Systemic Anti Cancer Treatment Protocol

Darolutamide Prostate Cancer

PROCTOCOL REF: MPHADARUR
(Version No: 1.0)

Approved for use:

In combination with androgen deprivation therapy (ADT) for the treatment of adult men with non-metastatic castrate-resistant prostate cancer who are at high risk of developing metastatic disease who fulfil the following criteria:

- Adenocarcinoma of the prostate without neuroendocrine differentiation or features of a small cell carcinoma.
- Current PSA level is ≥ 2ng/ml.
- Hormone-resistant (castrate-resistant) disease as defined by 3 rising PSA levels (after the nadir PSA level) and taken at least 1 week apart during androgen deprivation therapy.
- High risk of developing metastatic disease as defined by a PSA doubling time of ≤ 10 months.
- Serum testosterone level is <1.7nmol/L on gonadotrophin releasing hormone agonist/antagonist therapy or after bilateral orchidectomy.
- Has not received any previous 2nd generation androgen receptor inhibitors (such as enzalutamide, darolutamide, apalutamide) or CYP17 enzyme inhibitors (such as abiraterone) unless darolutamide has been accessed via a company early access scheme for this specific indication
- ECOG performance status 0-2.

****Patients must be registered on blueteq****

Dosage:

Drug	Dosage	Route	Frequency
Darolutamide	600mg	Oral	Twice a day continuously

- Until disease progression or unacceptable toxicity.
- Cycle length 28 days
- Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment for patients not surgically castrated.

Supportive treatments:

No routine supportive treatments recommended

Extravasation risk:

Not applicable

Administration:

1. The tablets should be swallowed whole with plenty of water, with or after food.
2. Tablets contain lactose- **caution in individuals who are lactose intolerant**.
3. Patient 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.
4. If the patient is engaged in a relationship with:
    a. A woman of childbearing potential- a highly effective contraceptive method (<1% failure rate per year) should be used during and for 1 week after completion of treatment with Darolutamide to prevent pregnancy.
    b. A pregnant woman- a barrier method should be used during and for 1 week after completion of treatment with Darolutamide. **Exposure of the foetus to an androgen receptor inhibitor has to be avoided, as this could affect development of the foetus.**

Drug Interactions

Darolutamide is a 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.

Please refer to the SmPC for the full list of drug interaction

Main Toxicities:

Darolutamide	
Haematological toxicity	Neutropenia
Cardiovascular	Ischaemic heart disease, heart failure prolonged QT
Musculoskeletal	Pain in extremity, musculoskeletal pain, fractures, fatigue.
Skin and subcutaneous tissue disorders	Rash
Hepatic	Raised AST and bilirubin
Musculoskeletal disorders	Fractures, myalgia, muscle spasms, muscular weakness, back pain.

Please refer to the SmPC or the full list of toxicities

Investigations and Treatment Plan:

	Pre	C1	C2	C3	C4	Ongoing
Informed Consent	X					
Clinical Assessment	X	X	X	X		First three cycles and then every 12 weeks
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X		X	X	X	Every cycle
U&E & LFTs	X		X	X	X	Every Cycle
Creatinine Clearance (Cockroft and Gault or eGFR)	X		X	X	X	Every Cycle
PSA	X	X	X	X	X	Every cycle
CT scan	X					If clinically indicated
Serum creatinine	X		X	X	X	Every cycle
Blood pressure measurement	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle
Height recorded	X					

Dose Modifications and Toxicity Management:

Grade of Toxicity	Dose Modification
Grade 2	Refer to clinical team Dose reduction to 300mg BD to be considered at the discretion of the clinical team [a,b]
Grade ≥ 3	Delay until improves to grade ≤ 2[a] When severity is ≤ 2, restart dose at 300mg BD[b] If grade 3 toxicity or higher occurs whilst on reduced dose, then patient should discontinue treatment permanently.

[a]As per trial if no recovery after 28 consecutive days treatment was permanently discontinued

[b]Once toxicity returns to baseline or is resolved clinician can dose escalate to 600mg BD.

[c]If dose is escalated to 600mg and a second toxicity of grade 3 or higher occurs then a permanent dose reduction to 300mg BD is required. If a third occurrence of grade 3 toxicity or higher occurs then treatment should be permanently discontinued.

Haematological Toxicity:

Darolutamide can cause neutropenia, bloods should be monitored prior to each cycle.

If neutrophils < 1.0 x 10^9/L and/or platelets < 100x 10^9/L, continue drug therapy but **discuss with the clinical team prior to the next cycle.**

If neutrophils < 0.5 x 10^9/L and/or platelets < 50x 10^9/L, **discuss with the clinical team before continuing treatment.**

Non-haematological toxicity:

Recent cardiovascular disease

- Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and symptomatic congestive heart failure were excluded from the clinical studies. Therefore, the safety of darolutamide in these patients has not been established.

If darolutamide is prescribed, patients with clinically significant cardiovascular disease should be treated for these conditions according to established guidelines.

Hepatic impairment

Mild hepatic impairment (Child-Pugh Class A, see table below)- No dose adjustment is necessary.
Moderate impairment (Child-Pugh Class B, see table below)- limited data. Use with caution.
Severe impairment (Child-Pugh Class C, see table below)- Not studied in this patient group.

For those with moderate or severe impairment, recommended starting dose: 300mg BD

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.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

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 one 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.
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.

Renal impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment (calculated creatinine clearance (CrCL) ≥ 30 mL/min by the Cockcroft and Gault formula). **For patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily.**

References:

Nubeqa Darolutamide. Summary of Product Characteristics, Bayer, 02/06/2020. Available from www.medicines.org.uk/emc Last Updated 02/06/2020.

NICE Technology Appraisal Final Appraisal Determination: darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer. Published 23rd October 2020.

Bayer integrated study protocol; A multinational, randomised, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer.