National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG118 Trametinib | Advice Document v1.0 |October 2024

Trametinib for the treatment of low grade serous ovarian cancer after at least one line of platinum-based chemotherapy. [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 trametinib 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 ovarian cancer
Medicine Name	Trametinib
Cancer type	Gynaecological Cancer
Proposed off-label[B] use	Low grade serous ovarian cancer after at least one line of platinum-based chemotherapy.
Medicine Details	Form: Film coated tablets Dose: 2mg orally once daily, continuously until disease progression or unacceptable toxicity.

Advice eligibility criteria	Patients with low grade serous ovarian carcinoma after at least one line of platinum based chemotherapy. Performance Status 0-1 Adequate cardiac, hepatic and renal function Able to swallow and absorb trametinib

[B] Trametinib has a marketing authorisation for the following indications:

- As monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- In combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
- In combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

1. Current management context

Low Grade Serous Ovarian Cancer incidence, prognosis and symptoms

In 2021, there were 576 diagnoses of ovarian cancer in Scotland[1]. Low-Grade Serous Ovarian Cancer (LGSOC) of the ovary accounts for about 5% of all epithelial ovarian cancers, which make up 90% of all ovarian cancers[2]. The median age at diagnosis for ovarian cancer in Scotland is 67 years[3]. The median age at diagnosis for LGSOC tends to be lower than that for high-grade epithelial ovarian cancer and has been reported at between 43 and 47 years[4]. Median overall survival (OS) for LGSOC has been reported to be around 90 months, compared to 41 months for high-grade ovarian cancer[5]. Ovarian cancer often presents with advanced disease, symptoms include abdominal pain and bloating, changes in bowel habits, and urinary and/or pelvic symptoms. In more advanced stages, patients can develop small and large bowel obstructions, pleural effusions, and respiratory symptoms[2].

LGSOC treatment pathway in Scotland

Low-Grade Serous Ovarian Cancer has a distinct biology compared to high-grade epithelial ovarian cancer. LGSOC tends to grow slowly but is more resistant to chemotherapy and has different driver mutations. Nearly all cases exhibit oestrogen or progesterone positivity and approximately 60% have mutations in the ERK/MAPK pathway[6].

Depending on patient fitness and the extent of the disease, cytoreductive surgery is the primary treatment at diagnosis and can also be considered at relapse. There is uncertainty about optimal treatments and sequencing[7]. In Scotland, there are no medicines specifically approved for LGSOC and treatment pathways have historically followed those for high grade serous ovarian cancer. Routinely accessible treatment options at diagnosis include platinum-based chemotherapy, which may include maintenance bevacizumab or hormonal therapy (eg letrozole or tamoxifen). Systemic chemotherapy options used at relapse include retreatment with platinum-based chemotherapy if the patient previously had a good response. Other options include non-platinum-based chemotherapy, such as paclitaxel with bevacizumab (if no prior exposure or resistance to bevacizumab), liposomal pegylated doxorubicin, or hormonal therapy. Patients may undergo multiple lines of treatment, with careful assessment of prior responses and management of toxicities required.

International context for proposed off-label use

The European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) support the use of trametinib for recurrent disease in LGSOC.

Pharmacology of trametinib

Trametinib works by inhibiting MEK1 and MEK2, which are part of the ERK/MAPK signalling pathway. By inhibiting this pathway, trametinib reduces one of the drivers of cancer growth in tumours where this pathway plays a role.

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 trametinib, low grade serous ovarian cancer and recurrent. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key study was critically appraised using the Cochrane risk of bias version 2.0 tool.

3. Clinical evidence review summary

Clinical Efficacy Evidence

The key study supporting this proposal of using trametinib is the GOG 281/LOGS study[8]. The GOG 281/LOGS study was a phase II/III randomised, open label, multicentre trial which compared trametinib with study standard of care (SOC) (physician choice of either paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole and tamoxifen) in patients with recurrent, LGSOC who had received at least one prior line of platinum chemotherapy, which aligns with the submitted proposal[8].The SOC treatments in the GOG 281/LOGS study did not include all treatments which are currently available in NHSScotland. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and measurable disease according to modified Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST version 1.1 were included. Patients could have received an unlimited number of prior therapies, however those who had received all five of the included SOC regimens were not eligible to participate. In the study, 260 patients were randomly assigned to receive either oral trametinib 2mg once daily (n=130) or physician choice SOC, with dosing aligned with use in NHSScotland (n=130); stratified by geographical location (UK and USA), number of previous regimens (1, 2, >3), performance status (0 or 1) and planned SOC regimen[8]. Treatment in both arms continued until either unacceptable toxicity or disease progression. At investigator discretion, SOC arm patients could stop treatment following 6 cycles. Patients in the SOC arm were allowed to cross over to receive trametinib after having a confirmed objective progression as per RECIST criteria. The primary outcome was investigator assessed progression-free survival (PFS) (defined as time from randomisation to disease progression or death). Secondary outcomes included objective response rate (ORR) (defined as the proportion of patients in each group with a clinical response according to RECIST criteria), overall survival (OS), quality of life (QoL) and adverse events (AE). The study also examined PFS and ORR after crossover as exploratory endpoints[8].

Results from the GOG 281/LOGS study[8]

At the final data cut off, July 2019, the median duration of follow up was 31 months (interquartile range [IQR] 15.7 to 41.9 months). The median age of patients was 56 years, 84% were stage III or IV, 72% had an ECOG performance score of 0, 49% of patients had received three or more prior lines of systemic therapy, with a mean number of 2.9 prior lines (range 1 to 10). Median number

of cycles was 8 (IQR 3 to 16) in the trametinib arm, the SOC median number of cycles ranged from 2 to 10. Investigator assessed progression-free survival in the intention to treat populations improved with trametinib versus study standard of care. Overall survival improvements were numerically in favour of trametinib, although a high proportion of patients in the SOC arm crossed over to trametinib confounding and potentially underestimating the survival benefit (table 1)[8].

Table 1| GOG 281/LOGS primary and secondary outcomes in the intention-to-treat population[8]

	Trametinib (n=130)	Study SOC (n=130)
Primary Outcome: Investigator assessed PFS		
Median follow up, months (IQR)	31 (18 to 43)	31 (16 to 41)
PFS events, %	101 (78%)	116 (89%)
Median PFS, months (95% CI)	13 (9.9 to 15)	7.2 (5.6 to 9.9)
Hazard ratio (95% CI)	0.48 (0.36 to 0.64) p<0.0001	
Secondary Outcomes		
Objective response rate, %	26%	6%
Odds ratio (95% CI)	5.4 (2.4 to 12.2)	
Progressive disease rate, %	7%	17%
Median DOR, months (IQR)	14 (7.2 to 19.9)	5.9 (4.0 to 12.2)
Overall Survival		
Overall deaths, %	51 (39%)	60 (46%)
Median OS[a], months (95% CI)	38 (32 to NE)	29 (23 to 52)
Hazard Ratio (95% CI)	0.76 (0.51 to 1.12)	
Exploratory Outcomes (standard of care group who crossed over to receive subsequent trametinib)		
	n=88	
Median PFS, months (95% CI)	11 (7.3 to 12.0)	NA
Objective response rate, %	15%	NA

SOC = Standard of care, PFS = progression-free survival, CI = confidence interval, DOR = duration of response, IQR = interquartile range, OS = overall survival, NE = non-evaluable, NA = not applicable
[a]confounded by crossover (88 (68%)) of patients in SOC crossed over to trametinib after progression

Patient reported outcomes

Quality of life (QoL) was included as a secondary outcome in the GOG 281/LOGS study. QoL data was collected using the functional assessment of cancer therapy-ovarian cancer trial outcome index (FACT-O TOI) and the adapted self-administered functional assessment of cancer therapy gynaecologic oncology group neurotoxicity questionnaire (FACT-GOG-Nx) subscale. Pre-planned assessments were conducted prior to cycle 1, week 12, week 24 and weeks 36 and 52 were conducted as exploratory assessments. Data from 88% (227/259), 77% (194/253), 63% (153/244), 60% (139/233), 56% (125/222) of patients were available at baseline and at 12-week, 24-week, 36 and 52 weeks follow up respectively. The study found no clinically significant difference in either QoL measurements at all time points[8]. Whilst QoL was numerically worse at the 12-week time point for those in the trametinib group (but not at later time points), this did not reach the threshold for clinically meaningful difference.

Safety evidence

Based on data from the GOG 281/LOGS study, in the trametinib (n=128) and SOC (n=127) groups respectively, the most frequently (>5%) reported grade 3 or higher adverse event (AE) were fatigue (8% versus 4%), small intestine obstruction (13% versus 7%), colon obstruction (5% versus 1%), abdominal pain (6% versus 17%), diarrhoea (10% versus 3%), nausea (9% versus 11%), vomiting (7% versus 8%), acneiform rash (6% versus 1%), maculopapular rash (7% versus 0%), anaemia (13% versus 10%), hypertension (12% versus 5%), urinary tract infection (7% versus 5%).

In the trametinib group, adverse events of special interest included pneumonitis (3 patients), QTc prolongation (2 patients), left ventricular systolic dysfunction (2 patients), retinal vascular disorder (2 patients), and retinal tear (1 patient). In the standard-of-care group, adverse events of special interest were left ventricular systolic dysfunction (1 patient) and decreased ejection fraction (1 patient). There were no deaths reported that could be attributed to trametinib. At least one dose reduction was required in 70% of patients, with 30% of patients requiring 2 dose reductions. Slightly more patients discontinued trametinib due to toxicity compared with the SOC group (36% versus 30%)[8].

Quality assessment of clinical evidence

The GOG281/LOGS study was a phase III open label randomised, multicentre study. Overall, the study was assessed to have low risk of bias. Randomisation was completed using automated systems, thus limiting the risk of selection bias. The study also required that clinicians preselected the SOC regimen prior to randomisation and stratification. In addition, the study used an open label design and investigator assessment rather than centralised assessment, therefore increasing the risk of outcome detection bias for subjective outcomes. More than half of patients (68%) in the control arm crossed over to receive trametinib following progression, the study then used the ITT population to estimate OS, while failing to adjust for crossover, which may underestimate the OS benefit in the trametinib arm[8].

Clinical effectiveness considerations

Trametinib improved PFS and ORR compared to the SOC arm, with a trend towards improved overall survival.

The GOG 281/LOGS study met its primary outcome, showing a statistically significant improvement in PFS for trametinib over the control arm. The median PFS for trametinib was 13 months, compared to 7.2 months in the SOC arm, with an ORR of 26% compared to 6% with SOC. In subgroup analyses, improved PFS and ORR were observed in the trametinib arm irrespective of the line of treatment and the range of individual SOC treatments. However, the study was not designed to detect differences in these subgroups and some subgroups' hazard ratios crossed 1[8].

There was a trend towards better OS in the trametinib group, although it was not statistically significant. The median OS was 38 months (95% CI 32.0 to non-evaluable) in the trametinib group and 29 months (23.5–51.6) in the SOC group. The OS is likely confounded by 68% of patients

crossing over to trametinib, which was not statistically adjusted for. Of those who crossed over, 65% had a longer PFS than they had on their prior therapy[8].

The results are likely generalisable to the Scottish population, although real world evidence suggests that patients treated in NHS Scotland have poorer performance status.

Over 20% of patients were recruited from the UK. Over half of patients received prior hormonal therapy, which may provide some reassurance that the prior treatments used in GOG 281/LOG are generalisable to the NHSScotland population.

The NHS Scotland Cancer Medicines Outcomes Programme – Public Health Scotland (CMOP-PHS) provided a management report on the use of trametinib in patients with Low Grade Serous Ovarian Cancer between 2019 and 2024[9]. This report was used to assess the generalisability of findings reported in the literature to patients in Scotland. The median age at diagnosis in the study aligns to the median age treated with trametinib for LGSOC in Scotland. Seventy-two percent of patients in the GOG281/LOGS study had a performance status of 0, which was better than those treated in NHSScotland. This may reduce the generalisability of the results although there may be some subjectiveness to this measure.

Patients were heavily pre-treated however there may be some generalisability concerns regarding the SOC arm.

The inclusion criteria were broad, allowing for an unlimited number of prior therapies. The patient population was heavily pre-treated, with approximately 50% having three or more prior lines of therapy. The proposed patient population aligns with the study eligibility criteria, providing reassurance on the generalisability of the study to the population treated in NHS Scotland.

The SOC arm treatment regimens used in the GOG 281/LOGS study included some treatments which are not commonly used in NHSScotland: tamoxifen and topotecan, and some that are commonly used: paclitaxel, letrozole and pegylated liposomal doxorubicin. Paclitaxel plus bevacizumab is also routinely used in NHSScotland but was not included in the SOC arm of the study. Outside of the GOG 281/LOGS study, there is a lack of controlled trial evidence supporting the use of any treatment in LGSOC. Consequently, the relative efficacy of trametinib against paclitaxel with or without bevacizumab, which is a comparator in NHSScotland but not included in the GOG 281/LOGS study, is unknown[10]. Furthermore, no detail was provided on whether study patients had prior bevacizumab treatment.

Investigator assessed response and open label design may overestimate the improved treatment effect of trametinib compared to the study SOC.

The assessment of treatment response was not carried out centrally or blinded, with both patients and clinicians aware of treatment allocation. Progression assessment was based on standard RECIST criteria; however, investigators and patients in the SOC arm may have been influenced by the availability of trametinib upon documented progression.

With the exception of small bowel obstruction, the safety profile is similar to the on-label non-ovarian cancer indications

The most common grade three or worse adverse events were skin rash, low blood counts, anaemia, hypertension, and diarrhoea. Adverse events of special interest, including cardiac dysfunction, pneumonitis, and eye disorders, occurred at low rates. Small bowel obstruction occurred at higher rates than in the SOC arm, possibly due to complications of LGSOC and the longer treatment duration than in the SOC arm, or trametinib toxicity itself. Seventy percent of patients required a dose reduction, and 36% discontinued trametinib due to toxicity, indicating the need for careful monitoring and management of trametinib toxicity.

4. Patient group summary

We received statements from three patient groups; Ovacome Ovarian Cancer Charity, Ovarian Cancer Action and Target Ovarian Cancer. Ovacome Ovarian Cancer Charity is a charitable incorporated organisation, while Ovarian Cancer Action and Target Ovarian Cancer are registered charities. Ovacome Ovarian Cancer Charity received 3.5 % in pharmaceutical funding in the year 2022 to 2023 and are targeted to receive 10% in 2023 to 2024. Ovarian Cancer Action and Target Ovarian Cancer received 2% and 5% in pharmaceutical funding respectively. A representative from Ovacome Ovarian Cancer Charity attended the NCMAG council meeting. The key points from the submissions are summarised below:

- Low grade serous ovarian cancer is rare, with significant implications on a patient's quality of life, accounting for around 5% of all epithelial ovarian cancers, patients report feeling isolated.
- Symptoms include significant abdominal pain and in younger patients a loss of fertility and premature menopause.
- Fear of recurrence or progression is common, partly due to poor response rates to chemotherapy.
- The patient groups feel that the introduction of trametinib in this patient group would be a positive step forward, not only are there reported survival benefits, trametinib is an oral treatment, which means patients could take it at home, reducing the need to attend additional administration appointments, which may have positive implications to a patient’s quality of life and reduce carer burden.
- The patient groups note that the side effects of trametinib can be significant but note that most are manageable with a dose reduction or improve over time. It is important to take

an individual approach when determining suitability for any medicine, but the addition of trametinib, is a welcome addition to a limited treatment landscape.

5. Benefit-risk balance

The proposal is for off-label use of trametinib in patients with LGSOC after at least one prior platinum-based regimen. In the GOG 281/LOGS study, trametinib was associated with a statistically significant improvement in PFS compared to the SOC arm and an improvement in ORR. The results are likely generalisable, although differences in the treatments in the study SOC arm and the treatments commonly use in NHSScotland, as well as the lack of detail on prior bevacizumab exposure may reduce generalisability. Except for small bowel obstruction (a recognised complication of ovarian cancer), there were no unexpected toxicities compared to the on-label uses of trametinib.

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 trametinib. Under the decision-making framework for value judgements, Council considered the clinical case to be compelling.

7. Economic evidence review summary

Economic Overview

One published cost-utility analysis, by Piao et al. (2023), was identified in the literature search. This study evaluated cost-effectiveness of trametinib in patients with recurrent LGSOC who had received at least one prior line of platinum chemotherapy, from the United States (U.S.) payer perspective. A partitioned survival analysis (PSA) was performed to estimate the movement between progression-free, progressed, and death health states.[11]

The clinical outcomes were sourced from the GOG 281/LOGS study[8], details of which are outlined in Section 3. The PSA extrapolations revealed that trametinib group provided an additional 0.58 quality-adjusted life years (QALYs) (1.14 life years) compared with the standard of care (SOC) group over the lifetime time horizon.

In line with GOG 281/LOGS study, the comparator in the model comprised of a basket of physician's choice SOC which included paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan, letrozole, and tamoxifen. Clinical engagement suggests that paclitaxel either alone or in combination with platinum-based drugs or bevacizumab, PLD and hormonal therapy are predominantly used in NHSScotland. Therefore, the study patient population aligns with the submitted proposal; however, the study SOC lacks generalisability to NHSScotland SOC. In addition, the analysis was conducted from the U.S. payer perspective (that is, medicine acquisition, medicine administration, adverse events and supportive care costs applicable to U.S. healthcare setting were included), which adds to the poor generalisability.

Type of Economic Evaluation

While the study by Piao et al. (2023) provides valuable insights into the cost-effectiveness of trametinib for recurrent LGSOC, its findings may not be directly applicable to the proposal. The model was not accessible; hence it could not be adapted to the Scottish healthcare setting. Therefore, a cost-comparison analysis using NHSScotland data on costs and SOC for the first year of treatment is presented.

Population, intervention, comparator and outcomes

The population used was adult patients with LGSOC after at least one prior platinum-based chemotherapy The intervention was trametinib 2 mg taken orally. Based on feedback from the clinical experts, a basket of comparators was considered as NHSScotland SOC.

The dosages of trametinib and NHSScotland SOC medicines were adjusted based on median relative dose intensity (RDI) to account for dose reductions or treatment interruptions. The RDI was sourced from the GOG 281/LOGS study.[8] For trametinib, the RDI was 75%. The RDI for medicines not included in the GOG 281/LOGS study was conservatively assumed to be 100%.

The duration of treatment was informed by median number of cycles from the GOG 281/LOGS study. The average duration for trametinib was 8 cycles. The duration of treatment for medicines that were not included in the GOG 281/LOGS study was assumed to be 6 cycles. Table 2 provides details of regimen and proportion of patients on each regimen in the NHSScotland SOC group.

As a cost-comparison analysis was performed, quality-adjusted life-years (QALYS) were not included in the analysis.

Table 2| List of medicines included as NHSScotland SOC basket

Sr. No.	Regimen	Proportion of patients	Regimen component	Dosing schedule description[a]
1	Single agent letrozole	10%	Letrozole	2.5 mg OD for 10 cycles. RDI= 100%.
2	Single agent tamoxifen	2%	Tamoxifen	20 mg BID for 4 cycles. RDI= 82%.
3	Single agent paclitaxel	35%	Paclitaxel	80 mg/m^2 BSA IV D1, 8, 15- IV over 1 hour on day 1, every 7 days, 3 weeks on, 1 week off for 4 cycles. RDI= 100%.
4	Single agent pegylated Liposomal Doxorubicin (PLD)	8%	PLD	40 or 50 mg/m^2 BSA IV D1 - IV over 1 hour on day 1, every 28 days for 6 cycles. RDI= 100%.
5	Bevacizumab + paclitaxel	35%	Bevacizumab	10 mg/kg on days 1 and 15 of 28-day cycle for 6 cycles. Assumed RDI= 100%.
			Paclitaxel (weekly)	80 mg/m^2 BSA on days 1,8,15 of 28-day cycle for 6 cycles. Assumed RDI= 100%.

Sr. No.	Regimen	Proportion of patients	Regimen component	Dosing schedule description[a]
6	Paclitaxel + carboplatin	10%	Paclitaxel (weekly)	Weekly regimen of 80mg/m^2 BSA 6 cycles. Assumed RDI= 100%.
			Carboplatin	AUC 2 for weekly for 6 cycles. Assumed 200 mg weekly dosing. Assumed RDI= 100%.

AUC = area under the curve, BID = twice a day, BSA = body surface area, IV = intravenous, OD = once daily, 1 cycle = 28 days, RDI = relative dose intensity, SOC = standard of care.
[a] For IV medicines, average bodyweight of 70 kg and BSA of 1.8 m^2 was used for dose calculation.

Costs

The cost comparison included acquisition costs, administration costs, monitoring costs and adverse event costs were included in the cost-comparison. The list price for trametinib is £4,800 per 30-pack of 2 mg tablets (BNF list price, excluding VAT, accessed August 2024). As described previously, the trametinib and NHSScotland SOC dosages were adjusted based on RDI to account for dose reductions or treatment interruptions. The cost of NHSScotland SOC was calculated as a weighted average of different treatment regimens in Table 2, using proportion of patients as the weights.

Based on average BSA (1.8 m^2) or bodyweight (70 kg), the acquisition cost for intravenous (IV) medications was calculated using BNF list price (accessed August 2024). The calculation included wastage. This meant that if the administered dose was less than the product's content, the remaining product was discarded, and the full cost of the product was used in the calculation.

The administration cost for IV medicines was calculated using the hourly infusion cost of £333 (according to NHS Reference Cost 2022/23, inflation-adjusted).

The monitoring costs for trametinib included ophthalmology outpatient consultation, ECG (Electrocardiogram) and ECHO (Echocardiogram) at baseline, and ECHO every three months in the first year and every four months thereafter. Monitoring costs for the first year of treatment are included in the cost-comparison.

The following Grade ≥3 adverse events (AE) occurring in >5% of patients in the GOG 281/LOGS study and requiring inpatient hospital stay were included: diarrhoea (trametinib: 10%, SOC: 3%), urinary tract infection (trametinib: 7%, SOC: 5%), small intestine obstruction (trametinib: 9%, SOC: 2%) and colon obstruction (trametinib: 0%, SOC: 3%). The AE costs were taken from the NHS Reference costs 2022/23 (November 2022, inflated to the latest cost year). The AE costs were multiplied by AE rates and applied as a one-off cost in the first year. Due to the absence of comparative safety evidence, additional AEs for medicines not included in the GOG 281/LOGS study were not considered in the AE cost calculation.

Results

All figured in cost-comparison exclude VAT.

Table 3 | Summary of cost-comparison results (list price)

Cost category	Trametinib	NHSScotland SOC[a]	Cost difference
Medicine acquisition	£26,880	£11,629	£15,251
Medicine administration	-	£6,511	- £6,511
Adverse event	£1,041	£486	£555
Monitoring (first year only)	£1,950	-	£1,950
Total costs per-patient	**£29,871**	**£18,627**	**£11,244**

[a] NHSScotland SOC refers to basket of comparators listed in the Table 2.

Using the BNF list price for the cheapest generic alternative (accessed August 2024), the medicine acquisition cost of 1.5 mg of trametinib (based on the 75% RDI-adjustment described previously) taken once daily for 8 cycles, was £26,880 per patient.

Compared with the NHSScotland SOC, trametinib increased medicine acquisition costs by £15,251 per patient (BNF list prices, accessed August 2024). Overall, on including medicine administration, adverse events and monitoring costs, the per-patient cost of treatment with trametinib was £11,244 more compared to the NHSScotland SOC.

The Council considered results using more favourable confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues.

Cost-effectiveness considerations

Generalisability of the cost comparison

NHSScotland Patient Access Scheme (PAS) prices for trametinib were used. The NHSScotland National Framework prices for the SOC medicines were considered in confidence to increase the generalisability of the net costs. The price was calculated using the pre-filled dose banded products if available; otherwise, the vial price was used. The Scottish Drug Tariff price for 28-day pack of 2.5 mg letrozole and 30-day pack of 20 mg tamoxifen was used as it would be dispensed from community pharmacy or primary care. The lowest price generic versions were used for calculation.

Limitations of the cost comparison

Due to an absence of a published cost-utility analysis, the analysis only compares costs. The results of the cost-comparison show that when only medicine acquisition costs are considered, trametinib for LGSOC after at least one prior platinum-based chemotherapy is a cost-increasing intervention compared to the SOC. However, as most SOC medicines are administered intravenously, a potential saving is expected with oral trametinib, based on NHSScotland confidential medicine acquisition and

administration costs. In addition, given the evidence from the GOG 281/LOGS study supporting the survival benefit of trametinib (hazard ratio for PFS = 0.48; hazard ratio for death = 0.76), it may offer a QALY gain compared to the SOC. For illustrative purposes, we have used the QALY gain (0.58) expected over a lifetime from the Piao et al. (2023) study to calculate an Incremental Cost-Effectiveness Ration (ICER). This resulted in an ICER of £19,386 per QALY gained, based on list price. However, this is a naïve calculation based on simplistic assumptions. The calculation for incremental costs accounts for first year of treatment only; hence, it assumes no additional costs for remainder of the modelled lifetime. In addition, the clinical efficacy of the NHSScotland SOC is assumed to be the same as that observed for the SOC arm in the GOG 281/LOGS study. In the absence of direct comparative evidence, the actual cost-effectiveness remains unknown.

The administration costs for oral medicines were assumed to be zero. However, in practice, delivery of oral chemotherapy medications may be associated with administration costs that could differ by healthcare setting. The first-year monitoring costs for patients on trametinib included one ophthalmology outpatient consultation, ECG and ECHO at baseline, and ECHO every three months. However, in practice, only a small proportion of patients may be prescribed these tests, thereby reducing the overall monitoring costs.

The clinical inputs like duration of treatment and RDI were sourced from GOG 281/LOGS study or from published literature for medicines not included in the trial. It was assumed that treatment would continue uninterrupted for the full duration. However, duration and dose may vary in real-world setting due to multiple patient-specific 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.

Due to the lack of comparative safety of trametinib against paclitaxel with bevacizumab, and paclitaxel with carboplatin, which are comparators in NHSScotland but not included in the GOG 281/LOGS study, any additional adverse events for these were not included in the cost calculations. Some patients in the SOC group may receive maintenance treatment with bevacizumab. This is not accounted for in the cost-comparison. In addition, the end-of-life care costs were not included. Based on hazard ratio for death of 0·76 (95% CI 0·51–1·12) in favour of the trametinib group, there may be higher costs for end-of-life care incurred in the SOC arm[8]. The exclusion of these aspects may potentially lead to an underestimation of total costs in the NHSScotland SOC arm.

There is uncertainty around subsequent treatments following trametinib and SOC. The cost-comparison analysis does not include potential costs, or cost avoidance, of these treatments. The direction of impact remains unknown.

Summary

The cost-comparison indicated that trametinib is a cost-increasing intervention compared to NHSScotland SOC for patients with LGSOC after at least one prior platinum-based chemotherapy. Trametinib increased the cost of treatment by £11,244 per patient (BNF list price, accessed August 2024). Although the overall treatment costs increased, the medicine administration costs reduce by £6,511 per patient compared to the NHSScotland SOC. Considering the clinical evidence supporting

the use of trametinib, it may offer clinical benefit compared to the NHSScotland SOC. However, in the absence of direct comparative efficacy between trametinib and the NHSScotland SOC, 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 consideration of 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 other relevant information including service impact and estimated net medicines budget impact under the decision-making framework for value judgements.

9. Service impact

As an oral treatment, trametinib will be service sparing as it replaces intravenous chemotherapy regimens such as weekly paclitaxel, weekly paclitaxel with bevacizumab, or pegylated liposomal doxorubicin. However, the treatment duration is likely to be longer than the fixed courses of approximately 6 months used for intravenous therapy. There may be increased cardiac and ophthalmology monitoring requirements associated with trametinib, which could have a greater impact compared to oral treatments like letrozole. It is estimated that less than 10 patients per year in NHSScotland may start treatment with trametinib. Overall, trametinib, as an oral therapy, is expected to be service sparing.

10. Budget impact

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

Patient uptake

The annual incidence of ovarian cancer in Scotland is expected to be 576, with 90% being epithelial ovarian cancers, of which LGSOC accounts for about 5% of the cases, which translates to approximately 26 annual cases.[2] Based on clinician opinion, less than 10 patients per year are expected to be eligible for second or later line treatment with trametinib, which translates to 40% of all LGSOC. Therefore, for budget impact calculation, the number of patients expected to be treated with trametinib was estimated to be 10 in Year 1.

Based on results of GOG 281/LOGS study, the median duration of all treatment regimens for this patient population is expected to range from 2 to 10 cycles. It was assumed that patients or treatment would not carry over to subsequent years. The uptake remained constant in subsequent years. The scenario 1 explores lower annual incidence.

Per patient medicine cost and treatment duration

These prices include VAT.

The trametinib and NHSScotland SOC dosages were adjusted based on median RDI from the GOG 281/LOGS study to account for dose reductions or treatment interruptions. Based on the 75% RDI-

adjustment applied, cost of trametinib was calculated based on 1.5 mg daily dose per cycle for 8 cycles, using 30-day pack size of 2 mg tablets (BNF List price, accessed August 2024). The RDI for medicines not included in the GOG 281/LOGS study was assumed to be 100%. Scenario 2 explored budget impact when medicine dosages were not adjusted using median RDI (Table 5).

The acquisition costs for medicines in the NHSScotland SOC basket was based on weighted average methodology using proportion of patients for each regimen. Table 2 provides details of regimen and proportion of patients on each regimen in the NHSScotland SOC group.

The duration of treatment was informed by median number of cycles from the GOG 281/LOGS study. Each cycle comprises of 28 days. The median duration for trametinib was 8 cycles. The duration of treatment for medicines that were not included in the GOG 281/LOGS study was assumed to be 6 cycles.

Comparator displacement

Based on feedback from clinical experts, the following regimens are likely to be displaced by trametinib: weekly paclitaxel with or without bevacizumab, PLD, platinum combinations and second-line hormonal therapy, potentially letrozole. In addition, some patients have been treated with trametinib on an individual request basis since 2019.

Results

All figured in the budget impact include VAT.

The net national medicines budget impact was estimated to be £183K (based on BNF list price) based on annual uptake of 10 patients. As previously mentioned, patients or treatment would not carry over to subsequent years, and the net total budget impact in those years was estimated to be £183K (BNF list price) based on a continuing uptake of 10 patients.

Table 4 | Budget impact analysis base case results

	List price	
	Year 1	**Subsequent years**
Acquisition cost		
Trametinib acquisition cost [a]	£32,256	£32,256
NHSScotland SOC acquisition cost [b]	£13,955	£13,955
Number of patients treated	10	10
Budget Impact		
BUDGET IMPACT - NET MEDICINE COSTS	£183,012	£183,012

[a] based on oral administration of 1.5 mg daily per cycle, for 8 cycles. The dose was adjusted for relative dose intensity (RDI) = 75%.
[b] based on weighted average of medicines in the NHSScotland SOC basket listed in Table 2 and adjusted using median RDI.

Scenario considerations

The following table presents budget impact scenarios, exploring changes in treatment duration, and annual patient numbers.

Table 5 | Scenario analyses (list prices)

#	Scenario	Base case	Trametinib acquisition cost per patient	NHSScotland SOC acquisition cost per patient	Number of patients treated	Budget impact – Net medicine costs	Number of patients treated	Budget impact – Net medicine costs
					Year 1		Subsequent years	
	-	-	£32,256	£13,955	10	£183,012	10	£183,012
1	Annual uptake of 5 patients	Annual uptake of 10 patients	£32,256	£13,955	5	£91,506	5	£91,506
2	Without RDI adjustment	With RDI adjustment	£43,008	£13,955	10	£290,530	10	£290,530
3	Trametinib median duration of 3 cycles	Trametinib median duration of 8 cycles	£12,096	£13,955	10	- £18,588	10	- £18,588
4	Trametinib median duration of 16 cycles	Trametinib median duration of 8 cycles	£64,512	£13,955	10	£505,572	10	£505,572

RDI = relative dose intensity; SOC = standard of care

Limitations

The proposal form noted that trametinib has been accessed through individual patient request prior to this review. Therefore, the Year 1 budget impact may be overestimated, as some eligible patients may already be receiving trametinib. Scenario 1 explores lower annual uptake (Table 5).

The per-patient medicine acquisition costs for trametinib assumed 8 cycles of treatment. In the GOG 281/LOGS study, median duration of treatment varied between 3 and 16 cycles. This variation was explored in scenarios 3 and 4, respectively (Table 5).

Some patients in the NHSScotland SOC group may require maintenance treatment with bevacizumab. Due to the uncertainty of the evidence, this is not accounted for in the cost-comparison, which may underestimate the SOC treatment costs.

Summary

The use of trametinib will increase the net medicines budget impact for this patient group when compared to NHSScotland SOC. For 8 cycles of trametinib, the medicine acquisition cost was expected to be £32K, compared to £14K for the NHSScotland SOC. Based on a potential uptake of 10 patients, the estimated net medicines budget impact was £183K. These figures are based on BNF list price and include VAT.

The Council considered the net medicines budget impact using more favourable 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.

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

NCMAG would like to acknowledge the patient group partners, Ovarian Cancer Action, Ovacome and Target Ovarian Cancer for their invaluable input.

NCMAG would also like to acknowledge Novartis for providing papers to support the proposal.

13. 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
