SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Darolutamide, Docetaxel and Androgen Deprivation Therapy (ADT)

Hormone Sensitive Metastatic Prostate Cancer (mHSPC)

PROTOCOL REF: MPHADADTMPC
Version No: 1.1

Approved for use in:

First-line treatment of metastatic hormone-sensitive prostate cancer (mHSPC) with darolutamide in combination ADT and docetaxel and satisfies the following criteria:

- TNM M1 Metastatic prostate cancer with both widespread bone metastasis and a serum PSA of 50 ng/mL or greater.
- Prior ADT PERMITTED provided commenced ≤ 12 weeks before this line of treatment.
- ECOG performance status (PS) of 0 or 1.
- Previous treatment with androgen receptor targeted agent such as enzalutamide or apalutamide or abiraterone PERMITTED if progressive metastatic disease occurs 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 on treatment.

******Blueteq registration required for Darolutamide****

Dosage:

Cycles 1 to 6

Drug	Dose	Route	Frequency	Duration
Docetaxel	**75mg/m2**	IV infusion	3 weekly	6 cycles
Prednisolone	**10mg**	Oral	Daily continuously	Continue throughout treatment with docetaxel
Darolutamide	**600mg**	Oral	Twice a day continuously	Until disease progression or unacceptable toxicity

Cycle 7 onwards

Drug	Dose	Route	Frequency	Duration
Darolutamide	**600mg**	Oral	Twice a day continuously 4 weekly cycle	Until disease progression or unacceptable toxicity

Supportive Treatments

Cycles 1 to 6 ONLY

- Metoclopramide 10mg orally up to three times a day for nausea and vomiting, maximum 5 consecutive days.
- GCSF secondary prophylaxis, - subcutaneous injection daily for 7 days starting on day 3, dose as follows:
    - Weight < 70kg- Filgrastim 300 micrograms daily SC.
    - Weight ≥ 70kg- Filgrastim 480 micrograms daily SC.
- Dexamethasone 8mg orally twice daily for 3 days, commencing in the morning, 24 hours prior to the docetaxel dose.

Extravasation risk

Docetaxel: VESICANT

Refer to Clatterbridge '[Prevention and Management of Extravasation Injuries]' Policy for further guidance.

Patient Counselling Points

Docetaxel

Please contact the triage line if any of the following symptoms occur:

- Signs of an infection such as fever (37.5°C or above); chills, cough, pain or burning when you pass urine.
- Signs of bleeding problems such as black, tarry stools, blood in urine or pinpoint red spots all over your skin.
- Uncontrolled nausea, vomiting, constipation or diarrhoea.
- New or worsening cough, chest pain or shortness of breath
- Redness, swelling, pain or sores where the needle was place or along the arm.
- Redness, swelling, pain or sores on your lips, tongue, mouth or throat.
- Skin rash or itching.
- Numbness or tingling in feet or hands or painful leg cramps.
- Signs of anaemia such as unusual tiredness, dizziness, shortness of breath or weakness.

Darolutamide

- The tablets are available as 300mg film-coated tablets, they should be swallowed whole with plenty of water, with or after food.
- 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 together to make up for a missed dose.
- Tablets contain lactose- caution in individuals who are lactose intolerant.
- Patients should avoid any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos within 7 days prior to start of treatment and until treatment discontinuation, as these have the potential to interact with darolutamide.
- If the patient is engaged in sexual activity with a woman of childbearing potential or woman who is pregnant, a condom should be used during treatment and for 1 week after completion of treatment with darolutamide.

Dosing in renal and hepatic impairment

Renal	**Docetaxel**	Excretion is predominately via hepatic metabolism. Renal impairment is unlikely to affect elimination. No dose adjustment required.
	Darolutamide	eGFR ≥ 30 ml/min 1.73 m2 No dose adjustment is necessary eGFR 15-29 ml/min 1.73 m2) not on haemodialysis, recommended **starting dose is 300mg Twice a day**

Hepatic

Docetaxel

Transaminases		ALP		Bilirubin	Dose
AST and/or ALT >1.5-5 x ULN	AND	> 2.5 – 5·0 x ULN	AND	Normal	75%
AST and/or ALT > 1.5- 5 x ULN	AND	≤ 2.5-6 xULN	AND/ OR	≤ 1-1.5 x ULN	50%
AST/ALT > 10 xULN	OR	> 6 xULN	OR	> 1.5 x ULN	NOT RECOMMENDED

Darolutamide
BASELINE ASSESSMENT ONLY

Mild hepatic impairment (Child-Pugh Class A = 5-6 points)- No dose adjustment is necessary
Moderate impairment (Child-Pugh Class B = 7-9 points)- limited data. Use with caution, consult clinical team.
Severe impairment (Child-Pugh Class C = 10 or more points)- Not studied in this patient group, consult clinical team.

For those with moderate or severe impairment, recommended starting dose is 300mg Twice a day.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3

		Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
		Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Interactions:

For more detailed interactions please refer to the SmPC for each agent

Docetaxel
Concomitant use medicines which induce, inhibit or are metabolised by cytochrome P450-3A such as ciclosporin, ketoconazole, erythromycin, may affect levels of docetaxel refer to summary of product of characteristics for more detailed information. In case of a combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. Therefore, close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor.
Darolutamide *Substrate of CYP3A4, P-gp and breast cancer resistance protein (BCRP).*

Potential for other medicinal products to affect Darolutamide exposure	*CYP3A4, P-gp and BCRP inhibitors* No clinically relevant drug-drug interaction is expected in case of **CYP3A4, P-gp or BCRP inhibitor** administration. Darolutamide may be given concomitantly with CYP3A4, P-gp or BCRP inhibitors. **Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure which may increase the risk of darolutamide adverse reactions.** It is recommended to monitor patients more frequently for darolutamide adverse reactions and **modify dose as needed.** *CYP3A4 and P-gp inducers* The **concomitant use of strong and moderate CYP3A4 or P-gp inducers with darolutamide is not recommended** unless there is no therapeutic alternatives. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.
Potential to affect exposures to other medicinal products	*BCRP, OATP1B1 and OATP1B3 substrates* **Co-administration of rosuvastatin should be avoided** unless there is no therapeutic alternative. Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin). Therefore, it is **recommended to monitor patients for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates.** In addition, the related recommendation in the product information of these substrates should be followed when co-administered with darolutamide.

Treatment schedule:

Cycles 1 to 6 every 21 days

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**8mg Twice a day for 3 days**	**Oral**	

		To commence 24hours prior to Docetaxel		
	Docetaxel	**75mg/m^2**	**IV**	In 250mL Sodium Chloride 0.9% over 1 hour
	Prednisolone	**10mg daily** (Continuously throughout docetaxel treatment)	**Oral**	
	Darolutamide	**600mg Twice a day**	**Oral**	

Pre-medication (to prevent hypersensitivity reactions and fluid retention):

- Dexamethasone 8mg orally twice daily for 3 days, commencing in the morning, 24 hours prior to the docetaxel dose.
- If oral dexamethasone has not been taken on the day of treatment, then a single IV dose of dexamethasone sodium phosphate 6.6mg (equivalent to dexamethasone 8mg oral dose) will need to be prescribed and administered 30 minutes before docetaxel. Need to ensure that patient has sufficient supply of dexamethasone to take remaining 3 doses. A single IV dose of dexamethasone sodium phosphate 13.2mg (equivalent to dexamethasone 8mg twice a day oral dose) can be administered if it is not possible to obtain supply of oral dexamethasone on the same day, BUT will still need Dexamethasone oral dexamethasone 8mg twice a day for the day after docetaxel.

Steroid Aftercare

Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death. Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case-by–case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration

of corticosteroid treatment. *Gradual* withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse.

Once the patient has completed their chemotherapy regime the steroid dose should be tapered as follows:

1. Stop pre-docetaxel dexamethasone tablets.
2. Taper prednisolone to 10mg daily for seven days then reduce to 5mg daily for seven days then stop.*

*This can be customised to suit each patient on an individual basis and those who are on steroids for longer than 6 months should have a longer tapering off period.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). Please refer to the CCC Hypersensitivity; Management Prevention Policy.

Cycle 7 onwards every 28 days

Day	Drug	Dose	Route	Frequency	Duration
1	**Darolutamide**	**600mg**	Oral	Twice a day continuously 4 weekly cycle	Until disease progression or unacceptable toxicity

Main toxicities:

Darolutamide with docetaxel	
Most common ADR (any grade)	Rash (17.3%) ALT/AST increase ~15% Hypertension (13.8%)
The most common **serious adverse reactions** were:	Febrile neutropenia (6.1%), Neutrophil count decreased (2.8%) Pneumonia (2.5%)

Docetaxel

Frequency and/or Grade	Toxicity
Haematological	Myelosuppression - Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs usually occur at a median of 7 days but this interval may be shorter in heavily pre-treated patients.
Gastrointestinal	Stomatitis, Abdominal pain and tenderness, diarrhoea - may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.
Neuropathies	Peripheral neurotoxicity
Hypersensitivity	Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. Minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. Severe reactions, such as severe 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.

Ocular	Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination.
Additional side effects	Cutaneous reactions - Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Nail changes, fluid retention, alopecia, steroid side effects Infertility - contraceptive measures must be taken by both men and women during treatment and for men at least 6 months after cessation of therapy.

Darolutamide

Frequency and/or Grade	Toxicity
Haematological	Neutropenia
Cardiovascular	Ischaemic heart disease, heart failure prolonged QT
Musculoskeletal	Pain in extremity, musculoskeletal pain, fractures, fatigue, muscle spasms, muscular weakness, back pain.
Skin and subcutaneous tissue disorders	Rash
Hepatic	Raised AST and bilirubin

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x			x	Every 6 weeks
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&Es and LFTs	x	x	x	x	Every cycle
PSA	x			x	Every 6 weeks (do not defer if PSA not recorded- to be added for next cycle)
Creatinine Clearance (Cockcroft and Gault)	x	x	x	x	Every cycle
ECHO	x				At baseline if cardiac risk factors exist (discretion of the clinic team) then as clinically indicated*
CT scan	x				If clinically indicated
Observations (*heart rate, temperature, respiratory rate and O_2 sats)*		x			At baseline then as clinically indicated
Blood pressure	x	x	x	x	Every cycle (applies for Darolutamide-containing cycles only)*
Weight recorded	x	x	x	x	Every cycle
Height recorded	x				

* Need to optimise management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia. Monitor for signs and symptoms of ischaemic heart disease (palpitations, SOBOE, chest pain). Refer to 'Dose modification and toxicity management' section.

Dose modification and toxicity management

Treatment with darolutamide should be continued if a cycle of docetaxel is delayed, interrupted, or discontinued PROVIDED satisfies proceed rules as outlined in 'Darolutamide' section below.

Docetaxel

Haematological Toxicity

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

Cycles 1 to 6 (docetaxel-containing cycles) - administer treatment on day 1 if:

Platelets	Neutrophils (ANC)
≥ 100 x 10^9/L	≥ 1.0 x 10^9/L

Delay 1 week and refer to advice below

Platelets	Neutrophils (ANC)
Plt ≤ 99 x 10^9/L	≤ 0.9 x 10^9/L

ULN = upper limit of normal
Platelets must be within normal range prior to Cycle 1

Haematological Toxicity	Actions*
If treatment delayed > 1 week due to neutropenia OR ANC < 0.5 x 10^9/L for more than 1 week OR Febrile neutropenia	**Dose reduce Docetaxel to 60mg/m^2 (when neutrophils ≥ 1.0 x 10^9/L)** **Consider the addition of secondary prophylaxis with GCSF with the next cycle**
If treatment delayed > 1 week due to thrombocytopenia OR Platelets < 50 x 10^9/L on day 1 of cycle	**Dose reduce Docetaxel to 60mg/m^2 (when platelets ≥ 100 x 10^9/L)**
***If the patient continues to experience these side effects at the lower dose, review treatment plan**	

Non-haematological Toxicity

Grading and Management of Toxicity

Toxicity should be grading according to the CTCAEv5 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1.

For dose modifications based on renal or hepatic toxicity refer to **'Dosing in renal and hepatic impairment'** section above. For any other:

- **Persistent/un-resolving G2 (despite treatment breaks and supportive measures)** hold treatment until resolved to G1 or less and consider dose reduction by 20%. Discuss with clinical team.
- **G3 toxicities-** hold treatment until resolved to G1 or less and refer to clinical team for review ahead of next cycle.
- **G4 toxicities-** discontinue treatment and refer to clinical team

Darolutamide

Dose Level	Dose
Starting dose	600 mg (TWO 300 mg tablets) twice daily
Dose reduction	300 mg (ONE 300 mg tablets) twice daily

Haematological Toxicity

C7 onwards OR darolutamide ONLY cycles- Administer treatment on day 1 if:

Haematological	
Platelets	**Neutrophils**
≥ 100 x 10^9/L	≥ 1.0 x 10^9/L
50 to 100 x10^9/L **But inform consultant prior to next cycle**	0.5 to 1.0 x10^9/L **But inform consultant prior to next cycle**

Non-haematological Toxicity

Recommended dose modifications for hypertension

Grade	Clinical Presentation	Actions
1	Systolic BP (SBP) 120 - 139 mm Hg or diastolic BP (DBP) 80 - 89 mm Hg	Proceed with treatment
2	• SBP 140 - 159 mm Hg or DBP 90 - 99 mm Hg if previously within normal limits. • Change in baseline medical intervention indicated. • Recurrent or persistent (≥ 24 hrs). • Symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg.	Proceed with treatment and inform clinical team. Clinical team to refer patient to GP for monitoring and management of hypertension.

	• Monotherapy indicated initiated	**Dose reduction to 300mg BD to be considered at the discretion of the clinical team**
3	• SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg. • Medical intervention indicated. • More than one drug or more intensive therapy than previously used indicated.	Stop treatment and inform clinical team. Resume treatment when recovered to ≤ grade 1 (Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) or to baseline grade. **After recovery, resume treatment at 300mg BD** If Grade 4 hypertension recurs, treatment should be permanently discontinued.
4	• Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis). • Urgent intervention indicated	

Recommended dose modifications for hepatotoxicity

Hepatotoxicity	
Grade 1 AST or ALT increase to 2.5 times the upper limit of normal (ULN) Bilirubin increase to 1.5 times ULN	Repeat LFTs at two-weekly intervals. No dose reduction is required.
Grade 2 AST or ALT increase to 2.5 to 5 times ULN Bilirubin increase to 1.5 to 3 times ULN	Repeat LFTs once a week No dose reduction is required
Grade 3 AST or ALT over 5 times the ULN Bilirubin over 3 times the ULN	Withhold treatment immediately, along with any other potentially hepatotoxic medications. Repeat LFTs weekly until return to baseline or grade 1. **Retreatment can be considered, resume treatment at 300mg BD**

Grade 4 AST or ALT 20 times the ULN Bilirubin to 10 times the ULN	Treatment should be discontinued and patients should not be re-treated.

Recommended dose modifications for OTHER toxicities

Toxicity Grade	Action
Grade 1 **Mild**	**Continue treatment increase monitoring and provide symptomatic treatment.**
Grade 2 **Moderate**	**Refer to clinical team** **Dose reduction to 300mg BD to be considered at the discretion of the clinical team**
Grade 3 and Grade 4 **Severe**	**Delay until improves to grade ≤ 2** **When severity is ≤ 2, restart dose at 300mg BD** **If grade 3 toxicity or higher occurs whilst on reduced dose, then patient should discontinue treatment permanently.** **Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion.**

References:

Nubeqa Darolutamide 300 mg film-coated tablets. SmPC, Bayer PLC. Available from www.medicines.org.uk/emc Last Updated 27/11/2022.

NICE Technology Appraisal TA903 Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer Publication date: 21 June 2023

Docetaxel Hospira 10mg/ml concentrate for solution for infusion, SmPC, Hospira Healthcare limited, Middlesex. Available from www.medicines.org.uk Last updated 20/1/20.

Clatterbridge cancer centre. *Steroid tapering guidance.* Available from: https://extranet.clatterbridgecc.nhs.uk/application/files/7115/3138/6265/Steroid_Tapering_Guidance_V2.0.pdf [Accessed on 25/5/23]

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Version History

		Author name and designation	Summary of main changes
		Rachel Pritchard **Urology SRG Pharmacist**	V1.0 New regimen protocol
		Rachel Pritchard **Urology SRG Pharmacist**	**V1.1** **Blueteq criteria added**