Clinical Commissioning Policy

Trametinib in recurrent or progressive low grade serous ovarian cancer (Adults) [2253]

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Summary

Trametinib is recommended to be available off-label as a routine commissioning treatment option for adults with recurrent or progressive low grade serous ovarian cancer within the criteria set out in this document.

Committee discussion

Clinical Panel considered the evidence base and the decision was made to progress the policy as for routine commissioning. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

NHS England has carefully reviewed the evidence to treat adults with recurrent or progressive low grade serous ovarian cancer with trametinib. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review informs this commissioning position can be accessed on the NHS England website.

Plain language summary

About low grade serous ovarian cancer

Low grade serous ovarian cancer (LGSOC) is a rare subtype of ovarian cancer. It is a type of epithelial cancer, which means that it 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, affected people are often younger at presentation and it is more resistant to chemotherapy. In most people the disease extends beyond the ovaries at diagnosis, and over 70% of people with LGSOC experience disease recurrence (Gershenson et al, 2022). People with LGSOC often survive for longer than people with other types of ovarian cancer and survival for people with recurrent disease can reach almost 10 years (Grisham and Iyer, 2018).

The symptoms of LGSOC are similar to the symptoms found in other types of ovarian cancer; these can include: pain, bloating, difficulty eating and changes to bladder and bowel habits. Due to the non-specific nature of these symptoms, people often present late, when the disease has already spread beyond the ovaries to affect other organs.

About current treatment

Current standard treatment for LGSOC is surgery that aims to remove all of the tumour deposits and obtain complete remission. Following surgery, adjuvant (additional) platinum-based chemotherapy and paclitaxel can be offered, although the benefit of this is uncertain. Individuals who experience recurrent LGSOC with operable disease following treatment will be considered for further surgery.

However, some people will present with, or go on to develop, disease that is either not amenable to surgical resection due to its widespread nature, or disease which may potentially be operable but where surgery has been declined or is unable to be performed due to other factors (e.g., other health problems). These individuals will receive first-line treatment with a platinum-based chemotherapy and paclitaxel.

Hormonal therapies can be given following surgery or following treatment with chemotherapy. Letrozole (an aromatase inhibitor) and tamoxifen (a selective oestrogen receptor modulator) are most commonly used. Endocrine therapy is generally continued until disease progression or unacceptable toxicity occurs.

Most people with LGSOC do not respond to platinum-based chemotherapy, and a majority will eventually experience disease progression or recurrence. Progressive disease is defined as disease which has not responded to platinum-based chemotherapy. Recurrent disease is defined as disease which initially responds to treatment with platinum-based chemotherapy +/- surgery, but which subsequently recurs. Once disease progression or recurrence occurs other treatment options can be offered including hormonal therapy (if the individual has not previously received this treatment) or further chemotherapy. Further chemotherapy options include paclitaxel alone, or pegylated liposomal doxorubicin hydrochloride (PLDH) (NICE Guidance TA389 2016). However, due to the chemotherapy resistant nature of LGSOC, the effectiveness of these treatments in preventing further disease progression is often limited.

People with LGSOC are initially treated by gynaecology oncology specialists and oncologists that specialise in the treatment of ovarian cancer. Once progression or recurrence occurs, most people will require support from palliative care specialists and community teams. The most frequent complications of recurrent LGSOC are those that arise from widespread peritoneal disease and include bowel obstruction, hydronephrosis, fistulation and general organ failure.

About trametinib

Trametinib is a mitogen-activated protein kinase (MEK) inhibitor which has been proposed as a potential treatment for recurrent or progressive LGSOC. Due to the chemotherapy resistant nature of the disease, recurrent LGSOC can be difficult to

manage, and treatment options are limited. The intervention, trametinib, is indicated in people with recurrent or progressive LGSOC who have received at least one line of platinum-based chemotherapy with or without surgery or hormonal agents.

Epidemiology and needs assessment

There were approximately 6287 cases of ovarian cancer in England every year in 2016 to 2018 (Cancer Research UK, 2022). LGSOC accounts for around 5% of these cases on average, therefore this translates to around 345 new cases of LGSOC per year in England. There were 3509 deaths from ovarian cancer per year on average in 2015 to 2017. It is estimated that 175 individuals (5%) will die from LGSOC per year (Cancer Research UK, 2022). LGSOC has a high relapse rate and approximately 70% of individuals diagnosed develop recurrence that would potentially require treatment with trametinib (Gershenson et al 2022).

Based on clinical consensus and data from patients accessing trametinib via the interim SACT treatment list which was established as part of the covid pandemic response, it is thought that approximately 85 people would benefit from the treatment each year.

Implementation

Inclusion criteria

Adults (aged 18 years and above) with a confirmed diagnosis of LGSOC who meet **ALL** of the following criteria:

- Disease progression or recurrence following treatment with at least one line of platinum-based chemotherapy **AND**
- An Eastern Cooperative Oncology Group (ECOG) performance status[1] of 0-1 at the time of treatment initiation

Exclusion criteria

Individuals are excluded if they meet **ANY** of the following criteria:

- Previous treatment with a MEK inhibitor

Stopping criteria

Treatment will be stopped in patients who meet **ANY** of the following criteria:

- Disease progression whilst on treatment **OR**
- Unacceptable toxicity **OR**
- Individual's decision to stop treatment

[1] ECOG performance status: see definitions section

Dosing

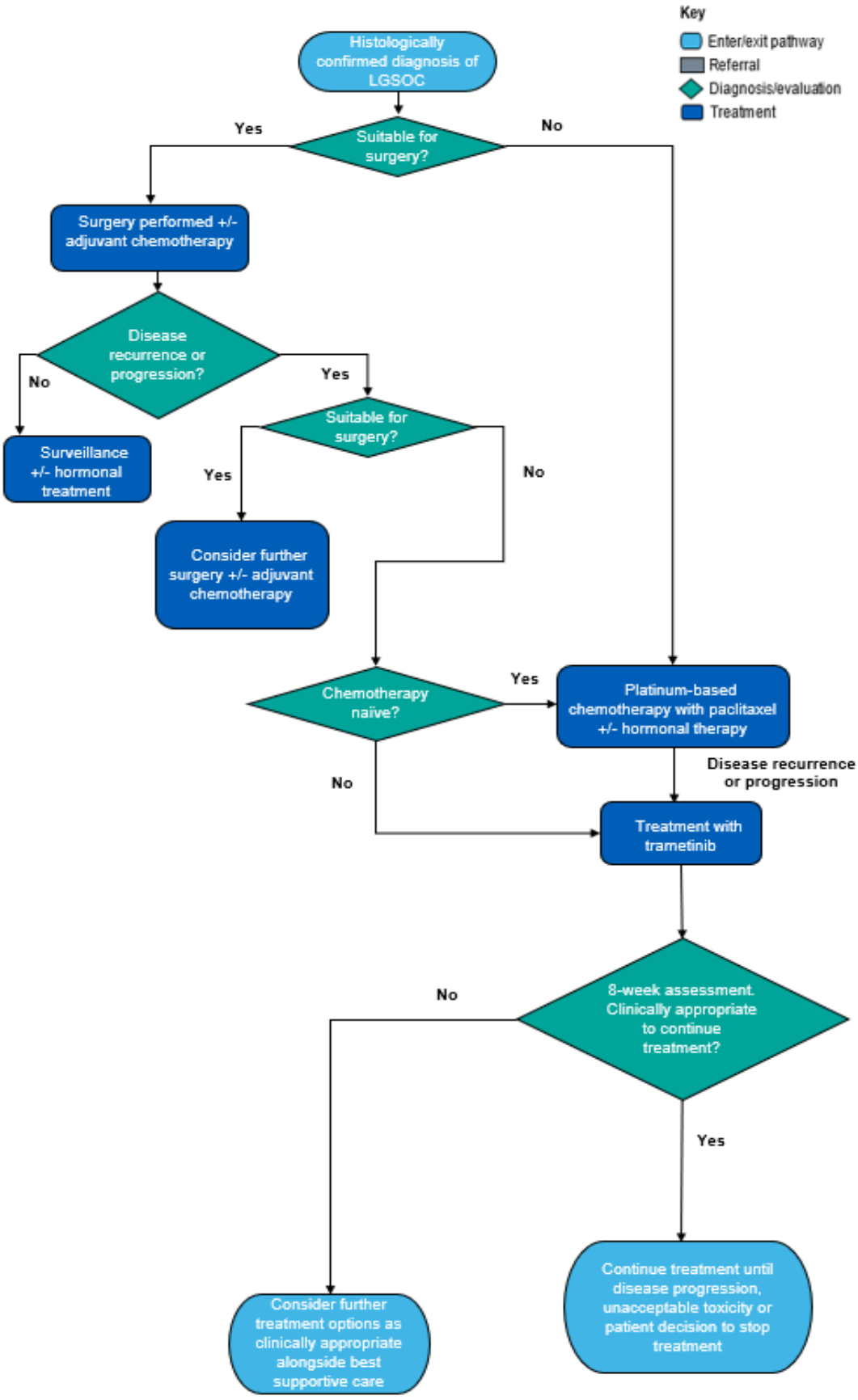
The use of trametinib for low grade serous ovarian cancer is off-label and Trust policy regarding off-label use of medicines should apply. Trametinib should be used as monotherapy at a maximum dose of 2mg orally once daily, as part of a 28-day cycle. Dose reduction(s) may be required down to either 1.5mg orally once daily or 1mg orally once daily. This decision should be made following appropriate clinical assessment.

Monitoring

A formal medical review to assess the tolerability of treatment, and to determine whether or not the treatment should continue to be carried out, should take place within the first 8 weeks of treatment initiation.

Patient pathway

NHS England


Key
Enter/exit pathway
Referral
Diagnosis/evaluation
Treatment
Histologically confirmed diagnosis of LGSOC
Suitable for surgery?
Yes
No
Surgery performed +/- adjuvant chemotherapy
Disease recurrence or progression?
No
Yes
Surveillance +/- hormonal treatment
Suitable for surgery?
Yes
No
Consider further surgery +/- adjuvant chemotherapy
Chemotherapy naïve?
Yes
No
Platinum-based chemotherapy with paclitaxel +/- hormonal therapy
Disease recurrence or progression
Treatment with trametinib
8-week assessment. Clinically appropriate to continue treatment?
No
Yes
Consider further treatment options as clinically appropriate alongside best supportive care
Continue treatment until disease progression, unacceptable toxicity or patient decision to stop treatment

Governance arrangements

Service Specification: Cancer: Chemotherapy (Adult) B15/S/a

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Please note that this is an off-label use of trametinib, therefore Trust policy regarding unlicensed medicines should apply.

Mechanism for funding

Trametinib is categorised as a high-cost drug to be reimbursed under the cost and volume process.

Audit requirements

All systemic anti-cancer treatments (SACT) must be recorded via the SACT portal as required within the NHS standard contract. There are no specific audit requirements, however data collection using case report forms (CRF) to facilitate a multicentre service evaluation is strongly encouraged.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Adjuvant	Treatment given after a primary treatment, such as surgery, to reduce the risk of the cancer returning.
Aromatase inhibitor	A group of anti-cancer drugs that act by preventing the conversion of androgens to oestrogens. They are used to reduce circulating levels of oestrogen which can help slow or inhibit the progression of certain types of cancer.
ECOG	The Eastern Cooperative Oncology Group (ECOG) is a performance status scale developed for standardization in cancer clinical research, which describes a patient's level of functioning in terms of their ability to care for themselves and carry out activities of daily living. It is scored from 0 to 5, with a score of 0 indicating patients who are fully active and independent and 5 indicating death.
Selective oestrogen receptor modulator	A group of anti-cancer drugs that bind to the oestrogen receptors. They are used to slow or inhibit the progression of certain types of cancer.

References

1. Cancer Research UK. Ovarian cancer incidence statistics (2022) Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence#heading-Zero (Accessed: January 23, 2023)
2. Cancer Research UK. Ovarian cancer mortality statistics (2022) Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/mortality#heading-Zero (Accessed: January 23, 2023)
3. Gershenson, D. M., Miller, A., Brady, W. E., Paul, J., Carty, K., Rodgers, W., Millan, D., Coleman, R. L., Moore, K. N., Banerjee, S., Connolly, K., Secord, A. A., O'Malley, D. M., Dorigo, O., Gaillard, S., Gabra, H., Slomovitz, B., Hanjani, P., Farley, J., Churchman, M., Gourley, C. (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 (London, England)*, *399*(10324), 541–553. https://doi.org/10.1016/S0140-6736(21)02175-9
4. Grisham, R. and Iyer, G., 2018. Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions. *Current Treatment Options in Oncology*, 19(11).
5. National Cancer Institute. 2022. *Trametinib to Treat Low-Grade Serous Ovarian Cancer*. [online] Available at: <https://www.cancer.gov/news-events/cancer-currents-blog/2022/trametinib-low-grade-serous-ovarian-cancer> [Accessed 22 August 2022].