Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance

Rucaparib (Ovary, fallopian tube, primary peritoneal)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Maintenance treatment of relapsed platinum-sensitive high-grade epithelial, ovarian, fallopian tube or primary peritoneal cancer that has completely or partially responded to platinum-based chemotherapy.
(NICE TA 1007)

Maintenance treatment of FIGO stage 3 or 4 high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer after complete or partial response to first-line platinum-based chemotherapy in patients without a BRCA mutation who are homologous recombination deficiency (HRD) positive.
(CDF)

Trial results

Relapsed: Phase 3 ARIEL-3 trial

- Rucaparib (n=375) vs placebo (n=189)
- Median PFS:
  - BRCA mutant population: rucaparib: 16.6 months vs placebo: 5.4 months
  - HRD population: 13.6 months vs 5.4 months
  - ITT population: 10.8 months vs placebo 5.4 months

First line: Phase 3 ATHENA-MONO trial

- Rucaparib (n=427) vs placebo (n=111)
- Median PFS:
  - HRD population: rucaparib: 28.7 months vs placebo: 11.3 months
  - ITT population: 20.2 months vs 9.2 months

Regimen details

Day	Drug	Dose	Route
Daily (28-day cycle)	Rucaparib	600mg BD	PO

Patients should start the maintenance treatment no later than 8 weeks after completion of their final dose of the platinum-based chemotherapy.

Cycle frequency
4 weeks

Number of cycles
Relapsed setting: Continuous until disease progression or unacceptable toxicity.
First line maintenance setting: Continuous until disease progression or unacceptable toxicity up to a maximum of 2 years.

Pre-medication
Nil

Supportive medication
Antiemetics if required.
Loperamide if required.

Emetogenicity
This regimen has mild emetic potential.

Administration
Rucaparib is available as 200mg, 250mg and 300mg tablets. The doses should be taken approximately 12 hours apart and tablets should be swallowed whole with water and should not be crushed or chewed. They may be taken with or without food.

If a dose is missed, it should be omitted and the next dose taken as planned. If a patient vomits after taking the dose they should not retake the dose and should take the next scheduled dose as planned.

Mandatory investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es (including creatinine)	14 days
LFTs	14 days
CA 125	14 days

Investigations – pre subsequent cycles

Investigation	Validity period
FBC*	Monthly
U&Es (including creatinine)	Monthly
LFTs	Monthly
CA 125	3 monthly

* Haematological toxicity is common during first 8-10 weeks of treatment.

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 – prior to commencing treatment, then see below
Platelets	> 100 x 10^9/L
Haemoglobin	> 90g/L
CrCl	≥ 30 mL/min
Bilirubin	≤ 3 x ULN
ALT/AST	See below
Alkaline Phosphatase	See below

Dose modifications

Rucaparib should be reduced as below:

Dose level	Rucaparib dose
Full dose	600mg BD
First dose reduction	500mg BD
Second dose reduction	400mg BD
Third dose reduction	300mg BD

Haematological toxicity

For any Grade 3 or 4 toxicity:
Neutrophils < 1.0 x 10^9/L
Platelets < 100 x 10^9/L
Haemoglobin < 80g/L

Delay treatment, check FBC weekly and on recovery continue with one dose level reduction.

If counts do not recover to ≤Grade 1 after 4 weeks, discontinue treatment and refer to haematology for further investigation.

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment. Rucaparib is not recommended if CrCl < 30mL/min unless potential benefit outweighs risk and the patient is closely monitored for adverse reactions.

Hepatic impairment

No starting dose adjustment is necessary for patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be monitored closely for hepatic function and adverse reactions. There are no data in patients with severe hepatic impairment. Rucaparib is not recommended if bilirubin > 3 x ULN.

Other toxicities

ALT/AST elevations

Grade	Management
Grade 3 without signs of liver dysfunction	Monitor LFTs weekly until ≤ Grade 2 Continue if bilirubin < ULN and ALP < 3 x ULN Withhold if ALT/AST does not improve within 2 weeks and when ≤ Grade 2 resume at same dose or with one dose level reduction.
Grade 4	Withhold until ≤ Grade 2. Then resume with one dose level reduction and monitor LFTs weekly for 3 weeks.

Any other Grade 3-4 reactions should be managed with dose interruptions and dose reductions as necessary.

Side Effects

Toxicity		ARIEL-3 study (relapsed)		ATHENA-MONO study (1st line)	
		Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)
Haematological	Anaemia	37	19	46.6	4.9
	Thrombocytopenia	28	5	23.8	7.1
	Neutropenia	18	7	27.8	14.6
Non-haematological	Nausea	75	4	56.2	1.9
	Fatigue	69	7	55.8	4.9
	Dysgeusia	39	0	21.2	0.2
	Vomiting	37	4	23.5	1.4
	Constipation	37	2	19.3	0
	ALT/AST increase	34	10	42.6	10.6
	Diarrhoea	32	1	24.0	1.4
	Abdominal pain	30	2	24.9	0.5
	Decreased appetite	23	1	17.9	0.5
	Headache	18	<1	20.0	0.5
	Photosensitivity reaction	17	1	NA	NA
	Arthralgia	15	1	20.2	0.2
	Dyspepsia	15	<1	NA	NA
	Blood creatinine increase	15	<1	11.1	0.2
	Cough	15	0	12.2	0
	Upper abdominal pain	14	1	NA	NA
	Insomnia	14	1	13.9	0.2
	Pruritus	13	0	16.2	0.2
	Dyspnoea	13	0	10.6	1.4
	Rash	12	<1	14.4	0.2
	Pyrexia	12	0	10.1	0
	Back pain	12	0	9.9	0.2
	Hypomagnesaemia	11	1	NA	NA
	Upper respiratory tract infection	11	0	NA	NA
	Abdominal distension	11	0	9.9	0.2
	Peripheral oedema	10	1	7.8	0

Specific drug related side effects:

Photosensitivity
Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they may burn more easily during rucaparib treatment; when outdoors, patients should wear a hat and protective clothing and use sunscreen and lip balm with sun protection factor (SPF) of 50 or greater.

Myelodysplastic syndrome/Acute myeloid leukaemia
Myelodysplatic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients treated with rucaparib. The duration of therapy with rucaparib in patients who developed MDS varied from <2 months to 6 years. The incidence of MDS/AML in the relapsed and first line setting is reported as 1% and 0.4% respectively. If MDS/AML is suspected the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If MDS/AML is confirmed, rucaparib should be discontinued.

Additional information
Nil

Significant drug interactions – for full details consult product literature/ reference texts
Caution if concomitant use of **strong CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, grapefruit juice) or inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's wort).**

Caution if concomitant use of **strong inhibitors of P-gp (e.g. amiodarone, clarithromycin, ciclosporin, diltiazem, felodipine, itraconazole, verapamil).**

If concomitant use of **medicinal products metabolized by CYP1A2**, particularly medicines which have a narrow therapeutic index (e.g., tizanidine, theophylline), dose adjustments may be considered.

If concomitant use of **medicinal products that are CYP2C9 substrates with a narrow therapeutic index** (e.g., warfarin, phenytoin), dose adjustments may be considered, if clinically indicated.
Warfarin: monitor INR closely
Phenytoin: therapeutic drug level monitoring required.

Caution if concomitant use of **medicinal products that are CYP3A substrates with a narrow therapeutic index** (e.g., alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine).

Rucaparib has potential to increase **metformin** renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered.

Caution if concomitant use of **BCRP substrates** (e.g., rosuvastatin) though no dose modification is recommended.

References

- Summary of Product Characteristics Rucaparib (Pharmaand) accessed 21st November 2024 via www.medicines.org.uk
- National Institute for Health and Care Excellence (TA1007) accessed 21st November 2024 via www.nice.org.uk
- NHS England. Cancer Drugs Fund List accessed 21st November 2024 via NHS England » Cancer Drugs Fund list
- Coleman, R et al; Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3). Lancet 2017; 390 (10106): 1949 – 1961
- Monk, B. J. et al. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GO-G3020/ENGOT-ov45). J Clin Oncol 2022 40(34):3952-3964.

Version	Issue date	Review date	Revision	Written/Checked/Authorised
2	Nov 2024	Nov 2027	Transferred to new protocol template Indication updated	Written/reviewed: Dr A Walther (Consultant Oncologist, UHBW NHS Trust), Dr R Bowen (Consultant Oncologist, RUH Bath NHS Trust) Checked: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

Schedule of investigations and treatment plan

Activity	Pre-tx	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed consent	x				
Clinical assessment	x	x	x	x	Every cycle, consider reducing to every other cycle if stable at 12 months
FBC	x	x	x	x	Every cycle, consider reducing to every other cycle if stable at 12 months
U&E & LFTs	x	x	x	x	Every cycle, consider reducing to every other cycle if stable at 12 months
CrCl	x	x	x	x	Every cycle, consider reducing to every other cycle if stable at 12 months
CA125	x			x	Every 3 months
Imaging as per guidance	x				Repeat if clinically indicated
Weight recorded	x				Repeat if necessary