CLINICAL PRIORITIES ADVISORY GROUP
06 09 2023

Agenda Item No	2.3
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2253

Title
Trametinib in recurrent or progressive low grade serous ovarian cancer (Adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
The policy proposition recommends that trametinib is made available as a routine commissioning treatment option for recurrent or progressive low-grade serous ovarian carcinoma (LGSOC), following at least one line of platinum-based chemotherapy, with or without surgery or hormonal agents. Trametinib is an off-label treatment for this indication. LGSOC is a rare subtype of ovarian cancer which originates from epithelial cells that are found on the surface of the ovaries. LGSOC is different from other, more common types of ovarian cancer, as it grows more slowly, often presents at a younger age and it is more resistant to chemotherapy. It is expected that c.85 people would be likely to receive the treatment each year under the policy. It should be noted that the treatment is currently available to patients for this indication because of its inclusion on the interim system anti-cancer therapy list, established as part of the covid pandemic response. As such the clinical commissioning policy proposition is submitted to CPAG as an in-year service development.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In patients with LSGOC, what is the clinical effectiveness and safety of trametinib and best supportive care compared to best supportive care alone or with standard 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 for cost effectiveness.

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.	

From the evidence selected, what are the criteria used by the research studies to define LSCOG?

Outcome	Evidence statement
Criteria to define LSGOC	The study characterised LGSOC by MAPK pathway aberrations of the tumour, and its reduced sensitivity to chemotherapy relative to high-grade serous carcinoma.
Abbreviations: MPAK: Mitogen-activated protein kinases;	

From the evidence selected, what dosage (size/ frequency/ duration) of trametinib was used?

Outcome	Evidence statement
Dosage of trametinib	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.
Abbreviations:	

mg: Milligrams;

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **Mobility:** Patients have a very variable ability to walk about.
- **Ability to provide self-care:** Patients have very variable problems in washing or dressing OR are unable to wash or dress.
- **Undertaking usual activities:** Patients very variable problems in doing their usual activities OR are unable to do their daily activities.
- **Experience of pain/discomfort:** Patients have very variable pain or discomfort.
- **Experience of anxiety/depression:** Patients have very variable experiences of being anxious or depressed.

Further details of impact upon patients:

The majority are diagnosed with ovarian cancer at later stages. This means they can experience symptoms impacting their health and quality of life. Treatment is aimed at minimising disease burden and maximising periods of wellness. As treatment lines are exhausted, those diagnosed fear being told there is no more treatment available to manage their ovarian cancer. This is particularly relevant for those with LGSOC who are aware that chemotherapy is a less effective treatment option for their disease.

Surgical treatment can have long term effects on abdominal organs with associated continence issues. It will result in immediate surgical menopause. Associated issues include fatigue and changes to body image and function affecting sexuality.

Further details of impact upon carers:

Carers can feel very isolated and anxious. Due to its comparative rarity they may not meet anyone else supporting those with LGSOC or facing the same issues of managing their cancer as a chronic condition.

Considerations from review by Rare Disease Advisory Group

Not applicable.

Pharmaceutical considerations

The policy proposition supports the use of trametinib as a treatment option for Low-grade serous ovarian carcinoma (LGSOC) in line with its marketing authorisation.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer PoC on the 26 May 2023