Systemic Anti Cancer Therapy Protocol

Talazoparib
Breast Cancer with BRCA1/2 Mutations

PROTOCOL REF: MPHATALBR
(Version No: 1.0)

Approved for use in:

- **No NHS funding available**
- Monotherapy for the treatment of HER2 negative, locally advanced or metastatic breast cancer with germline BRCA1/2 mutations
- Previous treatment with anthracycline and/or taxanes (either neoadjuvant, adjuvant or metastatic setting)
- ER positive patients should have received prior endocrine treatment

Dosage:

Drug	Dose	Route	Frequency
Talazoparib	**1mg**	orally	Once daily, supplied on a 4 weekly schedule

Treatment continues until disease progression or unacceptable toxicity

Administration:

Capsules should be swallowed whole, not chewed, opened or dissolved.
They can be taken with or without food.

Regular blood tests are required and dose adjustment is common

Appropriate contraceptive precautions must be taken, for female patients contraceptive measures should continue for 7 months after discontinuation of talazoparib; for males patients 4 months after discontinuation.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Domperidone 10mg three times a day when required

Extravasation risk:

Not applicable

Dosing in renal and hepatic impairment:

Renal	No adjustment required for CrCl 60mL/min and above For patients with CrCl between 30mL/min and 60mL/min the dose should be adjusted to 0.75mg daily For patients with severe renal impairment (CrCl between 15 to 30 mL/min), the recommended starting dose should be 0.5 mg once daily. If renal function deteriorates during treatment then patients should be reviewed by the clinical team.

Hepatic	No adjustments required for mild hepatic impairment Talazoparib has not been studied in patients with bilirubin above 1.5 times ULN Withhold treatment if bilirubin increases to 2 times ULN and/or AST/ALT increases to 3 times ULN from a normal baseline result. Ensure patient has a review with oncologist to arrange appropriate further investigations. If AST/ALT reaches 5 times ULN from a raised baseline result then treatment should discontinue.

Interactions:

Strong inhibitors of P-gp may lead to increased exposure to talazoparib and therefore should be avoided.

Strong inhibitors of P-gp include, but not limited to, amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole,

ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, and verapamil)

If co-administration with a strong P-gp inhibitor is unavoidable, dose of talazoparib should be reduced.

Treatment schedule:

Day	Drug	Dose	Route	Frequency
1	**Talazoparib**	**1mg**	**orally**	**daily**

Main toxicities:

Fatigue, anaemia, neutropenia, thrombocytopenia nausea, vomiting, alopecia, abdominal pain, decreased appetite and headache.

Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) occurred in 0.3% of patients treated with talazoparib in clinical studies.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X					
Clinical Assessment	X		X		X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	Every cycle
CT scan**	X					Every 3 months initially
Blood pressure measurement	X					Repeat if clinically indicated
Respiratory Rate	X					Repeat if clinically indicated

Weight recorded	X	X		X		Every cycle
Height recorded	X					

Dose Modifications and Toxicity Management:

	Dose level
Recommended starting dose	1mg (one 1mg capsule) once daily
First dose reduction	0.75mg (three 0.25mg capsules) once daily
Second dose reduction	0.5mg (two 0.25mg capsules) once daily
Third dose reduction	0.25mg (one 0.25mg capsule) once daily

Haematological toxicity:

Proceed on **cycle 1 day 1** if:

Hb > 90g/L	ANC ≥ 1.5 x 10^9/L	Plt ≥ 100 x 10^9/L

For cycle 2 onwards proceed on day 1 if:

Hb ≥ 80g/L	ANC ≥1.0 x 10^9/L	Plt ≥ 50 x 10^9/L

If patient deferred treatment can resumed at next lower dose level once blood results have recovered as follows:

Hb ≥ 90g/L	ANC ≥ 1.5 x 10^9/L	Plt ≥ 75 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Grade 1 or 2 toxicity	No requirement for dose adjustment If persists at grade 2 for over 7 days then consider dose adjustment
Grade 3 or 4 toxicity	Hold treatment Supportive care as appropriate (antiemetics, loperamide) Resume at reduce dose once recovered to grade 1

References:

1. https://www.medicines.org.uk/emc
2. Talazoparib in patients with germline BRCA mutated advanced breast cancer. Detailed safety analysis. Hurvitz et al. The Oncologist, 2019 24:1-12
3. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. Litton JK et al. NEJM 2018 379: 753-763