TALAZOPARIB (Talzenna) ENZALUTAMIDE (Xtandi)

INDICATION (ICD10) C61

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (TAL2)

1. Talazoparib plus enzalutamide for the treatment of metastatic progressive hormone-relapsed (castrate-resistant) prostate cancer adenocarcinoma or both widespread bone metastases typical of prostate cancer and a serum PSA of at least 50ng/ml.in patients who are treatment naïve to androgen receptor inhibitors and in whom chemotherapy is not yet clinically indicated or appropriate and has pre existing clinical conditions that preclude the use of abiraterone plus prednisolone (given with olaparib). Has not previously received any therapy with an androgen receptor inhibitor such as enzalutamide, abiraterone, apalutamide or darolutamide at any place in the prostate cancer treatment pathway or any previous PARP inhibitor therapy,. PS 0 or 1.

REGIMEN

TALAZOPARIB 0.5mg orally once daily
ENZALUTAMIDE 160mg orally once daily

CYCLE FREQUENCY AND NUMBER OF CYCLES

Continuously until disease progression.

ADMINISTRATION

Talazoparib available as 0.25mg and 1mg capsules
Enzalutamide available as 40mg tablets

ANTI-EMETICS

Minimal risk

CONCURRENT MEDICATION REQUIRED

Enzalutamide	None required
Talazoparib	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs PSA every cycle, increasing to every 3 cycles
Haemoglobin g/dl ≥8 (see dose modifications for further details)
Neutrophils x 10^9/L ≥1.5 (see dose modifications for further details)
Platelets x 10^9/L ≥100 (see dose modifications for further details)
Creatinine every cycle
Blood pressure monthly initially then 3 monthly
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Enzalutamide	Fatigue Hot flush Headache Hypertension Risk of seizures (<1%)
Talazoparib	Myelosuppression Myelodysplastic syndrome / acute myeloid leukaemia

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

Enzalutamide	Enzalutamide is a strong CYP3A4 enzyme inducer therefore there are a large number of interactions, check interactions carefully. Strong CYP2C8 inhibitors should be avoided.
Talazoparib	Lots of interactions check carefully. Strong inhibitors of P-gp may lead to increased talazoparib exposure. Concomitant use of strong P-gp inhibitors during treatment with talazoparib should be avoided.

DOSE MODIFICATIONS

Talazoparib

First dose reduction	0.35mg
Second dose reduction	0.25mg
Third dose reduction	0.1mg

Haematological

Talazoparib

Haemoglobin <8g/dl	Withhold talazoparib until levels resolve to ≥9. Then resume talazoparib at next lower dose.
Platelet count <50x10^9/L	Withhold talazoparib until levels resolve to ≥75. Then resume talazoparib at next lower dose.
Neutrophils <1.0x10^9/L	Withhold talazoparib until levels resolve to ≥1.5. Then resume talazoparib at next lower dose.

Non-haematological

Enzalutamide

If a patient experiences a ≥grade 3 toxicity or an intolerable adverse reaction, treatment should be withheld for one week or until symptoms improve to ≤grade 2. Resume treatment at the same dose, or a reduced dose (120mg or 80mg) if appropriate.

Talazoparib

Non-haematological adverse reaction grade 3 or grade 4, withhold until ≤grade 1. Consider resuming talazoparib at next lower dose or discontinue.

Hepatic impairment

Enzalutamide

No dose adjustment is necessary for patients with mild hepatic impairment (Child Pugh Class A). Caution is advised in patients with moderate hepatic impairment (Child Pugh Class B). It is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

Talazoparib
No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤1×ULN and aspartate aminotransferase (AST) >ULN, or total bilirubin >1.0 to 1.5×ULN and any AST), moderate hepatic impairment (total bilirubin >1.5 to 3.0×ULN and any AST) or severe hepatic impairment (total bilirubin >3.0×ULN and any AST.
Talazoparib in combination with enzalutamide is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as pharmacokinetics and safety have not been established in these patients.

Renal impairment
Enzalutamide
Caution advised in patients with severe renal impairment (CrCl <30ml/min).

Talazoparib

Mild renal impairment (CrCl 60-90mL/min)	No dose adjustment is required.
Moderate renal impairment (CrCl 30-59mL/min)	The recommended starting dose of talazoparib is 0.35mg once daily.
Severe renal impairment (CrCl 15-29mL/min)	The recommended starting dose of talazoparib is 0.25mg once daily.
CrCl <15mL/min or requiring haemodialysis	Talazoparib has not been studied.

REFERENCES
1. SPC
2. Blueteq criteria