DAROLUTAMIDE (Nubeqa) DOCETAXEL Prednisolone

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/) (DAR02)

1. Darolutamide in combination with docetaxel and androgen deprivation therapy (ADT) for the treatment of newly diagnosed TNM M1 histological or cytological diagnosed metastatic adenocarcinoma prostate cancer with both widespread bone metastases radiologically typical of prostate cancer and a serum PSA of ≥50 ng/mL that is hormone sensitive and has currently received androgen deprivation therapy (ADT) for no longer than 12 weeks, is fit enough for docetaxel chemotherapy, has consented to such treatment and has not yet commenced upfront docetaxel chemotherapy for metastatic hormone sensitive prostate cancer. Has not previously received any androgen receptor targeted agent such as enzalutamide or apalutamide or darolutamide or abiraterone unless the patient has progressive metastatic disease following completion of treatment with 2 years of ADT plus abiraterone with or without enzalutamide for high risk non-metastatic disease as part of the STAMPEDE trial (and did not progress whilst on such treatment and the patient meets all the other criteria listed on the form). PS 0 or 1. (TA903)

REGIMEN

Day 1 Premedication: Dexamethasone 8mg od PO or IV
DAROLUTAMIDE 600mg orally twice daily continuously
Androgen deprivation therapy (ADT)
DOCETAXEL 75mg/m^2 in 250ml sodium chloride 0.9% IV infusion over 60 minutes
Prednisolone 5mg tablet twice daily (morning and lunchtime) continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Docetaxel with prednisolone every 21 days up to maximum 6 cycles
Darolutamide to continue until progression. A formal medical review as to how darolutamide is being tolerated and whether treatment with darolutamide should continue or not will be scheduled to occur at least by the start of the third 3-weekly combination cycle of treatment.

ADMINISTRATION

Darolutamide available as 300mg tablets
Swallow whole with food.

ANTI-EMETICS

Low risk day 1

CONCURRENT MEDICATION REQUIRED

Darolutamide	Androgen deprivation therapy
Docetaxel	Ensure premedication given before docetaxel. This can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Prednisolone 5mg tablet twice daily (morning and lunchtime) continuously for duration of docetaxel cycles. 21 days after completion of last docetaxel dose start reducing prednisolone dose (5mg od for 1 week then 5mg alternate days for 1 week then stop). Loperamide prn every docetaxel cycle
GCSF	Consider GCSF

EXTRAVASATION AND TYPE OF LINE / FILTERS

Docetaxel – exfoliant

Filter not required
Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Darolutamide	Cardiac affects Hepatotoxicity Neutropenia Rash
Docetaxel	Cutaneous reactions, peripheral neuropathy or fluid retention, hypersensitivity reactions

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

Darolutamide	Statins – avoid some statins Strong or moderate CYP3A and Pgp inducers - avoid

DOSE MODIFICATIONS

Darolutamide
If a patient experiences a ≥grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600mg twice daily.
Dose reduction below 300mg twice daily is not recommended.

Haematological

Docetaxel
In patients who experienced either febrile neutropenia, neutrophil count <0.5x10^9/L for more than one week during docetaxel therapy, the dose of docetaxel should be reduced from 75 to 60mg/m². If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued.

Non haematological

Docetaxel
Discuss dose reductions if severe cutaneous reactions, peripheral neuropathy or fluid retention after previous course.
In patients who experienced severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 75 to 60mg/m². If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued

Hepatic impairment

Darolutamide

Moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300mg twice daily.

Docetaxel

ALT and/or AST >1.5xULN and ALP >2.5xULN	recommended SPC dose for 100mg/m^2 is give 75mg/m^2
Bilirubin >ULN and ALT or AST >3.5xULN with ALP >6xULN	should not be used unless strictly indicated.

Renal impairment

Darolutamide

Severe renal impairment (eGFR 15-29mL/min/1.73m^2) not receiving haemodialysis, the recommended starting dose is 300mg twice daily.

REFERENCES

1. ORBIS NHSE circular