AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: trametinib (Mekinist®) for the treatment of recurrent low-grade serous ovarian carcinoma (LGSOC) that has progressed after at least one previous platinum-based regimen **(OW30)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
May 2025

Key findings

Licence status
Trametinib is not licensed for treatment of recurrent low-grade serous ovarian carcinoma (LGSOC) that has progressed after at least one previous platinum-based regimen; its use for this indication is off-label.

Clinical evidence
The open-label GOG 281/LOGS study compared trametinib with the standard-of-care treatments (paclitaxel, pegylated liposomal doxorubicin, topotecan, tamoxifen, letrozole) in recurrent LGSOC. Median progression-free survival in the trametinib group was 13 months (95% CI 9.9 to 15.0), and 7.2 months (95% CI 5.6 to 9.9) in the standard-of-care group (hazard ratio 0.48 [95% CI 0.36 to 0.64]; $p < 0.0001$).

Safety
No new safety signals have been observed for the use of trametinib to treat LGSOC.

Patient factors
Trametinib is an oral treatment taken daily, that would be used in place of further chemotherapy treatments, such as paclitaxel and pegylated doxorubicin, which need to be given by intravenous infusion. This would mean less disruption of day-to-day life for patients, and their families and carers.

Cost effectiveness
One published cost-effectiveness analysis was conducted from the US payer perspective and has limited generalisability to the UK. Using data from the GOG 281/LOGS study, trametinib provided an additional 0.58 QALYs (1.14 life years). A cost comparison analysis conducted by AWTTC indicated that trametinib is a cost-increasing intervention compared to NHS Wales standard-of-care comparator treatments for patients with LGSOC after at least one prior platinum-based chemotherapy. Trametinib increased the cost of treatment by [commercial in confidence figure removed] per patient when using the confidential PAS price for trametinib and NHS contract prices for comparator treatments where applicable. Although the overall treatment costs increased, the medicine administration costs reduced by £3,328 per patient compared to NHS Wales standard-of-care. Considering the clinical evidence supporting the use of trametinib, it may offer clinical benefit compared to NHS Wales standard-of-care. However, in in the

absence of direct comparative efficacy between trametinib and NHS Wales standard-of-care, it is difficult to quantify treatment benefits in relation to costs and the actual cost-effectiveness remains unknown.

Budget impact
The addition of trametinib is estimated to increase the spend associated with this patient group in Wales by [commercial in confidence figure removed] per year. This is based on an estimated uptake of 13 patients per year receiving 8 cycles of trametinib treatment, and takes into account full displacement of comparator standard-of-care therapies.

Impact on health and social care services
Likely to be beneficial. Reduced use of services as patients would not need to attend a clinic or hospital to receive treatment by intravenous infusion as trametinib is an oral treatment. Some additional monitoring is required (eye examinations as clinically indicated, left-ventricular ejection function at Month 1 and then every 3 months during treatment).

Innovation and/or advantage
Recurrent LGSOC is usually resistant to standard chemotherapy. Being able to take an oral treatment at home is an advantage for patients, their families and carers, by not having to travel to a hospital for treatment.

Background

Low-grade serous ovarian carcinoma (LGSOC) is a rare subtype of ovarian cancer that grows slowly and is more resistant to chemotherapy than other ovarian cancer types[1].

Clinicians in Wales submitted trametinib (Mekinist®) for consideration for assessment as a treatment option for LGSOC that has progressed after at least one platinum-based regimen. They consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. The Scrutiny Panel of the All Wales Medicines Strategy Group (AWMSG) considered that trametinib was suitable for assessment though the One Wales medicines process for off-label medicines.

Trametinib is an inhibitor of enzymes called protein kinases; it specifically inhibits the MEK-1 and MEK-2 kinases, which are part of the ERK/MAPK signally pathway[2].

Trametinib is not licensed to treat LGSOC. During the COVID-19 pandemic, trametinib was available in England and Wales as an oral alternative to intravenous (iv) chemotherapy for LGSOC, under NICE guideline NG161: COVID-19 rapid guideline: delivery of systemic anticancer treatments, which established an interim Systematic Anti-Cancer Therapy (SACT) treatment list[3].

NICE guideline NG161 was withdrawn in September 2023 because current practice is to manage COVID-19 risk in line with risk of other respiratory infections[3], and trametinib use is routinely commissioned in the NHS in England and in Scotland to treat LGSOC[1,2]. However, in Wales the current route of access for treating LGSOC with trametinib is through the Individual Patient Funding Request (IPFR) process. [Confidential data removed].

Target group

The indication being considered is the treatment of low-grade serous ovarian carcinoma (LGSOC) that has progressed after at least one platinum-based chemotherapy regimen.

Clinicians advised that trametinib is likely to be used instead of further chemotherapy or hormone therapy options including paclitaxel (alone or with carboplatin), letrozole or pegylated liposomal doxorubicin, all of which have limited efficacy in preventing further disease progression.

Marketing authorisation date: Not applicable for this indication; off-label

Trametinib is licensed in the UK for use as monotherapy, or in combination with dabrafenib, to treat unresectable or metastatic melanoma with a BRAF V600 mutation[4]. It is also licensed for use in combination with dabrafenib to treat advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation, and as adjuvant treatment after complete resection of stage III melanoma with a BRAF V600 mutation[4].

[Commercial in confidence text removed].

Dosing information

Trametinib should be used as monotherapy at a maximum dose of 2 mg orally once daily, as part of a 28-day cycle[1]. Treatment is continued until disease progression occurs or toxicity stops treatment. Dose reduction due to adverse events may be required down to either 1.5 mg orally once daily or 1 mg orally once daily[1].

Clinical background

Ovarian cancer often presents with advanced disease; symptoms include abdominal pain and bloating, changes in bowel habits, and urinary and/or pelvic symptoms[5]. In more advanced stages, patients can develop small and large bowel obstructions, pleural effusions, and respiratory symptoms[5].

Around 90% of ovarian cancers are epithelial ovarian cancer, and low-grade serous ovarian carcinoma (LGSOC) accounts for 5% of these[5]. LGSOC is characterised by a younger age at diagnosis, relative resistance to platinum-based chemotherapy, and extended overall survival compared with high-grade serous carcinoma[6]. Median overall survival for LGSOC has been reported to be 90.8 months[7]. However, most patients with LGSOC are diagnosed in the advanced stages, over 70% of patients relapse, and response rates to salvage chemotherapy are low[6]. LGSOC has a high frequency of activating mutations in the mitogen-activated protein kinase (MAPK) pathway[6].

Incidence/prevalence

In 2021, 330 cases of ovarian cancer were diagnosed in Wales[8]. If 90% of those are epithelial ovarian cancer, and 5% of those are LGSOC, then we would expect around 15 cases of LGSOC to be diagnosed in Wales per year. Assuming that 70% of patients would have a recurrence of LGSOC, 11 patients per year would be eligible

for treatment with trametinib. This is slightly lower than the estimate provided by clinicians in Wales of 13 patients per year.

Current treatment options and relevant guidance

Standard treatment for LGSOC is surgery to achieve a complete or optimal cytoreduction[5]. After surgery, platinum-based chemotherapy and paclitaxel can be offered, though their benefit is uncertain. Further surgery may be considered for people who have recurrent LGSOC with operable disease. If surgery is not possible, a platinum-based chemotherapy and paclitaxel will be given as first-line treatment[1]. Paclitaxel plus cisplatin is the standard systemic chemotherapy used in LGSOC[5].

After chemotherapy or surgery, maintenance hormonal therapy can be given: often letrozole and tamoxifen. These are usually continued until disease progression or unacceptable toxicity[1,5]. For most people, LGSOC does not respond to platinum-based chemotherapy, and they will have disease progression or recurrence[1].

After disease progression or recurrence, the treatment options offered can include hormonal therapy (if not previously given) or further chemotherapy (options include paclitaxel alone or pegylated liposomal doxorubicin hydrochloride)[9]. However, these treatments show limited effectiveness in preventing further disease progression[5]. Once recurrence occurs, patients will require support from palliative care specialists and community teams. The most frequent complications of recurrent LGSOC include bowel obstruction, hydronephrosis, fistulation and general organ failure.

The European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment and follow-up of newly diagnosed and relapsed epithelial ovarian cancer, recommends that trametinib should be considered for treating recurrent LGSOC after prior platinum-based chemotherapy and hormone therapy[5].

Based on results from a phase II/III open-label randomised clinical trial (study GOG 281/LOGS), the US National Comprehensive Cancer Network (NCCN) recommends the use of trametinib as a category 2A option (defined as: based on lower level evidence) to treat recurrent LGSOC[10]. There is uniform NCCN consensus that the intervention is appropriate[10].

Summary of the evidence

A literature search was conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) in March 2025 to identify evidence about the use of trametinib to treat LGSOC. Searches were performed using MEDLINE, EMBASE and the Cochrane Library. The search terms used were trametinib, ‘low grade serous ovarian cancer’, and LGSOC. The primary outcomes intended were overall survival, progression-free survival (PFS), adverse events, health-related quality of life, resource use, response rates and/or symptom control. Conference abstracts, reviews, non-systematic reviews, letters and editorials were excluded. See the PRISMA diagram in Appendix 1.

A total of 71 clinical papers were retrieved during the literature search, from which 24 duplicates were removed. 44 clinical papers were excluded by inspecting titles and abstracts, and the full texts of 3 papers were reviewed for suitability in this report.

The literature search identified one clinical study of a randomised, open-label multicentre phase 2/3 trial of trametinib in LGSOC (study GOG 281/LOGS), one case report of LGSOC treated with trametinib, and a cost-effectiveness analysis of trametinib in LGSOC. Only the phase 2/3 trial and cost-effectiveness analysis were reviewed for this report.

Clinical effectiveness evidence

Efficacy

Study GOG 281/LOGS

The main evidence comes from this phase 2/3 randomised, open-label study conducted at 72 centres in the USA and 12 centres in the UK[6]. The study enrolled 260 patients (aged 42–65.6 years) with LGSOC who had previously received at least one platinum-based chemotherapy regimen, but not all five standard-of-care options, and who had measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST)[6].

Patients were randomised to receive either oral trametinib (2 mg once daily, one cycle = 28 days; n = 130) or one of five standard-of-care options:

- intravenous paclitaxel 80 mg/m^2 on Days 1, 8 and 15 of every 28-day cycle;
- intravenous pegylated liposomal doxorubicin 40–50 mg/m^2 on Day 1 every 28 days;
- intravenous topotecan 4 mg/m^2 on Days 1, 8 and 15 of every 28-day cycle;
- oral letrozole 2.5 mg once daily; or
- oral tamoxifen 20 mg twice daily[6].

Most patients had stage III ovarian cancer (96 in the trametinib arm and 93 in the standard-of-care arm); most patients (93 in each arm) had a performance status of 0; 62 patients in the trametinib arm and 55 in the standard-of-care arm had received one previous line of chemotherapy, and 36 patients in each arm had received three or more previous lines of chemotherapy[6].

Efficacy was measured by contrast CT or MRI lesion assessment at baseline, once every 8 weeks for the first 15 months, and then once every 3 months[6]. Quality of life was assessed using the FACT-O TOI (Functional Assessment of Cancer Therapy – Ovarian Cancer Trial Outcome Index) and the FACT-GOG Ntx (Functional Assessment of Cancer Therapy – Gynecologic Oncology Group-Neurotoxicity questionnaire) subscale. Quality of life assessments were done before Cycle 1 and at weeks 12, 24, 36 and 52 after starting treatment[6].

The primary endpoint was investigator-assessed progression-free survival; secondary outcomes included adverse events, objective tumour response rate (ORR – the proportion of patients in each group with a clinical response), quality of life and overall survival[6]. Treatment continued in both arms until unacceptable toxicity or disease progression (defined as a ≥20% increase in the sum of the diameters of target lesions). After disease progression, patients in the standard-of-care group could cross over to receive trametinib[6].

The median duration of follow-up was 31·3 months in the standard-of-care group and 31·5 months in the trametinib group[6]. At the data cut-off (July 2019) 229 patients (88%) had discontinued their assigned treatment due to disease progression, toxicity, patient choice, other disease or death. The median number of trametinib treatment cycles received was eight (IQR 3–16). Median progression-free survival in the trametinib group was 13 months (95% CI 9.9 to 15.0), and 7.2 months (95% CI 5.6 to 9.9) in the standard-of-care group (hazard ratio 0.48 [95% CI 0.36 to 0.64]; $p < 0.0001$)[6] . Results are shown in Table 1.

Table 1. Primary and secondary outcomes of Study GOG 281/LOGS[6]

Outcome	Trametinib (n=130)	Standard-of-care (n=130)	Hazard ratio (95% CI)
Primary outcome: progression-free survival (follow-up 31 months)			
PFS events (%)	101 (78%)	116 (89%)	
Median PFS (95% CI)	13 months (9.9 to 15)	7.2 months (5.6 to 9.9)	0.48 (0.36 to 0.64) P<0.0001
Secondary outcomes			
Objective response rate	26%	6%	Odds ratio 5.4 (2.4 to 12.2) P <0·0001
Median duration of response (IQR)	13.6 months (7.2 to 19.9)	5.9 months (4.0 to 12.2)	
Overall deaths (%)	51 (39%)	60 (46%)	
Median OS* (95%CI)	37.6 months (32 to NE)	29.2 months (23 to 51.6)	0.76 (0.51 to 1.12) P=0.056
Quality of life	NS	NS	
* OS analysis includes the effect of 88 patients who crossed over to trametinib after disease progression CI: confidence interval; IQR: interquartile range; NE: not evaluable; NS: not significant; OS: overall survival; PFS: progression-free survival;			

The median progression-free survival in 88 patients who crossed over to receive trametinib after disease progression on standard-of-care was 10.8 months (95% CI 7.3 to 12.0), and the objective response rate was 15% (95% CI 7.0 to 22.0; 13 of 88 patients)[6]. 66 standard-of-care patients who crossed over to trametinib had further disease progression or died; 43 of them (65%) had a longer time to disease progression on trametinib than they had on their preceding standard-of-care treatment[6].

Quality-of-life measurements showed no clinically significant differences between the trametinib and standard-of-care treatment groups[6].

Safety

The Summary of Product characteristics (SmPC) for trametinib lists very common adverse events as: hypertension, haemorrhage, cough, dyspnoea, gastrointestinal disorders (vomiting, diarrhoea, nausea, constipation, abdominal pain and dry mouth), skin rashes, pruritus, alopecia, fatigue, peripheral oedema, pyrexia and increases in levels of aspartate aminotransferases[4]. Trametinib should be used with caution in patients with impaired left ventricular function (LVEF). LVEF should be tested in all patients prior to starting treatment, after one month and then at 3-monthly intervals.

Due to potential risk of eye disorders, including retinal pigment epithelial dystrophy (RPED) and retinal vein occlusion (RVO), patients should report any new visual disturbances[4].

In the GOG 298/LOGS study, dose reductions occurred in 156 (11%) of 1,365 trametinib cycles completed[6]. 90 patients (70%) needed at least one dose reduction during the study period. 38 patients (30%) required two dose reductions; of these patients, 14 withdrew due to disease progression, 17 due to adverse events, and two for other reasons[6].

The most frequent grade 3 or 4 adverse events reported in the trametinib group were skin rash (17 [13%] of 128 patients), anaemia (16 [13%]), hypertension (15 [12%]), diarrhoea (13 [10%]), nausea (12 [9%]), and fatigue (10 [8%])[6]. 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). The most frequent grade 3 or 4 adverse events in the standard-of-care group were abdominal pain (22 [17%]), nausea (14 [11%]), anaemia (12 [10%]), and vomiting (10 [8%]). In the standard-of-care group, adverse events of special interest were left ventricular systolic dysfunction (1 patient) and decreased ejection fraction (1 patient)[6].

Small intestine obstruction occurred in nine (7%) patients in the standard-of-care group and in 16 (13%) patients in the trametinib group, and colon obstruction occurred in six (5%) patients in the standard-of-care group and in one (1%) patient in the trametinib group[6]. No grade 5 events reported were definitely attributable to trametinib. There were no treatment-related deaths[6].

A total of 46 (36%) of 128 patients discontinued trametinib due to toxicity, compared with 38 (30%) of 127 patients who discontinued standard-of-care treatment due to toxicity[6].

Patient factors

Trametinib is an oral treatment taken at home, and is more convenient for patients than some of the commonly used alternative treatments in Wales that require hospital attendance for intravenous infusions.

Discussion

The main evidence is the results of the GOG 281/LOGS study, which show that trametinib improved progression-free survival compared with the standard-of-care treatments. The trial was open label with both the patients and investigators aware of the treatment assignment. The primary endpoint was investigator-assessed and as cross over was allowed this may have had implications for those patients originally assigned to the standard of care arm allowing earlier crossover. To account for this the study protocol required objective evidence of progression using RECIST criteria. Overall survival improvements were numerically in favour of trametinib, although as a high proportion (68%) of patients in the standard-of-care group crossed over to receive trametinib, this may have resulted in confounding, potentially underestimating the survival benefit. Post-hoc sub-group analyses of individual treatments indicated that treatment with trametinib was favoured for all standard of care treatments although some did cross the hazard ratio threshold of 1. Similarly, trametinib treatment was found to be effective irrespective of treatment line.

Clinicians in Wales said that three of the five standard-of-care treatments used in the study, are treatments routinely used in Wales to treat LGSOC that has progressed

after at least one previous platinum-containing regimen. These results are likely to be generalisable to the patient population in Wales

The safety profile of trametinib is known, and no new safety signals were reported in the study. The majority of patients required dose reductions whilst receiving trametinib. More patients discontinued treatment due to toxicity in the trametinib arm but patients were generally on treatment for longer with trametinib than the standard of care group. The difference in rate of small intestinal obstruction between treatment arms was not accounted for by the authors of the paper but may be a complication of the disease itself. The quality of life data from the study showed no significant differences between trametinib and the standard-of-care treatments.

Patient submissions

AWTTC received two submissions from patient organisations: Ovarian Cancer Action, and Target Ovarian Cancer. The submissions highlight the experiences of patients with ovarian cancer and the challenges they face, focusing on LGSOC. The main points of the submissions are described below.

- Because LGSOC is a rare subtype of ovarian cancer, people diagnosed with LGSOC often feel isolated and without specific support.
- Treatment of LGSOC involves surgery and usually involves removing the ovaries and uterus, leading to loss of fertility and premature menopause. This is particularly difficult as LGSOC tends to affect younger women.
- Patients feel that there are not many treatments available to them. They are told that their disease doesn't respond well to chemotherapy, but have to undergo chemotherapy and its side effects because there are no other treatments available.
- Most people (over 70%) will experience a recurrence of LGSOC, and as the disease does not respond well to chemotherapy; this creates a sense of uncertainty for patients, who find that difficult to live with. Patients who have had a recurrence said that they found the news of the recurrence more distressing than the initial diagnosis of LGSOC.
- Patients say that knowing that trametinib was available as an option would give them a 'mental safety net' and reduce anxiety around recurrence for them, and their families and carers.
- Being able to take an oral treatment at home would mean less disruption of day-to-day life for patients, and improvements in progression-free survival would help them to return to a more normal routine like work and spending time with friends and family.
- It was noted that this treatment is available in England and that there is a current disparity in access for patients resident in Wales.

Cost-effectiveness evidence

Background

A literature search conducted by AWTTC identified one published cost-effectiveness analysis, by Piao et al. (2023)[11]. The analysis aimed to evaluate the cost-effectiveness of trametinib versus standard of care for recurrent LGSOC from the US payer perspective, based on the results of the study GOG 281/LOGS[11].

Context
The cost-effectiveness analysis compared cost and effectiveness of trametinib and standard-of-care groups in patients with recurrent LGSOC[11]. Life-years, quality-adjusted life-years (QALYs), lifetime costs and incremental cost-effectiveness ratios were calculated. The robustness of the model was explored using one-way and probabilistic sensitivity analyses[11].

The model contained three health states: progression-free survival (PFS), progressed disease (PD) and death[11]. The two treatment options were those evaluated in the GOG 281/LOGS study: trametinib and standard-of-care (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, tamoxifen). Treatment continued until unacceptable toxicity or disease progression. The model used a 28-day Markov cycle and a lifetime horizon. All costs and outcomes were discounted at a rate of 3% annually, and the half-cycle correction was applied in the model. The model used a willingness to pay (WTP) threshold of $150,000, because in the USA the WTP threshold is between $100,000 and $150,000 per QALY for cancer medicines[11].

A partitioned survival analysis was done to estimate the movement over time between PFS, PD and death states[11]. The progression and overall mortality risk for each treatment arm were estimated based on the PFS and overall survival curves from study GOG 281/LOGS. Log-logistic models provided the best fit for overall survival curve and log-normal models provided the best fit for PFS curve according to the Akaike information criterion (AIC). Age-specific background mortalities due to other causes were also considered, which were obtained from the US life tables[11].

Only direct medical costs were considered, including medicine costs and costs of administration[11]. Doses were those used in the GOG 281/LOGS study, using a body surface area of 1.86m^2 to calculate dose size. After disease progression, 69% of patients could cross over to receive trametinib. Medicine and administration costs were based on US data from Centers for Medicare and Medicaid Services. The model included the cost of Grade 3–5 adverse events with an incidence of 5% or more reported in the study. Health-related quality of life was used to adjust the survival time. The utility of PFS was 0.61 and utility of PD was 0.50, derived from published studies[11,12].

As well as one-way and probabilistic sensitivity analyses, a scenario analysis was done, in which it was assumed that the median time for patients in the standard-of-care group to receive trametinib after progression was equal to the median time to receive trametinib for patients in the trametinib group[11].

Results
Trametinib provided an additional 0.58 QALYs (1.14 life years), and an incremental cost of $248,214 compared with the standard-of-care[11]. The ICER was $424,097 per QALY gained compared with the standard-of-care group[11].

One-way sensitivity analyses suggested that the model was sensitive to the hazard ratio of overall survival and progression-free survival between the trametinib group and the standard-of-care group, utility of PFS and the cycle cost of trametinib[11]. Probabilistic sensitivity analyses showed a 6% probability of the trametinib group being cost effective at a willingness-to-pay threshold of $150,000 per QALY gained[11].

The study concluded that trametinib was not cost-effective for patients with recurrent LGSOC at the assumed willingness to pay threshold of $150,000 per QALY[11]. A 39% reduction in the cost of trametinib would make trametinib cost-effective compared to standard-of-care for recurrent LGSOC[11].

Cost comparison analysis

In their evidence report, the National Cancer Medicines Advisory Group (NCMAG) in Healthcare Improvement Scotland conducted a cost-comparison analysis using NHSScotland data on costs and standard of care for treatment[2]. AWTTC has applied a similar methodology to conduct a cost comparison analysis using inputs pertinent to the NHS in Wales.

The proposed daily dosing regimen is 2 mg trametinib taken orally once daily as part of a 28-day cycle. The list price for 2 mg trametinib (pack size 30 tablets) is £4,800[13]**;** however, there is a patient access scheme (PAS) in place, reducing the pack cost to [commercial in confidence figure removed] (excluding VAT).

Treatment with trametinib would continue until disease progression or unacceptable toxicity. Costs are calculated for 8 cycles of trametinib; this was the median number of cycles reported in the GOG281/LOGS study.

Currently, patients in Wales with recurrence of LGSOC are offered various standard-of-care regimens. Clinicians in Wales indicate that these are either paclitaxel with or without carboplatin, pegylated liposomal doxorubicin (PLD) or letrozole. Dosing details of these regimens and the proportion of patients likely to receive each treatment are given in Table 2. The proportion of patients was informed by clinical expert opinion. The duration of treatment of paclitaxel, letrozole and PLD was informed by median number of cycles from the GOG 281/LOGS study. The duration of treatment for carboplatin plus paclitaxel was assumed to be the standard treatment length of 6 cycles.

Table 2. Standard of care (SOC) comparator treatments in NHS Wales

Regimen	Proportion of patients	Dosing schedule and number of cycles
Letrozole	30%	2.5 mg once daily.10 cycles of 28 days each.
Paclitaxel	40%	80 mg/m^2 BSA intravenous infusion once weekly for 3 weeks. 4 cycles.
Pegylated liposomal doxorubicin (PLD)	20%	50 mg/m^2 BSA intravenous infusion every 28 days. 6 cycles.
Carboplatin + paclitaxel	10%	AUC 2 (200 mg) carboplatin intravenous infusion weekly + 80 mg/m^2 BSA paclitaxel intravenous infusion weekly. 6 cycles
AUC: area under the curve; BSA: body surface area		

The cost comparison between trametinib and the standard-of-care comparators used in NHS Wales is given in Table 3. These include medicine acquisition costs, administration costs and monitoring costs. Acquisition costs for comparators are given using both the lowest list price and the NHS Wales contract price if applicable. All acquisition costs exclude VAT. Costs for paclitaxel and PLD were calculated using

a body surface area (BSA) of 1.71 m^2 which is the average BSA for a female patient with cancer in the UK[14]. Vial wastage is assumed.

Administration costs for medicines given by intravenous infusion were sourced from the NHS reference costs 2023/24[15]. Monitoring costs for the first year of treatment with trametinib are included which are one ophthalmology outpatient consultation, one electrocardiogram and four echocardiograms.

A weighted average cost for a basket of the NHS Wales standard-of-care comparators listed in Table 2 has also been calculated using the proportion of patients estimated for each treatment as the weights.

Additionally, adverse event (AE) treatment costs were estimated for trametinib and for the basket of standard-of-care comparator treatments based on the rates of grade ≥3 adverse events requiring inpatient treatment occurring in >5% of patients reported in the GOG 281/LOGS study. These were diarrhoea (trametinib: 10%, standard-of-care: 3%), urinary tract infection (trametinib: 7%, standard-of-care: 5%), small intestine obstruction (trametinib: 9%, standard-of-care: 2%) and colon obstruction (trametinib: 0%, standard-of-care: 3%). AE treatment costs were sourced from the NHS reference costs 2023/24 and multiplied by AE rates. Due to the absence of comparative safety data for one of the comparator treatments (carboplatin + paclitaxel), which was not included in the GOG 281/LOGS study, any additional AEs for this treatment have not been considered in the costings.

A summary of the cost-comparison results for trametinib and the NHS Wales basket of standard-of-care comparator treatments is given in Table 4.

Table 3. Costs of trametinib and standard-of-care per patient for first year of treatment

Regimen	Cost	Reference
Trametinib		
2 mg x 30 tablets	¶¶	Patient Access Scheme (PAS)
Single cycle acquisition cost	¶¶	
Acquisition cost for 8 cycles	¶¶	
Administration cost	£0	
Monitoring cost	£1,107	NHS reference costs 2023/24; codes BZ24E, EY51Z, RD51A
Total cost for trametinib	¶¶	
Letrozole		
2.5 mg x 28 tablets	£1.48	Drug Tariff
Single cycle acquisition cost	£1.48	
Acquisition cost for 10 cycles	**£14.80**	
Administration cost	£0	
Total cost for letrozole	**£14.80**	

Regimen	Cost		Reference
Paclitaxel			
	List*	**NHS Wales†**	
100 mg vial	£200.35	¶¶	*BNF †All Wales Drug Contract
30 mg vial	£66.85	¶¶	*BNF †All Wales Drug Contract
Single cycle acquisition cost	£1002.15	¶¶	
Acquisition cost for 4 cycles	**£4008.60**	¶¶	
Administration cost	£5,104		NHS reference costs 2023/24; codes SB12Z, SB15Z
Total cost for paclitaxel	**£9,112.60**	¶¶	
Pegylated liposomal doxorubicin (PLD)			
	List*	**NHS Wales†***	
50 mg vial	£712.49	¶¶	*BNF †All Wales Drug Contract
Single cycle acquisition cost	£1,424.98	¶¶	
Acquisition cost for 6 cycles	**£8,549.88**	¶¶	
Administration cost	£2,548		NHS reference costs 2023/24; codes SB12Z, SB15Z
Total cost for PLD	**£11,097.88**	¶¶	
Paclitaxel plus carboplatin			
(see above for paclitaxel costs)	**List***	**NHS Wales†**	
Carboplatin 150 mg vial	£60.59	-	*BNF †All Wales Drug Contract
Carboplatin 50 mg vial	£20.20	-	*BNF †All Wales Drug Contract
Cost of carboplatin per cycle	£242.37	-	
Single cycle acquisition cost of carboplatin + paclitaxel	£1,244.52	¶¶	
Acquisition cost for 6 cycles of carboplatin + paclitaxel	**£7,467.12**	¶¶	
Administration cost	£7,770		NHS reference costs 2023/24; codes SB13Z, SB15Z
Total cost for carboplatin + paclitaxel	**£15,237.12**	¶¶	
¶¶ commercial in confidence figure removed			

Table 4: Summary of cost-comparison results

Cost category	Trametinib	SOC†	Cost difference
Medicine acquisition (list prices)	¶¶ (PAS)	£4,064.57	¶¶
Medicine acquisition (NHS Wales contract prices)		¶¶	¶¶
Medicine administration	£0	£3,328.20	- £3,328.20
Adverse event treatment*	£1,393.79	£713.41	£680.38
Monitoring	£1,107	£0	£1,107
Total cost per patient (list prices)	¶¶	**£8,106.18**	¶¶
Total cost per patient (NHS Wales contract prices)		¶¶	¶¶

* calculated using NHS reference costs 2023/24 codes FD10G, FD10C, LA04L
† refers to NHS Wales basket of comparators listed in Table 2
PAS: patient access scheme; SOC: standard-of-care
¶¶ commercial in confidence figure removed

Compared with the standard-of-care basket of comparators used in NHS Wales, trametinib increased medicine acquisition costs per patient by [commercial in confidence figure removed] when comparators were costed at list price and [commercial in confidence figure removed] if NHS Wales contract prices were used. Overall, on including medicine administration, adverse events and monitoring costs, the additional per-patient cost of treatment with trametinib was [commercial in confidence figure removed] (using comparator list prices) and [commercial in confidence figure removed] (when using comparator contract prices) in comparison to standard of care treatments used in NHS Wales. AWTTC considers that the costs using NHS Wales contract prices for comparator treatments provide a better estimate of the expected actual costs.

Limitations of the cost comparison analysis

The first-year monitoring costs for trametinib have been included in the cost comparison, however, in practice, only a small proportion of patients may undergo all tests, thereby reducing the overall monitoring costs.

Monitoring costs for comparator treatments over and above those considered standard for most patients on chemotherapy have not been included. Although rates of grade ≥3 adverse events are reported in the GOG281/LOGS study both for the trametinib group and the standard-of-care group, no further detail is given about proportions requiring treatment and the level of intervention required. Therefore, it is difficult to attribute costs for the treatment of adverse events for either trametinib or standard-of-care comparators with certainty.

The lack of comparative safety of trametinib with one of the standard-of-care comparators used in NHS Wales but not included in the GOG281/LOGS study, means that any adverse events due to this treatment were not included in the cost calculations. Conversely, some adverse events reported in the GOG281/LOGS study and so included in the adverse event treatment costings may be due to standard-of-care treatments included in the study but not used in NHS Wales. Thus, adverse event treatment costs for standard-of-care comparators may be subject to uncertainty. However, the data presented suggests that rates of grade ≥3 adverse events are broadly similar between the two groups and so it would seem reasonable to assume that adverse treatment costs for trametinib and standard-of-care comparator treatments would also be of a similar magnitude.

The administration costs for oral medicines was assumed to be zero. However, oral treatments maybe associated with administration costs that may differ depending on healthcare setting.

Cost effectiveness discussion

There is no direct comparative evidence of cost-effectiveness. The cost-effectiveness analysis conducted from the US payer perspective has limited generalisability to the UK based on differences in treatment and service costs. The utility used in the model was sourced from previous studies, and might not accurately represent the utility in the GOC 281/LOGS study[11]. Although goodness of fit parameter distribution was tested based on the AIC, there is still inherent uncertainty in the extrapolated survival curve[11].

The NHSScotland cost-comparison analysis used the QALY gain (0.58) from the Piao et al. study to calculate an ICER of £19,386 per QALY gained, based on list prices[2]. If the same QALY gain is applied to the results of the cost comparison analysis for NHS Wales given in Table 4, an ICER of [commercial in confidence figure removed] per QALY gained (using comparator list prices) or [commercial in confidence figure removed] per QALY gained (using comparator NHS Wales contract prices) results, based on the PAS price for trametinib. However, as stated in the NCMAG report, this naïve calculation which is based on simplistic assumption, is for illustrative purposes only and should be interpreted with caution. 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 standard-of-care comparator treatments used in NHS Wales is assumed to be the same as that observed for the standard-of-care arm in the GOG 281/LOGS study.

In summary, the cost comparison indicated that trametinib is a cost-increasing intervention compared to the usual standard of care treatments offered to patients in Wales with LGSOC that has progressed after at least one previous platinum-based regimen. The clinical evidence supports the clinical effectiveness of trametinib for this patient population but in the absence of direct comparative efficacy between trametinib and comparative standard-of-care treatments used in NHS Wales, it is difficult to quantify treatment benefits in relation to costs. Therefore, the actual cost-effectiveness of trametinib for this indication remains unknown.

Budget impact

Clinicians in Wales estimate that 13 patients with LGSOC in Wales per year would receive treatment with trametinib. Budget impact has been calculated based on the proposed daily dosing regimen 2 mg trametinib taken orally once daily as part of a 28-day cycle, for 8 cycles. Trametinib would displace standard-of-care treatment options; details of standard-of-care regimens used in NHS Wales and the proportion of patients expected to receive each treatment are given in Table 2.

Medicine acquisition costs, administration, monitoring and adverse event treatment costs for trametinib and the standard-of-care comparators per patient are given in Table 3. Costs for the standard-of-care medicines considered as an NHS Wales standard-of-care basket were calculated based on weighted average methodology using proportion of patients for each regimen and are given in Table 4.

For the budget impact, standard-of-care comparator costs have used All Wales contract prices where applicable. Trametinib has been costed at the PAS price available to NHS Wales. 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. Therefore, it is assumed that patients would not continue treatment after Year 1 and so the annual budget impact is assumed to remain the same in subsequent years.

Table 5. Estimated net annual cost for trametinib versus NHS Wales standard-of-care

	Per patient	For 13 patients
Medicine acquisition costs		
Trametinib	¶¶	¶¶
NHS Wales SOC	¶¶	¶¶
Net medicine acquisition cost	¶¶	¶¶
Administration costs		
Trametinib	£0	£0
NHS Wales SOC	£3,328.20	£43,266.60
Monitoring costs		
Trametinib	£1,107	£14,391
NHS Wales SOC	£0	£0
Adverse event treatment costs		
Trametinib	£1,393.79	£12,487.67
NHS Wales SOC	£713.41	£9,274.33
Total annual cost		
Trametinib	¶¶	¶¶
NHS Wales SOC	¶¶	¶¶
Net annual overall cost of trametinib	¶¶	¶¶
All costs exclude VAT when applicable SOC: standard-of-care ¶¶ commercial in confidence figure removed		

The introduction of trametinib to treat recurrent LGSOC in Wales will increase the spend for this patient group. Based on an estimated uptake of 13 patients receiving 8 cycles of trametinib, the annual net budget impact is expected to be [commercial in confidence figure removed] more, assuming full displacement of all NHS Wales standard-of-care treatments.

Budget impact issues

- Budget impact estimates include monitoring, administration and adverse event treatment costs for both trametinib and standard-of-care treatments where possible. However, these may be subject to uncertainty and not all costs may have been captured. Monitoring costs associated with trametinib may be over-estimated as, in practice, only a small proportion of patients may receive all tests. Adverse event treatment costs are based on rates of adverse events for both trametinib and standard-of-care comparators from the GOG 281/LOGS study. However, the standard-of-care treatments used in this study are not fully reflective of those used in NHS Wales
- Dose reductions and treatment interruptions for both trametinib and standard-of-care comparators have not been accounted for in the budget impact. In the GOG 281/LOGS study, 70% of patients treated with trametinib had to have reductions in their dose resulting in a median relative dose intensity (RDI) of 75% equating to 1.5 mg per day per patient. For the three NHS Wales standard-of-care comparators included in the study, RDI was 100%. Using the PAS price of [commercial in confidence figure removed] for 0.5 mg x 30 trametinib capsules (excluding VAT), a 25% reduction in daily dose will lead to a commensurate reduction in the medicine acquisition cost for trametinib (cost per 28-day cycle for 1.5 mg = [commercial in confidence figure removed]; cost per 28-day cycle for 2 mg = [commercial in confidence figure removed]). Therefore, the medicine acquisition costs for trametinib may be lower than those presented.
- Budget impact estimates are sensitive to small changes in patient numbers. The budget impact uses clinical expert estimates of 13 treated patients per year. This is higher than would be predicted based on published incidence data which indicate 11 patients in Wales per year would be eligible for treatment with trametinib. The NCMAG report based their budget impact estimates on 10 patients in Scotland who would receive trametinib; this was based on clinician opinion. Therefore, the budget impact may be lower than that presented.
- Administration costs for oral treatments (i.e. trametinib and letrozole) were assumed to be zero but may be associated with administration costs. However, these are expected to be minimal in comparison to administration costs associated with standard-of-care treatments delivered by intravenous infusion.
- Medicine acquisition costs may be liable to VAT which has not been included in budget impact calculations. Trametinib may be delivered to patients at home through a homecare provider which will make it VAT-exempt although there may be other additional costs associated with homecare provision.

Equality and health impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for

public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015. No potential negative impacts were identified.

Additional factors

Prescribing unlicensed medicines

Trametinib (Mekinist®) is not licensed to treat this indication and is therefore 'off label'. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

References

1. NHS England. Clinical commissioning policy. Trametinib in recurrent or progressive low grade serous ovarian cancer (adults). Nov 2023. Available at: https://www.england.nhs.uk/publication/clinical-commissioning-policy-trametinib-in-recurrent-or-progressive-low-grade-serous-ovarian-cancer/. Accessed Apr 2025.
2. NHS Scotland, and Healthcare Improvement Scotland. National Cancer Medicines Advisory Group (NCMAG) programme: NCMAG118 trametinib. Advice Document v1.0. Oct 2024. Available at: https://www.healthcareimprovementscotland.scot/publications/ncmag118-trametinib-advice-document-october-2024/. Accessed Apr 2025.
3. National Institute for Health and Care Excellence. NICE Guideline, NG161. COVID-19 rapid guideline: delivery of systemic anticancer treatments. Mar 2020 (updated Aug 2022). Available at: https://www.nice.org.uk/guidance/ng161. Accessed Apr 2025.
4. Novartis Pharmaceuticals UK Ltd. Mekinist®. 2 mg film-coated tablets. Summary of Product Characteristics. Dec 2024. Available at: https://www.medicines.org.uk/emc/product/5072/smpc. Accessed Apr 2025.
5. Gonzalez-Martin A, Harter P, Leary A et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology.* 2023;34(10):833-848.
6. Gershenson DM, Miller A, Brady WE et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre phase 2/3 trial. *The Lancet.* 2022;399:541-553.
7. Gockley A, Melamed A, Bregar AJ et al. Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. *Obstetrics & Gynecology.* 2017;129(3):439-447.
8. Public Health Wales. Cancer Reporting Tool Wales. Mar 2025. Available at: https://publichealthwales.shinyapps.io/Cancer_Reporting_Tool_PHW/. Accessed Apr 2025.
9. National Institute for Health and Care Excellence. Technology Appraisal TA389. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer. Apr 2016. Available at: https://www.nice.org.uk/guidance/ta389. Accessed Apr 2025.
10. Armstrong DK, Alvarez RD, Backes FJ et al. Ovarian cancer, version 3.2022. Featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network.* 2022;20(9):972-980.
11. Piao H, Wu M, Qin S et al. Trametinib for patients with recurrent low-grade serous ovarian cancer: a cost-effectiveness analysis. *Gynecologic Oncology.* 2023;168:17-22.
12. Nica A, Lee JYJ, Hong NL et al. Cost-effectiveness of maintenance hormonal therapy in patients with advanced low grade serous ovarian cancer. *Gynecologic Oncology.* 2021;160(1):206-213.
13. BMJ Group and the Royal Pharmaceutical Society. British National Formulary. Mar 2025. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Apr 2025.
14. Sacco JJ, Botten J, Macbeth F et al. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One.* 2010;5(1):e8933.

15. NHS England. 2023/24 National Cost Collection Data Publication. Nov 2024. Available at: https://www.england.nhs.uk/publication/2023-24-national-cost-collection-data-publication/. Accessed Feb 2025.
16. Haddaway NR, Page MJ, Pritchard CC et al. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews.* 2022;18(2):e1230. Accessed Apr 2025.

Appendix 1. PRISMA flow diagram[16]