NHS England Evidence Review:

Trametinib for recurrent or advanced low grade serous ovarian cancer

NHS England URN: 2253

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Trametinib for recurrent or advanced low grade serous ovarian cancer

Completed: December 2022

Prepared by NICE on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of trametinib compared with standard of care in people with recurrent or advanced low grade serous ovarian cancer, who have received at least one line of platinum-based chemotherapy. Trametinib is licensed for melanoma and non-small cell lung cancer with BRAF V600 mutation. Use for recurrent or advanced low grade serous ovarian cancer is off label (Summary of product characteristics).

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with trametinib more than others.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of trametinib compared with standard of care in people with recurrent or advanced low grade serous ovarian cancer (LGSOC) who have received at least one line of platinum-based chemotherapy. The searches for evidence published since 2012 were conducted on 04 October 2022 and identified 18 references. The titles and abstracts were screened, and 3 full text papers were obtained and assessed for relevance

One international, randomised controlled, open label study was included in the evidence review (Gershenson et al. 2022). The study was conducted in 72 hospitals in the USA and 12 hospitals in the UK. It included 260 participants and compared clinical effectiveness and safety of trametinib to standard of care treatments.

In terms of clinical effectiveness:

- Overall Survival. The study provided moderate certainty evidence that trametinib may improve overall survival compared with standard of care; median overall survival was 37.6 months in the trametinib arm and 29.2 months in the standard of care arm (one-sided p value 0.056). This was not statistically significant.

- Progression free survival. The study provided moderate certainty evidence that trametinib statistically significantly increases progression free survival compared with standard of care. Median progression free survival was 13.0 months in the trametinib arm and 7.2 months in the standard of care arm (one-sided $p<0.0001$).

- Quality of life. The study provided moderate certainty evidence that there was little difference in quality of life between people receiving trametinib or standard of care. However, results for one quality of life assessment were not reported and statistical analysis was not undertaken.

- Hospitalisation. No evidence was identified.

- Tumour response. The study provided moderate certainty evidence that overall tumour response was better with trametinib compared with standard of care. The objective tumour response rate was 26% for the trametinib arm and 6% for the standard of care arm ($p<0.0001$). However, this was a secondary endpoint and, although statistical significance was reported, the study was not powered for this outcome.

- Treatment adherence. No evidence was identified.

- Activities of daily living. No evidence was identified.

In terms of safety:

- Frequency of treatment discontinuation due to toxicity. The study provided moderate certainty evidence that a higher proportion of people discontinued trametinib (36%) due to toxicity compared with standard of care treatments (30%), but no statistical analysis was reported.

- Most frequent grade ≥3 adverse events. The study provided moderate certainty evidence about the most frequent grade ≥3 adverse events, including acneiform or maculo-papular

skin rash (13%), anaemia (13%), hypertension (12%) and nausea and vomiting (16%) for trametinib.

- Frequency of other adverse events of special interest. The study provided moderate certainty evidence about adverse events of special interest, including decreased ejection fraction (8%), pneumonitis (2%), QTc prolongation (2%), left ventricular systolic dysfunction (2%), retinal vascular disorder (2%), and retinal tear (1%) for trametinib.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from treatment with trametinib.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The study, comparing trametinib with standard of care options, was a randomised controlled, open label study that appeared appropriately designed and well reported, with similar baseline characteristics across both arms. However, open label studies are subject to bias due to participants and investigators being unblinded, which can have an impact on patient reported outcomes or investigator assessed outcomes, such as quality of life and tumour response.

The study allowed participants in the standard of care arm to crossover to the trametinib arm after disease progression. This was investigator assessed, which may potentially have influenced participants moving to the trametinib arm prematurely, which could have introduced bias. The authors attempted to control for this this by requiring an objective definition of progression as a ≥20% increase in the sum of the diameters of target lesions, as per RECIST version 1.1 criteria.

No relevant studies identified in the search included adults with advanced LGSOC. The study discussed in this review included adults with recurrent low grade serous ovarian or peritoneal carcinoma, with the majority (at least 90%) of participants having the ovary reported as the disease site. Therefore, the results reflect use of trametinib in adults with recurrent LGSOC and not advanced LGSOC, which was also included in the scope of this evidence review.

In the study, all participants in the standard of care arm were allocated a treatment chosen by the enrolling physician from 5 options, which included chemotherapy and endocrine therapy. Importantly, these choices of standard of care treatment reflect practice within the UK. The results reported for the standard of care arm combined the outcomes of all 5 treatments options, which needs to be considered when interpreting the results.

The study was downgraded for risk of bias because it was an open label design. However, a secondary endpoint, overall survival, was not downgraded for risk of bias due to being an objective measure. Overall survival was downgraded based on imprecision because the 95% confidence intervals crossed two zones and the difference between the two arms did not reach statistical significance.

Conclusion

The study included in this evidence review provided evidence for the clinical effectiveness and safety of trametinib for people with recurrent LGSOC, who had received at least one line of platinum-based chemotherapy. No evidence was found for the use of trametinib in people with advanced LGSOC, who had received at least one line of platinum-based chemotherapy.

The study provided moderate certainty evidence for two critical outcomes, overall survival and quality of life. The study provided moderate certainty evidence that trametinib may improve overall survival compared with standard of care, but this was not statistically significant. Median overall survival was 37.6 months in the trametinib arm and 29.2 months in the standard of care arm (one-sided p value 0.056). In terms of quality of life, few differences were reported between people receiving trametinib or standard of care. Although at one time point (week 12) the participants reported a worse quality of life score than the standard of care arm, this may be accounted for by a higher frequency of adverse events reported in the trametinib arm compared with the standard of care group. The results for one quality of life assessment, FACT-GOG-Ntx, were not reported.

The study provided moderate certainty evidence for a third critical outcome, progression free survival. The study reported that trametinib increased progression free survival compared with standard of care; median progression free survival was 13.0 months in the trametinib arm and 7.2 months in the standard of care arm (one-sided $p<0.0001$). This was statistically significant. The study also provided moderate certainty evidence for one important outcome, tumour response. Overall tumour response was better with trametinib compared with standard of care. The objective tumour response rate was 26% for the trametinib arm and 6% for the standard of care arm ($p<0.0001$). This was a secondary endpoint and, although statistical significance was reported, the study was not powered for this outcome. No evidence was identified for the remaining important outcomes, hospitalisation, treatment adherence and activities of daily living.

The adverse events reported in the study for trametinib reflect the adverse events profile in the summary of product characteristics. Some participants in the trametinib arm reported decreased ejection fraction 10/128 (8%), pneumonitis 3/128 (2%), QTc prolongation 2/128 (2%), left ventricular systolic dysfunction 2/128 (2%), retinal vascular disorder 2/128 (2%), and retinal tear 1/128 (1%), varying from grade 1 to 4. Also, the study reported that a higher proportion of people discontinued trametinib due to toxicity. Toxicity was not defined in the study.

No evidence was found to identify subgroups of patients that may benefit from trametinib more than the wider population of interest. Also, no evidence was identified regarding the cost effectiveness of trametinib in this population.

The findings of this evidence review are important for people with recurrent LGSOC, who have received at least one line of platinum-based chemotherapy because it provides a potential new treatment option for a rare cancer.

The findings of the evidence review are important because they suggest that progression free survival and tumour response may be increased with trametinib compared with standard of care options and that there were no apparent differences in quality of life between the two arms. Although the study was appropriately designed and well reported, open label studies are subject to bias due to participants and investigators being unblinded which can have an impact on patient reported outcomes or investigator assessed outcomes. Also, the results reflect use of trametinib in adults with recurrent LGSOC and not advanced LGSOC.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with recurrent or advanced LGSOC, what is the clinical effectiveness of trametinib compared with standard of care?
2. In people with recurrent or advanced LGSOC, what is the safety of trametinib compared with standard of care?
3. In people with recurrent or advanced LGSOC, what is the cost effectiveness of trametinib compared with standard of care?
4. From the evidence selected, are there any subgroups of patients that may benefit from trametinib more than the wider population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 4 October 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

One paper was identified for inclusion. Table 1 provides a summary of this included study and full details are given in Appendix E. The study was an international, randomised controlled, open label, multicentre phase 2/3 study (Gershenson et al. 2022).

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Gershenson et al. 2022 International, randomised, open label, multicentre, phase 2/3 study 72 hospitals in the USA and 12 hospitals in the UK	• 260 people aged 18 years or older with recurrent ovarian or peritoneal low grade serous carcinoma • Participants had previously received at least one platinum-based chemotherapy regimen but not all 5 standard of care options. • Participants were allowed to have an unlimited number of previous therapy regimes, including chemotherapy and hormonal therapy • Median ages across the 2 study arms were 55.3 to 56.6 years. • Of the participants, 79% were from the USA and over 85% were white. • Participants had received a median of 1.7 to 1.9 previous lines of systemic therapy • Disease site was in the ovary for 91% and peritoneum for 9% of participants.	**Intervention** Participants received oral trametinib 2 mg once daily Treatment continued until either unacceptable toxicity or disease progression The trametinib regimen allowed two dose reductions, to 1.5 mg or 1 mg, for haematological or other adverse events **Comparison** Participants received one of five physician's choice SOC options: • paclitaxel 80 mg/m² by body surface area IV infusion over one hour on days 1, 8, and 15 of a 28 day cycle until progression or unacceptable toxicity or until 6 cycles have been administered. • pegylated liposomal doxorubicin 40 or 50 mg/m² by body surface area IV infusion over one hour on day 1 every 28 days until progression or unacceptable toxicity or until 6 cycles have been administered • topotecan 4 mg/m² by body surface area IV infusion over 30 minutes on days 1, 8, and 15 of a 28 day cycle until progression or unacceptable toxicity or until 6 cycles have been administered • oral letrozole 2.5 mg once daily continuous treatment until progression or unacceptable toxicity • oral tamoxifen 20 mg twice daily continuous treatment until progression or unacceptable toxicity Treatment continued until either unacceptable toxicity or disease progression. Participants were allowed to have more than 6 cycles of chemotherapy and allowed to discontinue therapy after six cycles at the investigator's discretion. For the SOC regimens, dose adjustments were made according to standard of care at the investigator's discretion After disease progression, participants in the SOC arm could cross over to receive trametinib.	**Critical outcome** • Overall survival: median overall survival, analysis included the effect of 88/130 (68%) of participants who crossed over from the SOC arm to the trametinib arm. • Progression free survival: Median progression free survival. This was the primary endpoint of the study • Quality of life: Mean scores, assessed using the FACT-O TOI at baseline, 12 weeks, 24 weeks, 36 weeks, and 52 weeks. **Important Outcomes** • Tumour response rate: objective tumour response rate defined as the proportion of participants in each arm with a clinical response. **Safety** • Adverse events

Abbreviations

FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index; SOC; standard of care

5. Results

In people with recurrent or advanced LGSOC, what is the clinical effectiveness and safety of trametinib compared with standard of care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall Survival **Certainty of evidence:** Moderate	Overall survival is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. In total, 1 randomised controlled, open label study provided evidence relating to overall survival as a secondary endpoint. Participants were randomly assigned 1:1 to receive either trametinib (2mg once daily) or one of five standard of care options. Overall survival analysis was completed at data cut off, July 2019, and the median duration of follow-up was 31.3 months (IQR 15.7-41.9) in the standard of care arm and 31.5 months (IQR 18.1-43.3) in the trametinib arm. The overall survival analysis included 260 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 130 received trametinib and 130 received a standard of care option, in the intent to treat population. This overall survival analysis includes the effect of 88 of 130 (68%) participants in the standard of care arm who crossed over to trametinib following disease progression. In the study, the median overall survival reported was 37.6 months (95% CI 32.0-non-evaluable) in the trametinib arm (n=130) and 29.2 months (23.5-51.6) in the standard of care arm. The HR for death was 0.76 (95% CI 0.51-1.12, one-sided p value 0.056). This was not statically significant. **(MODERATE)** **The study provided moderate certainty evidence that trametinib may improve overall survival compared with standard of care. Median overall survival was 37.6 months in the trametinib arm and 29.2 months in the standard of care arm (one-sided p value 0.056). This was not statistically significant.**
Progression free survival **Certainty of evidence:** Moderate	Progression free survival is important to patients because it reflects how long the disease does not worsen during treatment, although it does not provide information about patients' health and wellbeing during that time. In total, 1 randomised controlled, open label study provided evidence relating to investigator assessed progression free survival (defined as the time from randomisation to disease progression or death), which was the primary endpoint of the study. Participants were randomly assigned 1:1 to receive either trametinib (2mg once daily) or one of five standard of care options. The study was designed to have an 80% power to detect a 50% or greater improvement in progression free survival in the trametinib arm compared with the standard of care arm. The design targeted 213 progression free survival events among 250 patients at the final analysis. The primary analysis was completed after 217 progression free survival events in 101 of 130 (78%) in the trametinib arm and in 116 of 130 (89%) in the standard of care arm. The intent to treat population was 260 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 130 received trametinib and 130 received a standard of care option. Disease progression was assessed by radiological and clinical review according to RECIST version 1.1 criteria. In the study, the median progression-free survival reported was 13.0 months (95% CI 9.9-15.0) in the trametinib arm compared with 7.2 months (5.6-9.9) in the standard of care arm (HR 0.48 [95% CI 0.36-0.64]; one-sided p<0.0001). **(MODERATE)** **The study provided moderate certainty evidence that trametinib statistically significantly increases progression free survival compared with standard of**

	care. Median progression free survival was 13.0 months in the trametinib arm and 7.2 months in the standard of care arm (one-sided p<0.0001).
Quality of life **Certainty of evidence:** Moderate	Quality of life is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being. In total, 1 randomised controlled, open label study provided evidence relating to quality of life in people, this was a secondary endpoint. The quality of life analysis included 198 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 100 received trametinib and 98 received a standard of care option. Quality of life was assessed by use of the FACT-O TOI, higher scores indicate better quality of life. Assessments were completed at baseline (n=198), week 12 (n=182), week 24 (n=143), week 36 (n=131) and week 52 (n=115). A five-point difference between the trametinib group and standard of care group was considered the minimal clinically important difference. The study also assessed quality of life using the adapted self-administered FACT-GOG-Ntx subscale, a higher score indicates less neurotoxicity. In the study, no significant differences were found in the mean scores between trametinib and standard of care at all times points except for week 12. At week 12, people in the trametinib arm (n=91) reported a worse quality of life by 3.6 points (95% CI -6.8 to -0.5; adjusted p=0.048), which was statistically significant but less than the outlined minimal clinically important difference. **(MODERATE)** The study did not report any results for the FACT-GOG-Ntx subscale but stated no differences in patient reported neurotoxicity were seen between the two groups using this subscale. **The study provided moderate certainty evidence that there was little difference in quality of life between people receiving trametinib or standard of care. However, results for one quality of life assessment were not reported.**
Important outcomes	
Hospitalisation **Certainty of evidence:** Not applicable	Hospitalisation is important to patients because frequent hospital attendances can have a negative impact on the psychological health of patients. **No evidence was identified for this outcome.**
Tumour response **Certainty of evidence:** Moderate	Tumour response is important to patients because it provides an indication of how the disease is responding to treatment. In total, 1 randomised controlled, open label study provided evidence relating to tumour response, objective tumour response rate (ORR), defined as the proportion of patients with a complete or partial response, which was a secondary endpoint. Participants were randomly assigned 1:1 to receive either trametinib (2mg once daily) or one of five standard of care options. The intent to treat population include 260 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 130 received trametinib and 130 received a standard of care option. Tumour response was assessed by radiological and clinical review according to RECIST version 1.1 criteria. In the study, the ORR for the of trametinib arm was 26% (34/130) and for the standard of care arm was 6% (8/130), (odds ratio 5.4, 95% CI 2.4-12.2, p<0.0001). **(MODERATE)** **The study provided moderate certainty evidence that overall tumour response was better with trametinib compared with standard of care. The objective tumour response rate was 26% for the trametinib arm and 6% for the standard of care arm (p<0.0001). However, this was a secondary endpoint and, although statistical significance was reported, the study was not powered for this outcome.**

Treatment adherence **Certainty of evidence:** Not applicable	Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of disease progression. **No evidence was identified for this outcome.**
Activities of daily living **Certainty of evidence:** Not applicable	Activities of daily living is important to patients as it indicates their ability to independently care for themselves. **No evidence was identified for this outcome.**
Safety	
Frequency of treatment discontinuation due to toxicity **Certainty of evidence:** Moderate	Safety of trametinib is important to patients as it reflects the risks involved in taking this medication and allows a risk to benefit assessment to be undertaken. In the study the safety analysis included 255 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 128 received trametinib and 127 received a standard of care option. The study reports 46/128 (36%) discontinued trametinib due to toxicity and 38/127 (30%) discontinued standard of care due to toxicity. No statistical analysis was presented for safety data and toxicity was not defined in the study. **(MODERATE)** **The study provided moderate certainty evidence that a higher proportion of people discontinued trametinib due to toxicity compared with standard of care, but no statistical analysis was reported.**
Most frequent grade ≥3 adverse events **Certainty of evidence:** Moderate	Safety of trametinib is important to patients as it reflects the risks involved in taking this medication and allows a risk to benefit assessment to be undertaken. In the study, the safety analysis included 255 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 128 received trametinib and 127 received a standard of care option. Adverse events were described according to CTCAE definitions. The most frequent grade 3 to 4 adverse events reported in the trametinib arm were acneiform or maculo-papular skin rash 17/128 (13%), anaemia 16/128 (13%), hypertension 15/128 (12%), diarrhoea 13/128 (10%), fatigue 10/128 (8%) and nausea and vomiting 22/128 (16%). In the standard of care arm the most frequent grade 3 to 4 adverse events reported were abdominal pain 22/127 (17%), nausea and vomiting 24/127 (19%) and anaemia 12/127 (10%). Grade 3 or higher gastrointestinal disorders adverse events were reported for 37/128 (29%) in the trametinib arm and in 35/127 (28%) in the standard of care arm. No statistical analysis was presented for safety data. **(MODERATE)** **The study provided moderate certainty evidence about the most frequent grade ≥3 adverse events.**
Frequency of other adverse events of special interest **Certainty of evidence:** Moderate	Safety of trametinib is important to patients as it reflects the risks involved in taking this medication and allows a risk to benefit assessment to be undertaken. In the study the safety analysis included 255 adults who had recurrent low grade serous ovarian or peritoneal carcinoma, 128 received trametinib and 127 received a standard of care option. Rash, diarrhoea, visual disorder, hepatic disorders, pneumonitis, and cardiac related adverse events were considered adverse events of special interest because they are either a known class effect of MEK inhibitors or are potentially life threatening. The frequency of other adverse events of special interest in the trametinib arm was a decrease in ejection fraction 10/128 (8%; eight grade 2 events and two grade 3), pneumonitis 3/128 (2%; one each grade 1, 2, and 3), QTc prolongation 2/128 (2%; one grade 1 and one grade 4), left ventricular systolic dysfunction 2/128 (2%; both grade 3), retinal vascular disorder 2/128 (2%; one grade 2 and one grade 3), and retinal tear 1/128 (1%; grade 3). Of the 20 patients with these special interest adverse events, 3/10 (15%) who had a decrease in ejection fraction and 1/2 (50%) who had QTc prolongation were able to restart trametinib. In the standard of care arm, the frequency of other adverse events of special interest reported were left ventricular systolic dysfunction 1/127 (1%; grade 3) and

	decreased ejection fraction 1/127 (1%; grade 3). No statistical analysis was presented for safety data. **(MODERATE)** **The study provided moderate certainty evidence about adverse events of special interest.**

Abbreviations

CI, confidence interval; CTCAE, common terminology criteria for adverse events; FACT-GOG-Ntx, Functional Assessment of Cancer Therapy Gynecologic Oncology Group-Neurotoxicity questionnaire; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index; IQR, Interquartile range; MEK, Mitogen activated protein kinase; OR, odds ratio; ORR, objective tumour response rate; p, P value; RECIST, Response Evaluation Criteria in Solid Tumours

In people with recurrent or advanced LGSOC, what is the cost effectiveness of trametinib compared with standard of care?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified regarding the cost effectiveness of trametinib for people with recurrent or advanced LGSOC, who have received at least one line of platinum-based chemotherapy.**

Abbreviations

LGSOC, Low grade serous ovarian cancer

From the evidence selected, are there any subgroups of patients that may benefit from trametinib more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was found to identify subgroups of people with recurrent or advanced LGSOC, who have received at least one line of platinum-based chemotherapy that may benefit from trametinib more than the wider population of interest.**

Abbreviations

LGSOC, Low grade serous ovarian cancer

6. Discussion

The evidence review included one study. This was a randomised controlled, open label study comparing trametinib with standard of care options that appeared appropriately designed and well reported, with similar baseline characteristics across both arms. However, open label studies are subject to bias due to participants and investigators being unblinded which can have an impact on patient reported outcomes or investigator assessed outcomes, such as quality of life and tumour response.

The study allowed participants in the standard of care arm to crossover to the trametinib arm after disease progression. This was investigator assessed, which may potentially have influenced participants moving to the trametinib arm prematurely, which could have introduced bias. The authors attempted to control for this this by requiring an objective definition of progression as a ≥20% increase in the sum of the diameters of target lesions, as per RECIST version 1.1 criteria.

No relevant studies identified in the search included adults with advanced low grade serous ovarian cancer. The study discussed in this review, included adults with recurrent low grade serous ovarian or peritoneal carcinoma, with the majority (at least 90%) of participants having the ovary reported as the disease site. Therefore, the results reflect use of trametinib in adults with recurrent low grade serous ovarian cancer and not advanced low grade serous ovarian cancer.

In the study all participants in the standard of care arm were allocated a treatment chosen by the enrolling physician from 5 options, which included chemotherapy and endocrine therapy. The choices of standard of care treatment reflect practice within the UK. The results reported for the standard of care arm combined the outcomes of all 5 treatments options, which needs to be considered when interpreting the results.

The study was downgraded for risk of bias because it was an open label design. However, a secondary endpoint, overall survival was not downgraded for risk of bias due to being an objective measure but was downgraded based on imprecision because the 95% confidence intervals crossed two zones. This outcome was not statistically significant.

No evidence was identified for the important outcomes of hospitalisation, treatment adherence or activities of daily activities. No evidence was identified regarding subgroups of patients that may benefit from trametinib more than the wider population of interest. No evidence was identified regarding the cost effectiveness of trametinib.

7. Conclusion

One randomised controlled, open label study provided evidence for the clinical effectiveness and safety of trametinib for people with recurrent LGSOC, who had received at least one line of platinum-based chemotherapy. No evidence was found for the use of trametinib in people with advanced LGSOC, who had received at least one line of platinum-based chemotherapy.

The study provided moderate certainty evidence for two critical outcomes, overall survival and quality of life. The study provided moderate certainty evidence that trametinib may improve overall survival compared with standard of care, but this was not statistically significant. Median overall survival was 37.6 months in the trametinib arm and 29.2 months in the standard of care arm (one-sided p value 0.056). In terms of quality of life, few differences were reported between people receiving trametinib or standard of care. Although at one time point (week 12), the participants in the trametinib arm reported a worse quality of life score than the standard of care arm. This may be accounted for by a higher frequency of adverse events reported in the trametinib arm compared with the standard of care arm. The results for one quality of life assessment, FACT-GOG-Ntx, were not reported.

The study provided moderate certainty evidence for a third critical outcome, progression free survival, which was the primary endpoint. Trametinib statistically significantly increased progression free survival compared with standard of care. Median progression free survival was 13.0 months in the trametinib arm and 7.2 months in the standard of care arm (one-sided $p<0.0001$). The study also provided moderate certainty evidence for one important outcome, tumour response. Overall tumour response was better with trametinib compared with standard of care. The objective tumour response rate was 26% for the trametinib arm and 6% for the standard of care arm ($p<0.0001$). However, although statistical significance was reported, this was a secondary endpoint and the study was not powered for this outcome. No evidence was identified for the remaining important outcomes, hospitalisation, treatment adherence and activities of daily living.

The adverse events reported for trametinib in the study reflect the adverse events profile in the summary of product characteristics. Some participants in the trametinib arm reported, decreased ejection fraction 10/128 (8%), pneumonitis 3/128 (2%), QTc prolongation 2/128 (2%), left ventricular systolic dysfunction 2/128 (2%), retinal vascular disorder 2/128 (2%), and retinal tear 1/128 (1%), varying from grade 1 to 4. Also, the study reported that a higher proportion of people discontinued trametinib due to toxicity. Toxicity was not defined in the study.

No evidence was found to identify subgroups of patients that may benefit from trametinib more than the wider population of interest. Also, no evidence was identified regarding the cost effectiveness of trametinib in this population.

The findings of this evidence review are important for people with recurrent LGSOC, who have received at least one line of platinum-based chemotherapy because it provides a potential new treatment option for a rare cancer.

The findings of the evidence review are important because they suggest that progression free survival and tumour response may be increased with trametinib compared with standard of care options and that there were no apparent differences in quality of life between the two arms. Although the study was appropriately designed and well reported, open label studies are subject to bias due to participants and investigators being unblinded which can have an impact on patient reported outcomes or investigator assessed outcomes. Also, the results reflect use of trametinib in adults with recurrent low grade serous ovarian cancer and not advanced low grade serous ovarian cancer.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with recurrent or advanced LGSOC, what is the clinical effectiveness of trametinib compared with standard of care?
2. In people with recurrent or advanced LGSOC, what is the safety of trametinib compared with standard of care?
3. In people with recurrent or advanced LGSOC, what is the cost effectiveness of trametinib compared with standard of care?
4. From the evidence selected, are there any subgroups of patients that may benefit from trametinib more than the wider population of interest?

P-Population and Indication	Individuals with recurrent or advanced LGSOC who have received at least one line of platinum-based chemotherapy (such as carboplatin or cisplatin) [Patients may or may not have received either hormonal therapy or surgery.] Particular subgroups of interest: none
I-Intervention	Palliative treatment with trametinib [Starting dose of 2mg OD]
C-Comparator	• Palliative treatment without trametinib [For example, with one or more of the following: platinum-based chemotherapy, paclitaxel, pegylated liposomal doxorubicin (PLDH), hormonal therapies (including letrozole or tamoxifen)] • No palliative treatment
O-Outcomes	**Clinical Effectiveness** Minimally clinically important difference (MCIDs) are not known unless stated. *Critical to decision-making:* • **Overall Survival** *Overall survival is important to patients as individuals with relapsed LGSOC have a high mortality rate due to advanced cancer. Improved survival is an important marker of effective treatment*. • **Progression free survival** *This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival*

	and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. • **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy.* [Examples of generic quality of life tools include QLQ-OV28, QLQ-C30 and the EQ-5D Examples of disease specific quality of life tools include, but are not limited to: o Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index (FACT-O TOI) o Adapted self-administered Functional Assessment of Cancer Therapy Gynaecologic Oncology Group-Neurotoxicity questionnaire (FACT-GOG-Ntx) subscale.] *Important to decision-making:* • **Hospitalisation** *This outcome is important to patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life and inform their treatment decision making*. • **Tumour response** *Response rate is important to patients as it represents whether the treatment can improve tumour burden.* [Examples include, but are not limited to: o Change in CA-125 – a biomarker of ovarian cancer o Change in tumour burden on imaging modalities such as CT, PET/CT, or MRI scanning. o Clinical assessment of response which might be assessed by a validated scoring system such as the Response Evaluation Criteria in Solid Tumours (RECIST)] • **Treatment adherence**

Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of treatment failure and add to tumour progression.

[Examples include, but not limited to:
- Missed doses (observed by research staff review of medication/returned medication)
- Self-reported adherence measures (e.g., questionnaire methods)
- Interview methods]

- **Activities of daily living (ADLs)**
ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. The complications of recurrent LGSOC can lead to progressively worsening physical symptoms and altered ability to complete ADLs without assistance.

[ADLs can be measured using assessments such as:
- Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal)
- ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL)
- Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work and other activities).]

Safety

The safety of trametinib is important to patients as it informs treatment decisions and allows comparison of interventional approaches.

[Examples of measures include, but are not limited to:
- Frequency of adverse events
- Frequency of serious adverse events
- Frequency of grade 3 or 4 adverse events
- Adverse events leading to discontinuation
- Treatment related adverse events – e.g., GI side effects including gastrointestinal perforation and colitis.]

	Cost effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 03 October 2022

Database: Medline

Platform: Ovid
Version: 1946 to October 3 2022
Search date: 04/10/2022
Number of results retrieved: 21
Search strategy:

Database: Ovid MEDLINE(R) <1946 to October 03, 2022>
Search Strategy:
---
1 exp Ovarian Neoplasms/ (92976)
2 (ovar* adj4 (cancer* or carcinoma* or tumo* or neoplasm* or malignan*)).tw. (89470)
3 1 or 2 (113994)
4 (trametinib or mekinist).tw. (1244)
5 (gsk 1120212* or gsk1120212* or jtp 74057 or jtp74057 or snr 1611 or tmt 212 or tmt212).tw. (51)
6 4 or 5 (1269)
7 3 and 6 (21)

Database: Medline in-process

Platform: Ovid
Version: 1946 to October 03 2022
Search date: 04/10/2022
Number of results retrieved: 0
Search strategy:

As above

Database: Medline epubs ahead of print

Platform: Ovid
Version: October 03 2022
Search date: 04/10/2022
Number of results retrieved: 0
Search strategy:

As above

Database: Embase

Platform: Ovid
Version: 1974 to 2022 October 03

Search date: 04/10/2022
Number of results retrieved: 262
Database: Embase <1974 to 2022 October 03>
Search Strategy:
---
1 exp ovary cancer/ (138054)
2 (ovar* adj4 (cancer* or carcinoma* or tumo* or neoplasm* or malignan*)).tw. (145104)
3 1 or 2 (182983)
4 trametinib/ (7741)
5 (trametinib or mekinist).tw. (3737)
6 (gsk 1120212* or gsk1120212* or jtp 74057 or jtp74057 or snr 1611 or tmt 212 or tmt212).tw. (553)
7 or/4-6 (8005)
8 3 and 7 (330)
9 nonhuman/ not human/ (5064630)
10 8 not 9 (318)
11 limit 10 to english language/ (318)
12 limit 11 to (books or chapter or conference abstract or conference paper or "conference review" or editorial or letter or note) (54)
13 11 not 12 (264)
14 limit 13 to dc=20120101-20221004 (262)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 10 of 12, Month year 2022
CENTRAL – Issue 10 of 12, Month year 2022
Search date: 04/10/2022
Number of results retrieved: CDSR 0 ; CENTRAL 77

Search Name: trametinib
Date Run: 04/10/2022 04:28:48
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees	2219
#2	(ovar* near/4 cancer* or carcinoma* or tumo* or neoplasm* or malignan*):ti,ab,kw	174417
#3	#1 or #2	174417
#4	(trametinib or mekinist):ti,ab,kw (Word variations have been searched)	331
#5	(gsk 1120212* or gsk1120212* or jtp 74057 or jtp74057 or snr 1611 or tmt 212 or tmt212):ti,ab,kw	41
#6	#4 or #5	342
#7	#3 and #6	250
#8	conference:pt	207715
#9	#7 not #8	143
#10	(clinicaltrials or trialsearch):so	433878
#11	#9 not #10	77

Reference list checking

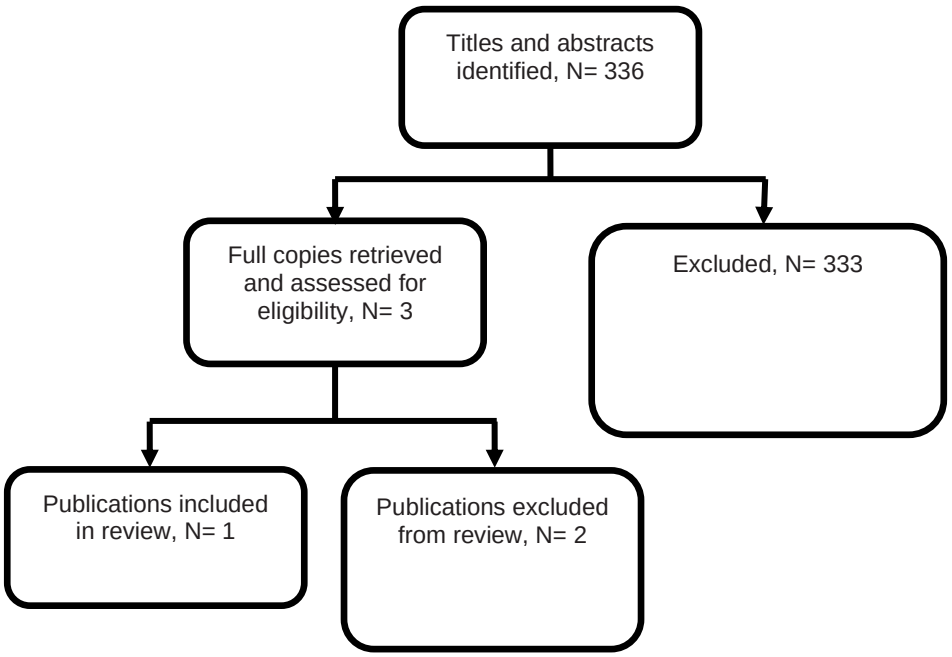
Reference list of most clinically useful study was checked. 0 additional references were deemed relevant and added to EPPI reviewer.

Narrative reviews or reviews of grading ovarian cancers.

Appendix C Evidence selection

The literature searches identified 336 references. These were screened using their titles and abstracts and 3 references were obtained in full text and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 2 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Bussies PL., Schlumbrecht M. (2020) Dual Fulvestrant-Trametinib Therapy in Recurrent Low-Grade Serous Ovarian Cancer. *Oncologist* 25(7), e1124–e1126	Excluded as a case report
Champer, M., Miller, D., Kuo, D. Y. (2019). Response to trametinib in recurrent low-grade serous ovarian cancer with NRAS mutation: A case report. *Gynecologic Oncology Reports*. 28, p26–28.	Excluded as a case report
Gershenson DM., Miller A., et al. (2022) 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. *Lancet*. 399(10324),p541-553.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Musacchio L, Valsecchi AA, et al. (2022) MEK inhibitor as single agent in low grade serous ovarian and peritoneal cancer: a systematic review and meta-analysis. Cancer Treat Rev. 110,102458. doi: 10.1016/j.ctrv.2022.102458. Epub ahead of print.	Systematic review and meta-analysis of MEK inhibitors in low grade serous and peritoneal cancer includes all MEK inhibitors not just trametinib
Pauly, N., Ehman, S., et al. (2020) Low-grade Serous Tumours: Are We Making Progress?. *Curr Oncol Rep*. 22 (1),8. doi: 10.1007/s11912-020-0872-5. PMID: 31989304.	Literature review

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Gershenson DM., Miller A., et al. (2022) 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. Lancet. 399:541–553. **Study location** 72 hospitals in the USA and 12 hospitals in the UK. **Study type** International, randomised controlled, open label, multicentre, phase 2/3 trial **Study aim** The aim of the study was to evaluate the efficacy and safety of the MEK inhibitor, trametinib, at its licensed dose in other malignancies, compared with physician's choice standard of care in women with recurrent low grade serous carcinoma. **Study dates** February 2014 to April 2018	**Inclusion criteria** People aged 18 years or older with recurrent ovarian or peritoneal low grade serous carcinoma who had previously received at least one platinum-based chemotherapy regimen. People were allowed to have an unlimited number of previous therapy regimes, including chemotherapy and hormonal therapy but not all five standard of care options. **Exclusion Criteria** People with serous borderline tumours or tumours containing low grade and high grade serous carcinomas. People who had received all five standard of care options. **Total sample size** 260 people were included in the intention-to-treat analysis 255 people were included in the safety analysis 198 were included in the quality-of-life analysis **No. of participants in each treatment group** Standard of care arm, n=130 Trametinib arm, n=130 **Baseline characteristics**	**Interventions** Participants were randomly assigned 1:1 to receive either trametinib or one of five standard of care options. Participants assigned the trametinib arm received oral trametinib 2 mg once daily Treatment continued until either unacceptable toxicity or disease progression (defined as a ≥20% increase in the sum of the diameters of target lesions, as per RECIST version 1.1 criteria) The trametinib regimen allowed two dose reductions, to 1.5 mg or 1 mg, for haematological or other adverse events **Comparators** Participants assigned to the standard of care arm received one of 5 physician's choice standard of care options: • paclitaxel 80 mg/m² by body surface area IV infusion over one hour on days 1, 8, and 15 of a 28 day cycle until progression or unacceptable toxicity or until 6 cycles have been administered. • pegylated liposomal doxorubicin 40 or 50 mg/m² by body surface area IV infusion over one hour on day 1 every 28 days until progression or unacceptable toxicity or until 6 cycles have been administered	**Critical outcomes** **Overall Survival** At data cut-off, July 2019, the overall survival analysis included 260 participants in the intent to treat population. Of the 260 participants, 111 (43%) had died, with 51/130 in the trametinib arm and 60/130 in the standard of care arm. Median overall survival was 37.6 months (95% CI 32.0–non-evaluable) in the trametinib arm and 29.2 months (23.5–51.6) in the standard of care arm. The HR for death was 0.76 (95% CI 0.51–1.12; one-sided p value 0.056) The overall survival analysis includes the effect of 88/130 (68%) participants in the standard of care arm who crossed over to trametinib following disease progression **Progression free survival** The primary analysis was completed after 217 progression free survival events, 101/130 (78%) in the trametinib arm and in 116/130 (89%) in the standard of care arm. Median progression free survival was 13·0 months (95% CI 9.9–15.0) in the trametinib arm and 7·2 months (5.6–9.9) in the standard of care arm (HR 0.48 [95% CI 0.36–0.64]; one-sided p<0.0001) **Quality of life** Quality of life was assessed by use of the FACT-O TOI and the adapted self-administered FACT-GOG-Ntx subscale. The compliance rates of quality of life assessments in patients were 88% (227 of 259 participants) at baseline and 77% (194 of 253) at 12 weeks, 63% (153 of 244) at 24 weeks,	This study was assessed using the Cochrane Risk of Bias tool (see Appendix F). Domain1: Risk of bias arising from the randomisation process: LOW Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): LOW Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention): LOW Domain 3: Missing outcome data: LOW Domain 4: Risk of bias in measurement of the outcome: SOME CONCERNS Domain 5: Risk of bias in selection of the reported result: LOW Overall risk of bias judgement: SOME CONCERNS Source of funding: NRG Oncology, Cancer Research UK, Target Ovarian Cancer, and Novartis

	Median ages across the 2 study arms were 55.3 to 56.6 years, 79% of participants were from the USA and over 85% were white. Participants had received a mean of 1.7 to 1.9 previous lines of systemic therapy. The disease site was ovary for 91% and peritoneum for 9% of participants. Baseline demographic and disease characteristics were similar between the arms.	• topotecan 4 mg/m² by body surface area IV infusion over 30 minutes on days 1, 8, and 15 of a 28 day cycle until progression or unacceptable toxicity or until 6 cycles have been administered • oral letrozole 2.5 mg once daily continuous treatment until progression or unacceptable toxicity • oral tamoxifen 20 mg twice daily continuous treatment until progression or unacceptable toxicity These treatments were selected for participants before randomisation. Treatment continued until either unacceptable toxicity or disease progression (defined as a ≥20% increase in the sum of the diameters of target lesions, as per RECIST version 1.1 criteria). Participants were allowed more than 6 cycles of chemotherapy and also allowed to discontinue therapy after 6 cycles at the investigator's discretion. For the standard of care regimens, dose adjustments were made according to standard of care at the investigator's discretion. After disease progression. After disease progression, participants i in the standard of care arm could cross over to receive trametinib.	60% (139 of 233) at 36 weeks, and 56% (125 of 222) at 52 weeks after cycle 1. 198 participants, 98 in the standard of care arm and 100 in the trametinib arm completed the baseline assessment and at least one follow-up assessment were evaluable for quality of life analysis. Mean scores were calculated at baseline, week 12, week 24, week 36 and week 52. Participants in the trametinib arm reported a worse quality of life by 3.6 points (95% CI -6.8 to -0.5; adjusted p=0.048) at 12 weeks compared with the standard of care arm. This was less points that the outlined clinically important difference of 5 points. No significant differences in quality of life between the two arms at other timepoints were reported, including in an exploratory examination of differences at weeks 36 and 52. No patient-reported neurotoxicity differences between the two arms using the FACT-GOG-Ntx subscale were reported. These results were not reported in the study. **Important outcomes** **Hospitalisation** Not reported **Tumour response** The ORR, defined as the proportion of participants in each arm with a clinical response. The ORR of the trametinib arm was 26% (34/130), with 59% (77/130) having stable disease for a minimum of 8 weeks. The ORR of the standard of care arm was 6% (8/130), with 71% having stable disease (92/130) (OR 5.4 [95% CI 2.4–12.2]; p<0.0001) The ORR for the individual therapies within the standard of care arm: letrozole 14% (6/44), paclitaxel 9% (1/11), pegylated liposomal doxorubicin 3% (1/40), tamoxifen 0% (0/27), and topotecan 0% (0/8). The median duration of response was 13.6 months (IQR 7.2-19.9; 95% CI 8.1-18.8) in the	

			trametinib arm and 5.9 months (4.0-12.2; 2.8-12.2) in the standard of care arm. **Treatment adherence** Not reported **Activities of daily living** Not reported **Safety** Treatment-emergent adverse events occurred in 20% or more of treated patients in both arms. Adverse events were described according to CTCAE definitions. The most frequent grade 3 or 4 adverse events in the trametinib arm were acneiform or maculo-papular skin rash, 17/128 participants (13%), anaemia, 16/128 participants (13%), hypertension, 15/128 participants (12%), diarrhoea, 13/128 participants (10%), nausea, 12/128 participants (9%), and fatigue, 10/128 participants (8%). The frequency of adverse events of special interest in the trametinib group which ranged from grade 1 to 4 included decrease in ejection fraction, 10/128 participants (8%), pneumonitis, 3/128 participants (2%), QTc prolongation 2/128 participants (2%), left ventricular systolic dysfunction, 2/128 participants (2%), retinal vascular disorder, 2/128 participants (2%), and retinal tear, 1/127 participants (1%). In the standard of care arm, the most frequent grade 3 or 4 adverse events were abdominal pain, 22/127 participants (17%), nausea 14/127 participants (11%), anaemia 12/127 participants (10%), and vomiting, 10/127 participants (8%). In the standard of care arm, adverse events of special interest included; 1/127 (1%) participant had left ventricular systolic dysfunction and 1/127 participants (1%) had decreased ejection fraction. Both were grade 3. Overall, grade 3 or higher gastrointestinal disorders occurred in 37/128 participants (29%) in the trametinib arm and in 35/127 participants (28%) in the standard of care arm. Small	

			intestine obstruction was reported in 16/128 participants (13%) in the trametinib arm and in 9/127 participants (7%) in the standard of care arm. Colon obstruction occurred in 1/128 participants (1%) in the trametinib arm and 6/127 participants (5%) in the standard of care arm. The 128 participants in the trametinib arm completed a total of 1365 cycles. The median number of cycles received was eight (IQR 3-16). Dose reductions occurred in 156 (11%) of all trametinib cycles. 90/128 participants (70%) required at least one dose reduction during the study period, 38/128 participants (30%) required two dose reductions. Of these participants, 14 withdrew due to disease progression, 17 due to adverse events, and two for other reasons. Five (4%) patients were on treatment at the data cut off date. A total of 46/128 participants (36%) discontinued trametinib due to toxicity[a] compared with 38/127 participants (30%) who discontinued standard of care therapy due to toxicity.	

Abbreviations

CI, confidence interval; CTCAE, common terminology criteria for adverse events; FACT-GOG-Ntx, Functional Assessment of Cancer Therapy Gynecologic Oncology Group-Neurotoxicity questionnaire; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index; MEK, Mitogen activated protein kinase; OR, odds ratio; ORR, objective tumour response rate; p, P value; RECIST, Response Evaluation Criteria in Solid Tumours

a Toxicity was not defined in the study

Appendix F Quality appraisal checklists

Cochrane risk-of-bias tool for randomized trials checklist

Domain 1: Risk of bias arising from the randomization process	
1.1 Was the allocation sequence random?	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No
Risk-of-bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	
Risk-of-bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Probably yes
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	No
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	No
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	

Risk-of-bias judgement	Low
Domain 3: Missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	
Risk-of-bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	Probably no
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
Risk-of-bias judgement	Some concerns
Domain 5: Risk of bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Probably yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Probably no
5.3 ... multiple eligible analyses of the data?	Probably no
Risk-of-bias judgement	Low
Overall risk-of-bias judgement	Low

Appendix G GRADE profiles

Table 2: Question: In people with recurrent or advanced LGSOC, what is the clinical effectiveness and safety of trametinib compared with standard of care?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Trametinib	Standard of care	Result (95%CI)		
Overall Survival (randomised controlled, open label, multicentre, phase 2/3 trial)									
Median overall survival (Kaplan-Meier)									
1 RCT Gershenson et al. 2022	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	37.6 months (95% CI 32.0-non-evaluable) (n=130)	29.2 months (95% CI 23.5-51.6) (n=130)	HR for death was 0.76 (95% CI 0.51-1.12) one-sided p value 0.056	Critical	Moderate
Progression free survival (randomised controlled, open label, multicentre, phase 2/3 trial)									
Median progression free survival (Kaplan-Meier)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	No serious imprecision	13.0 months (95% CI 9.9-15.0) (n=130)	7.2 months (95% CI 5.6-9.9) (n=130)	HR 0.48 (95% CI 0.36-0.64) one-sided p<0.0001	Critical	Moderate
Quality of life (randomised controlled, open label, multicentre, phase 2/3 trial)									
Quality of life at baseline (Mean scores from the FACT-O TOI- higher score indicates better quality of life)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	74.5 (13.7) (n=100)	74.5 (16.6) (n=98)	No statistical analysis	Critical	Moderate
Quality of life at week 12 (Mean scores from the FACT-O TOI- higher score indicates better quality of life)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	70.6 (13.5) (n=91)	74.2 (16.0) (n=91)	95% CI -6.8 to -0.5 adjusted p=0.048	Critical	Moderate
Quality of life at week 52 (Mean scores from the FACT-O TOI- higher score indicates better quality of life)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	73.3 (14.3) (n=58)	72.1 (16.9) (n=57)	No statistical analysis	Critical	Moderate

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Trametinib**	**Standard of care**	**Result (95%CI)**		
Tumour response (randomised controlled, open label, multicentre, phase 2/3 trial)									
Objective tumour response rate (the proportion of patients in each group with a clinical response)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	34 (26%) (n=130)	8 (6%) (n=130)	OR 5.4 (95% CI 2.4-12.2) p<0.0001	Important	Moderate
Treatment discontinuation due to toxicity (randomised controlled, open label, multicentre, phase 2/3 trial)									
Frequency of treatment discontinuation due to toxicity[a] (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	46 (36%) (n=128)	38 (30%) (n=127)	No statistical analysis	Important	Moderate
Most frequent grade ≥3 adverse events reported for trametinib (randomised controlled, open label, multicentre, phase 2/3 trial)									
Frequency of grade ≥3 fatigue (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	10 (8%) (n=128)	5 (4%) (n=127)	No statistical analysis	Important	Moderate
Frequency of grade ≥3 gastrointestinal disorders adverse events- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	37 (29%) (n=128)	35 (28%) (n=127)	No statistical analysis	Important	Moderate
Frequency of grade ≥3 diarrhoea (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	13 (10%) (n=128)	4 (3%) (n=127)	No statistical analysis	Important	Moderate
Frequency of grade ≥3 nausea and vomiting (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	22 (16%) (n=128)	24 (19%) (n=127)	No statistical analysis	Important	Moderate
Frequency of grade ≥3 acneiform or maculopapular rash (the proportion of patients in each group- lower result is beneficial)									

1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	17 (13%) (n=128)	1 (1%) (n=127)	No statistical analysis	Important	Moderate
Frequency of grade ≥3 anaemia (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	16 (13%) (n=128)	12 (10%) (n=127)	No statistical analysis	Important	Moderate
Frequency of grade ≥3 hypertension (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	15 (12%) (n=128)	6 (5%) (n=127)	No statistical analysis	Important	Moderate
Frequency of other adverse events of special interest reported for trametinib (randomised controlled, open label, multicentre, phase 2/3 trial)									
Frequency of decreased ejection fraction (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	10 (8%) (n=128)	1 (1%) (n=127)	No statistical analysis	Important	Moderate
Frequency of pneumonitis (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	3 (2%) (n=128)	Not clear[b]	No statistical analysis	Important	Moderate
Frequency of QTc prolongation (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	2 (2%) (n=128)	Not clear[b]	No statistical analysis	Important	Moderate
Frequency of left ventricular systolic dysfunction (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	2 (2%) (n=128)	1 (1%) (n=127)	No statistical analysis	Important	Moderate
Frequency of retinal vascular disorder (the proportion of patients in each group- lower result is beneficial)									
1 RCT	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	2 (2%) (n=128)	Not clear[b]	No statistical analysis	Important	Moderate

Gershenson et al. 2022									
Frequency of retinal tear (the proportion of patients in each group- lower result is beneficial)									
1 RCT Gershenson et al. 2022	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	1 (1%) (n=128)	Not clear[b]	No statistical analysis	Important	Moderate

Abbreviations

CI, confidence interval; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index; OR, odds ratio; ORR, objective tumour response rate; p, P value; RCT, randomised controlled trial

1 Downgraded as 95% CI spans two zones
2 Downgraded as open label trial

a Toxicity was not defined in the study
b Adverse events of special interest were not documented in the adverse events table; therefore it is difficult to conclude if the standard of care arm experienced some of these adverse events.

Glossary

CTCAE	Common Terminology Criteria for Adverse Events The U.S. National Cancer Institute produced the CTCAE. CTCAE aids the reporting of adverse events that occur in patients enrolled in cancer therapy clinical trials. CTCAE is a standard classification and severity grading scale for adverse events in such clinical trials and other oncology settings.
FACT-GOG-Ntx	Functional Assessment of Cancer Therapy Gynecologic Oncology Group-Neurotoxicity This is a self-assessed scoring system that consists of 38 items, which assess the symptoms of peripheral neuropathy, including sensory, motor, and auditory problems and cold sensitivity during chemotherapy.
FACT-O TOI	Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index This is a scoring system that measures the general quality of life of people with ovarian cancer.
RECIST	Response Evaluation Criteria in Solid Tumours This provides a methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumours, using validated and consistent criteria to assess changes in tumour burden.

References

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