Bevacizumab and Olaparib

Indication

Maintenance treatment of stage III or IV high grade epithelial ovarian, fallopian tube or primary peritoneal cancer following a complete or partial response to first-line platinum-based chemotherapy and bevacizumab and where the cancer is associated with homologous recombination deficiency (HRD).

NICE TA693

ICD-10 codes

Codes pre-fixed with C48, 53, 56, 57.

Regimen details

Day	Drug	Dose	Route
1	Bevacizumab	15mg/kg	IV infusion
Continuous	Olaparib tablets	300mg BD	Oral

Olaparib must be started no later than 9 weeks from the date of the last cycle of platinum-based chemotherapy.

Cycle frequency

Bevacizumab - 21 days
Olaparib - continuous

Number of cycles

Bevacizumab – until disease progression or unacceptable toxicity up to a maximum of 15 months (from the start of bevacizumab treatment, including any doses administered in combination with chemotherapy)

Olaparib – until disease progression or unacceptable toxicity up to a maximum of 2 years

Administration

Bevacizumab is administered as an intravenous infusion in sodium chloride 0.9% to a final concentration of between 1.4 to 16.5mg/mL. Doses up to 1650mg are administered in 100mL sodium chloride 0.9%, doses greater than 1650mg are administered in 250mL sodium chloride 0.9%.

The first infusion must be given over 90 minutes. If tolerated, the next infusion can be given over 60 minutes; if this is also tolerated, subsequent infusions can be given over 30 minutes.

Bevacizumab should not be initiated for at least 28 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 28 days following surgery. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Olaparib is available as 100mg and 150mg tablets. Tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If a dose is missed it should be omitted and the next dose taken as planned.

Grapefruit and grapefruit juice should be **avoided** whilst taking olaparib.

Olaparib capsules should not be substituted for olaparib tablets due to differences in the dosing and bioavailability of each formulation.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential.

Additional supportive medication
Antiemetics if required.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.

Extravasation
Bevacizumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period**
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
CA 125	7 days
Blood pressure (BP)	on day 1
Proteinuria (dipstick)	on day 1

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Monthly
U+E (including creatinine)	Monthly
LFTs	Monthly
Calcium	Monthly
Magnesium	Monthly
CA125	3 monthly
Blood pressure	Before each bevacizumab dose (more frequently if hypertension)
Proteinuria (dipstick)	Before each bevacizumab dose*

* If 3+ on dipstick perform 24 hour urinalysis and delay bevacizumab until <2g/24 hours.

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	> 1.5 x 10^9/L
Platelets	> 75 x 10^9/L
CrCl	> 50 mL/min
Bilirubin	< 3 x ULN
ALT/AST	< 5 x ULN
Proteinuria	1+ or 2+ on dipstick, <2g/24 hours on urinalysis
Blood pressure	<140/90 mmHg

Dose modifications

Dose reduction is not recommended for Bevacizumab; doses should be withheld, or treatment discontinued.

For Olaparib, treatment should generally be continued for grade 1 toxicities and supportive management optimised. Higher grade toxicities may require dose interruptions and/or reductions. If at all possible, Olaparib treatment should not be stopped permanently unless for disease progression.

Olaparib

Dose level	**Olaparib dose**
Full dose	300mg BD
First dose reduction	250mg BD
Second dose reduction	200mg BD
Third dose reduction	Discontinue

- **Haematological toxicity**

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after a 4 weeks delay, bone marrow analysis and/or blood cytogenetic analysis are recommended.

- **Renal impairment**

Bevacizumab - There is no data regarding administration of bevacizumab in patients with renal impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

Olaparib

CrCl (mL/min)	**Olaparib dose**
> 50	300mg BD
31-50	200mg BD
≤ 30	Not recommended

- **Hepatic impairment**

Bevacizumab - There is no data regarding administration of bevacizumab in patients with hepatic impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

Olaparib - No dose adjustment is required in mild or moderate hepatic impairment (Child Pugh A-B). Olaparib is not recommended for use in patients with severe hepatic impairment (Child Pugh C).

- **Other toxicities**

Olaparib

Pneumonitis

Fatal pneumonitis has been reported in patients taking olaparib. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib should be discontinued.

Bevacizumab

Toxicity	Definition	Dose adjustment
Infusion related reactions	Grade ≤ 2	**90 minute infusion**: premedication prior to next dose and give over 90 minutes (if tolerated may reduce infusion duration for future cycles with premedication) **60 minute infusion**: all subsequent doses should be given over 90 minutes with premedication. **30 minute infusion**: all subsequent doses should be given over 60 minutes with premedication.
	Grade >2	Discontinue bevacizumab
Hypertension	Grade 1 Increase of >20 mmHg (diastolic) or >140/90 mmHg (previously within normal limits) asymptomatic and transient (<24 hours)	Recheck 1 hour later: - if <140/90 mmHg – administer as normal - if 140/90 mmHg - 150/100 mmHg –administer and recheck BP 48 hours later (commence antihypertensives if BP remains >140/90 mmHg). - if >150/100 mmHg – omit and recheck BP 48 hours later(commence antihypertensives if BP remains >140/90 mmHg).
	Grade 2 Recurrent or persistent (> 24 hours) increase by 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Withhold bevacizumab. Commence antihypertensive medication. Once BP <140/90 mmHg restart treatment.
	Grade 3 ≥160/100mmHg	Withhold bevacizumab. If persistent, escalate antihypertensive treatment If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.
Proteinuria	1+ or 2+	Continue bevacizumab.
	3+	Continue bevacizumab, with 24 hour urinalysis prior to next cycle, then: - if <2g continue treatment with 24 hour urinalysis prior to each dose. If falls to <1g return to dipstick analysis. - if ≥2g withhold until repeat urinalysis <2g then restart treatment with 24 hour urinalysis prior to each dose.
	4+	Withhold bevacizumab. 24 hour urinalysis. Then treat as above.
	Nephrotic syndrome	Permanently discontinue bevacizumab

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects (bevacizumab)**

Infusion related toxicity
Arterial/venous thromboembolism
GI perforation, fistulas
Haemorrhage
Osteonecrosis of the jaw
Reversible posterior leukoencephalopathy
Congestive heart failure
Wound healing complications

Serious side effects (olparib)

Pneumonitis
Myelodysplastic syndrome and AML
Myelosuppression
Anaemia

- **Other side effects (bevacizumab)**

Hypertension
Proteinuria
Headache
Dizziness

- **Other side effects (olaparib)**

Fatigue
Diarrhoea
Nausea
Dyspepsia
Cough
Stomatitis
Taste disturbance
Decreased appetite
Increased creatinine
Rash

Significant drug interactions – for full details consult product literature/ reference texts

Bevacizumab: No documented significant reactions.

Olaparib:

Strong or moderate CYP3A inhibitors: (e.g. itraconazole, telithromycin, clarithromycin, erythromycin, diltiazem, fluconazole, verapamil) co-administration is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced. See SPC for further information.

Strong or moderate CYP3A inducers: (e.g. phenytoin, rifampicin, carbamazepine, nevirapine, phenobarbital, St John's Wort, efavirenz, rifabutin) co-administration is not recommended. If a patient already receiving olaparib requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced. See SPC for further information.

Sensitive CYP3A substrates or substrates with a narrow therapeutic margin: (e.g. simvastatin, cisapride, cyclosporin, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) use with caution and close clinical monitoring.

Hormonal contraceptives: efficacy may be reduced, use alternative forms of contraception.

Substrates of P-gp: (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine) use with caution and close clinical monitoring.

In vitro, olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Additional comments

Bevacizumab is contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies.

Bevacizumab should be used with caution in patients with:
• Untreated central nervous system metastases
• History or risk factors for thromboembolic events
• Significant cardiac risk factors for development of congestive heart failure

Olaparib and Bevacizumab should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting treatment, during therapy and for 1 month after receiving the last dose. Two highly effective and complementary forms of contraception are recommended.

References

- Summary of Product Characteristics – Olaparib (Astra Zeneca) accessed 23rd November 2021 via www.medicines.org.uk
- Summary of Product Characteristics – Bevacizumab (Roche) accessed 23rd November 2021 via www.medicines.org.uk
- National Institute for Clinical Excellence (TA693) accessed 23rd November 2021 via www.nice.org.uk
- Ray-Coquad, I. *et al*. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 2019; 381:2416-2428.

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Date: November 2021