# Docetaxel and Darolutamide (Prostate)

## Indication

Newly diagnosed hormone-sensitive metastatic prostate cancer in combination with androgen deprivation therapy (ADT).

(NICE TA903)

NB. Darolutamide should start within 12 weeks of starting ADT and docetaxel should be started within 6 weeks of starting darolutamide treatment.

## ICD-10 codes

C61

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 | Docetaxel | 75mg/m$^2$ | IV infusion |
| 1-21 | Prednisolone | 5mg BD | Oral |
| 1-21 | Darolutamide | 600mg BD | Oral |

## Cycle frequency

21 days

## Number of cycles

Docetaxel/Prednisolone: up to 6 cycles
Darolutamide: continued until disease progression or unacceptable toxicity

## Administration

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free Sodium Chloride 0.9% over 60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions.

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Darolutamide is available as 300mg tablets. Tablets should be taken with food, swallowed whole with water and not broken or crushed.

If a dose is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose. The patient should not take two doses to make up for a missed dose.

## Pre-medication

Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24h prior to chemotherapy. Or dexamethasone 8mg 12 hours, 3 hours and 1 hour before docetaxel infusion. (Note: Patients must receive 3 doses of dexamethasone prior to treatment).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

## Emetogenicity

This regimen has mild-moderate emetic potential – refer to local policy

## Additional supportive medication

Mouthwashes as per local policy
Proton-pump inhibitor
Loperamide if required
Consider primary GCSF prophylaxis as per local practice

## Extravasation

Docetaxel is an exfoliant (Group 4)

## Investigations – pre first cycle

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| Calcium | 14 days |
| LFTs | 14 days |
| PSA | 14 days |
| ECG (for QT interval) | 14 days |

## Investigations – pre docetaxel containing cycles

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 96 hours |
| U+E (including creatinine) | 7 days |
| Calcium | 7 days |
| LFTs | 7 days |
| PSA | Every 2 cycles or as clinically indicated |
| ECG (for QT interval) | As indicated |

## Investigations – pre darolutamide single agent cycles

| **Investigation** | **Validity period** |
|---|---|
| FBC | Monthly, increasing to 2-monthly as appropriate |
| U&E | Monthly, increasing to 2-monthly as appropriate |
| LFTs | Monthly, increasing to 2-monthly as appropriate |
| PSA | Monthly, increasing to 2-monthly as appropriate |
| ECG | As indicated |

## 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 | ≥ 100 x $10^9$/L |
| Bilirubin | ≤ ULN |
| AST/ALT | ≤ 1.5 x ULN |
| Alkaline Phosphatase* | < 2.5 x ULN |
| Creatinine clearance (CrCl) | > 30ml/min |

## Dose modifications

- **Haematological toxicity**

If neutrophils <1.5 x $10^9$/L and/or platelets <100 x $10^9$/L delay docetaxel administration by 1 week or until recovery.

If symptomatic neutropenia, platelets < 25 x $10^9$/L or if delayed on 2 occasions reduce docetaxel dose to 60mg/$m^2$. If toxicity occurs at a 60mg/$m^2$ dose or if delayed by more than 2 weeks, discuss with consultant and consider stopping docetaxel.

If neutrophils <1 x $10^9$/L, consider withholding darolutamide

- **Renal impairment**

**Docetaxel**: docetaxel has not been studied in severe renal impairment but no need for dose reduction is expected

**Darolutamide**: No dose adjustment is required for patients with mild or moderate renal impairment (≥30ml/min). For patients with creatinine clearance of 15-29ml/min, not receiving haemodialysis, the recommended starting dose is 300mg BD. There is no data for patients with CrCl < 15ml/min

- **Hepatic impairment**

**Docetaxel:**

| **AST/ALT** (x ULN) | | **Alkaline phosphatase*** (x ULN) | **Docetaxel dose** |
|---|---|---|---|
| ≤ 1.5 | and | < 2.5 | 100% |
| > 1.5 | or | ≥ 2.5- 6 | 75% |
| > 3.5 | or | ≥ 6 | Discuss with consultant |

*unless due to bone metastases only.
If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

**Darolutamide**: No dose adjustment is necessary for patients with mild hepatic impairment.
For patients with moderate or severe hepatic impairment (Child-Pugh B or C), the recommended starting dose is 300mg BD.

**Child Pugh Classification:**

| **Score** | 1 | 2 | 3 |
|---|---|---|---|
| Bilirubin (µmol/L) | <34 | 34-50 | >50 |
| Albumin (g/L) | >35 | 28-35 | <28 |
| PT (s prolonged) | <4 | 4-6 | >6 |
| Encephalopathy | none | mild | marked |
| Ascites | none | mild | marked |

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

- **Other toxicities**

**Docetaxel:**
Grade 3 cutaneous reactions – once recovered reduce dose to 60mg/m$^2$. If symptoms return, discontinue treatment.

Grade 2 neuropathy - once recovered reduce dose to 60mg/m$^2$. If symptoms return, discontinue treatment.

Grade 3 or 4 neuropathy – discontinue treatment permanently.

Any other grade 3 or 4 toxicity- discuss with consultant.

**Darolutamide:**
If patient experiences ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300mg BD until symptoms improve. Treatment may then be resumed at a dose of 600mg BD.

Dose reduction below 300mg BD is not recommended as efficacy has not been established.

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

- **Serious side effects**

QT prolongation
Ischaemic heart disease
Heart failure
Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Interstitial pneumonitis
Teratogenicity
Infertility
Seizures

- **Frequently occurring side effects**

Fatigue
Rash
Deranged LFTs
Diarrhoea
Constipation
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Peripheral neuropathy
Arthralgia and myalgia
Hypertension

- **Other side effects**

Alopecia
Fluid retention
Phlebitis
Skin toxicity
Nail changes

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

**Docetaxel:**

**CYP3A4 Enzyme inducers/inhibitors**: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.

**Darolutamide:**

**Strong and moderate CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St John's Wort, phenytoin and rifampicin):** reduces darolutamide exposure, consider alternative medicines with no or weak potential to induce CYP3A4 or P-gp

**Strong CYP3A4 and P-gp inhibitors (e.g. itraconazole):** increases darolutamide exposure, monitor closely for toxicity and dose reduce as needed

**BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin):** darolutamide may increase plasma concentrations of these substrates, monitor closely for toxicity if concomitant use cannot be avoided.

**Rosuvastatin:** 5-fold increase rosuvastatin exposure via BCRP, OATP1B1 and OATP1B3 inhibition, avoid.

**Medicinal products which prolong the QT interval**: avoid concomitant use. These can include some antiarrhythmics, methadone, moxifloxacin and antipsychotics

## Additional comments

Nil

## References


- National Institute of Health and Care Excellence – TA903 – accessed 29th June 2023 via www.nice.org.uk
- Summary of Product Characteristics Docetaxel (Hospira) – accessed 29th June 2023 via www.medicines.org.uk
- Summary of Product Characteristics Darolutamide (Bayer) – accessed 29th June 2023 via www.medicines.org.uk
- Smith, M.R. *et al.* Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med 2022; 386:1132-1142


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Date: July 2023