab plus ipilimumab acquisition cost per patient	CAPOX and FOLFOX acquisition cost per patient	Annual patient uptake	Budget impact – Net medicine costs
-		Base case	CIC	CIC	26	CIC (budget increase)
1	20 patients ^A	26 patients	CIC	CIC	20	CIC (budget increase)

CIC = commercial in confidence

VAT = value added tax

^A Considering uncertainty around the true population expected to access treatment, an estimate of 20 patients has been presented as a scenario

Limitations

A limitation of the analysis is the uncertainty around the true budget impact, as the patient number expected to receive nivolumab plus ipilimumab is not known. The base case is likely to represent the upper estimate of annual patient uptake and could therefore lead to an overestimate of budget impact, as not all the eligible population will be suitable for, or choose, neoadjuvant nivolumab plus ipilimumab regimen. Scenario 1 was therefore considered in Table 2 to explore a lower patient uptake.

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 January 2026, including VAT), the use of neoadjuvant nivolumab plus ipilimumab regimen is estimated to increase the net medicines budget for this patient group when compared to NHSScotland SOC.

10. 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.

11. Acknowledgements

NCMAG would like to acknowledge:

- NICHE-2 study Principal investigator, Dr Myriam Chalabi and her team for their valuable input.

12. References

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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