OLAPARIB (Lynparza) BEVACIZUMAB

INDICATION (ICD10) C56, C57

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

As maintenance treatment in patients with high grade epithelial stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma who are in response following platinum-based FIRST line chemotherapy AND whose cancer has a positive status for homologous recombination deficiency as defined by the presence of either a deleterious or suspected deleterious BRCA 1/2 germline and/or somatic mutation or genomic instability where the following criteria have been met:

2. Proven histological diagnosis of predominantly high grade serous or high grade endometrioid or high grade clear cell ovarian, fallopian tube or primary peritoneal carcinoma.Please enter below as to which is the predominant histology in this patient:- high grade serous adenocarcinoma or- high grade endometrioid adenocarcinoma or- high grade clear cell carcinoma

3.Has had germline and/or somatic BRCA testing and if appropriate has also had the Myriad homologous recombination deficiency (HRD) test for genomic instability.

4. HAS documented evidence of a positive status for homologous recombination deficiency (HRD) defined by the presence of either deleterious/suspected deleterious BRCA 1 and/or BRCA 2 mutation(s) or genomic instability as defined by a score of ≥42 by the Myriad HRD test (for which AstraZeneca is paying). Note: there is no access to the maintenance combination of olaparib plus bevacizumab unless the patient has documented evidence of homologous recombination deficiency.

5. Recently diagnosed FIGO stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma. Note: maintenance olaparib plus bevacizumab in this indication is not funded for patients with recently diagnosed and treated stage I-IIC disease.

6. One of the following scenarios applies to the surgical management of the patient in relation to the stage of the disease:

- the patient has stage III disease and had an upfront attempt at optimal cytoreductive surgery and had no visible residual disease at the end of surgery or- the patient has stage III disease and had an upfront attempt at optimal cytoreductive surgery and had visible residual disease at the end of surgery or
- the patient has stage III disease and had an interval attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery or
- the patient has stage III disease and had an interval attempt at optimal cytoreductive surgery and had visible disease at the end of surgery or- the patient has stage III disease and has had a biopsy only with no upfront or interval attempt at cytoreductive surgery or
- the patient has stage IV disease and had an upfront attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery or
- the patient has stage IV disease and had an upfront attempt at optimal cytoreductive surgery and had visible residual disease at the end of surgery or- the patient has stage IV disease and had an interval attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery or- the patient has stage IV disease and had an interval attempt at optimal cytoreductive surgery and had visible disease at the end of surgery or
- the patient has stage IV disease and has had a biopsy only with no upfront or interval attempt at cytoreductive surgery

7. Has just completed 1st line platinum-based chemotherapy and has received a minimum of 4 cycles of platinum-based treatment.

8. Either received bevacizumab as part of 1st line platinum-based chemotherapy or not.

9. Is in response to the recently completed 1st line platinum-based chemotherapy and has achieved a partial or complete response to treatment according to the definitions given below and has no evidence of progressive disease on the post-treatment scan or a rising CA125 level.

- achieved a complete response at the end of 1st line platinum-based chemotherapy ie has no measurable or non-measurable disease on the post-chemotherapy scan and the CA-125 is normal or
- achieved a complete response at the end of 1st line platinum-based chemotherapy ie has no measurable or non-measurable disease on the post-chemotherapy scan and the CA-125 has not decreased to within the normal range or
- achieved a partial response at the end of 1st line platinum-based chemotherapy ie has had a ≥30% reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy and the CA125 is normal or
- achieved a partial response at the end of 1st line platinum-based chemotherapy ie has had a ≥30% reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy and the CA125 has not decreased to within the normal range

10. The patient is currently no more than 9 weeks from the date of the last infusion of the last cycle of 1st line chemotherapy.
11. Not previously received any PARP inhibitor.
12. Olaparib will be used in combination with bevacizumab.
13. Olaparib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum total treatment duration of 2 calendar years, whichever is the sooner. Note: There is a 2 calendar year stopping rule for the duration of treatment with olaparib as this was the basis of AstraZeneca's submission to NICE for consideration of cost effectiveness.
14. The maintenance dose of bevacizumab is 15mg/Kg and that maintenance bevacizumab will be given until whichever is the sooner of: disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum total bevacizumab treatment duration of 15 calendar months (as measured from the start of bevacizumab-containing treatment, whether this was with chemotherapy or as maintenance therapy).
15. ECOG performance status (PS) of either 0 or 1. Note: a patient with a performance status of 2 or more is not eligible for olaparib in combination with bevacizumab.
16. A first formal medical review as to whether maintenance treatment with olaparib in combination with bevacizumab should continue or not will be scheduled to occur at least by the start of the third 3-weekly cycle of treatment
17. When a treatment break is needed of more than 6 weeks beyond the expected cycle length of 3-weekly treatment (i.e. when given with bevacizumab) or 4-weekly treatment (after completion of bevacizumab), I will complete a treatment break approval form to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19.
18. Olaparib in its tablet formulation is to be otherwise used as set out in its Summary of Product Characteristics.
19. Bevacizumab is to be otherwise used as set out in its Summary of Product Characteristics.

REGIMEN

For calendar months 1 to 15 after initiation

Day 1	BEVACIZUMAB	15mg/kg in 100ml sodium chloride 0.9% IV infusion
Days 1 to 21	OLAPARIB	300mg tablet orally twice daily

For calendar months 16 to 24 after initiation

Days 1 to 21	OLAPARIB	300mg tablet orally twice daily

Bevacizumab - The initial dose should be administered over 90 minutes, if tolerated well the second infusion may be administered over 60 minutes.
If the 60 minute infusion is well tolerated all subsequent infusions may be administered over 30 minutes.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Bevacizumab every 21 days to stop 15 calendar months after 1st dose (irrespective of number of doses received ie stop 15 months after initiation even if there have been treatment delays)

Olaparib continuously to stop 2 calendar years after 1st dose (irrespective of number of doses received ie stop 2 years after initiation even if there have been treatment delays)

ANTI-EMETICS

Low emetic risk all days

CONCURRENT MEDICATION REQUIRED

Bevacizumab	None

EXTRAVASATION AND TYPE OF LINE / FILTERS

Bevacizumab – neutral

Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs, creatinine day 1, minimum every cycle for 15 months then alternate months
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
Blood pressure every cycle
Urinalysis for proteinuria every cycle
CA125 baseline and day 1 every cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Hypertension Wound healing complications
Olaparib	Diarrhoea Myelosuppression Nausea, vomiting Raised creatinine

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS (not exhaustive list check SPC/BNF/Stockleys)

Olaparib	Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 100mg twice daily. If a moderate CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 150mg twice daily.

DOSE MODIFICATIONS

Non-haematological

Bevacizumab

Hypertension

Baseline blood pressure should be <150/100mmHg.

Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg	Antihypertensive therapy may be required.
Blood pressure >180/110mmHg	It is advised that bevacizumab therapy is withheld until blood pressure controlled.

Proteinuria

Urine dipstick result. 1+ or 2+ on dipstick (0.3–2.9g/L)	Continue with bevacizumab. No additional evaluation required.
3+ on dipstick (3-19g/L)	May have dose of bevacizumab as scheduled, but 24 hour urine to measure 24 hour protein to be done a few days before next cycle due. If 24hr protein result <2g, continue with bevacizumab, with continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to <1g/24hr, return to dipstick analysis. If ≥2g, withhold bevacizumab until repeat 24 hour urine collection shows <2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.
4+ on dipstick (≥20g/L)	Withhold bevacizumab. 24 hour urine required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Wound healing

Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28–60 days before elective surgery.

Olaparib

When dose reduction is necessary, the olaparib dose may be reduced to 250mg twice daily and further to 200mg twice daily.

Hepatic impairment

Olaparib

No dose adjustment required for patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Olaparib is not recommended for use in patients with severe hepatic impairment.

Renal impairment

Olaparib

No dose adjustment is necessary for patient with CrCl >50ml/minute.

The recommended starting dose is 200mg twice daily for patients with CrCl 31–50ml/minute.

Olaparib is not recommended for patients with CrCl ≤30ml/min.

REFERENCES

CDF list