Indication	Darolutamide in combination with docetaxel, prednisolone and androgen deprivation therapy (ADT) for the treatment of newly diagnosed metastatic hormone-sensitive prostate cancer. Patients must not have received any previous androgen receptor targeted agents (e.g. enzalutamide, darolutamide, apalutamide) 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 (ISRCTN78818544) with no disease progression.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat combination therapy every 21 days for 6 cycles. Monotherapy repeated every 28 days. Darolutamide monotherapy to continue until disease progression, unacceptable toxicity or patient choice. 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 cycle of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Patients must be prescribed androgen deprivation therapy (ADT). • Monitor FBC, U&Es and LFTs and BP with each cycle for 1st 8 cycles and then every 3 months thereafter if clinically indicated. • **Haematological parameters: Cycles 1-6** If neuts >/= 1.5 and PLT >/=100 continue with treatment. If neuts 1.0-1.4 and Plts >/= 100 d/w consultant. If neuts <1.0 or Plts <100 delay docetaxel one week and consider dose reduction. • Ensure dexamethasone pre-medication (8mg PO BD for 3 days, starting the morning of the day prior to the next cycle of docetaxel) is prescribed and given to the patient at new patient chat. • **Hepatic impairment:** **Darolutamide:** No dose adjustment in mild hepatic impairment (Child-Pugh class A). In moderate to severe impairment (Child-Pugh classes B and C) the recommended starting dose is 300mg twice daily. Darolutamide has not been studied in patients with severe hepatic impairment treatment is at clinician's discretion. **Docetaxel:** If AST and/or ALT > 1·5- 5 x ULN consider dose reduction in liver impairment. Not recommended in severe liver impairment. • **Renal impairment:** **Darolutamide:** No dose adjustment in mild to moderate renal impairment (CrCl >30 mL/min). In patients with severe renal impairment (CrCl < 30 mL/min) not receiving haemodialysis the recommended starting dose is 300mg twice a day. **Docetaxel:** no dose adjustment required. • **Dose Modification:**

	Darolutamide: If a patient experiences a >/= Grade 3 toxicity or an intolerable adverse reaction dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily. Dose reduction below 300mg twice daily is not recommended. **Docetaxel:** Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1. If docetaxel is stopped due to unacceptable toxicity, that can be clearly determined to be linked to docetaxel, treatment with darolutamide can be continued. **Prednisolone:** Dose may be omitted on the days of dexamethasone pre-medication. Dose may be adjusted at clinician's discretion. • Monitor for signs and symptoms of ischaemic heart disease. • Advise patients of the risk of developing a seizure while receiving darolutamide. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** • **Darolutamide:** o Use of strong and moderate CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort, phenytoin, and rifampicin) during treatment with darolutamide is not recommended, unless there is no therapeutic alternative. o Concomitant use of darolutamide with a combined P-gp **and** strong CYP3A4 inhibitor may increase the risk of adverse reactions, patients on this combination should be monitored closely for adverse reactions, dose modification of darolutamide may be required. o Medicines that may prolong the QT interval should be prescribed with caution. o Co-administration of rosuvastatin should be avoided. o Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin), monitor patients for adverse reactions. • **Docetaxel:** o Concomitant use with medicines which induce, inhibit or are metabolised by cyto-chrome P450-3A (eg ciclosporin, ketoconazole and erythromycin) may affect levels of docetaxel use with caution. o Avoid concomitant use with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin and ritonavir), if treatment cannot be avoided consider dose reduction of docetaxel and monitor patient closely for signs of toxicity. • **Missed Dose:** If a dose is missed it should be taken as soon as the patient remembers, do not take 2 doses together to make up for a missed dose. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	KMCC protocol URO-038 V1 SPC accessed online 06.06.2023 CDF list v1.266 accessed online 06.06.2023

NB For funding information, refer to CDF and NICE Drugs Funding List

Cycle 1 -6 repeat every 21 days

Day	Drug	Dose	Route	Infusion duration	Administration
1	Metoclopramide	20mg	IV		
	DOCETAXEL	**75mg/m^2**	IV	1 hour	Sodium Chloride 0.9% 250ml
TTO	Drug	Dose	Route	Directions	
Day 1	**DAROLUTAMIDE**	**600mg**	PO	BD. Swallow whole with food. Tablets available as 300mg.	
	PREDNISOLONE	**5mg**	PO	BD continuously (dispense 3 weeks supply) Take with or just after food, or a meal. On the final cycle of docetaxel, the patient should commence a reducing prednisolone dose: 5mg BD for 1 week and then 5mg OD for 2 weeks.	
	Dexamethasone	8mg	PO	BD for 3 days, starting the morning of the day prior to the next cycle of docetaxel. Take with or just after food, or a meal. Do not dispense on last cycle of docetaxel.	
	Metoclopramide	10mg	PO	Up to 3 times a day when required (Maximum of 30mg per day including 20mg pre-chemo dose). Do not take for more than 5 days continuously	
	NB ADT must be prescribed.				

Cycle 7 onwards repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**DAROLUTAMIDE**	**600mg**	PO	BD. Swallow whole with food. Tablets available as 300mg.
	NB ADT must be prescribed.			