# BC Cancer Protocol Summary for Treatment of Metastatic Castration Sensitive Prostate Cancer using Darolutamide and DOCEtaxel

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| ***Protocol Code:*** | *UGUMCSPDD* |
| ***Tumour Group:*** | *Genitourinary* |
| ***Contact Physician:*** | *Dr. Krista Noonan* |

## ELIGIBILITY:

Patients must have:

- Metastatic castration sensitive prostate cancer (mCSPC),
- No prior systemic treatment for metastatic prostate cancer (excluding ADT*), and
- A BC Cancer "Compassionate Access Program" (CAP) request must be approved prior to treatment

* Previous ADT permitted if patient received:
  - Less than 6 months of androgen deprivation therapy (ADT) for mCSPC immediately prior to starting this protocol, and
  - No ADT for adjuvant treatment of non-metastatic prostate cancer within 1 year of starting this protocol

Patients should have:

- Fitness for treatment containing DOCEtaxel,
- Good performance status, and
- Total bilirubin less than ULN, AST/ALT less than 5 x ULN, alkaline phosphatase less than 6 x ULN

Notes:

- Patients currently being treated with GUPDOCADT who have not progressed, may switch to UGUMCSPDD if all other eligibility criteria are met
- Patients with mCSPC are eligible to receive any of the following, but not their sequential use:
  - apalutamide (GUMCSPAPA),
  - enzalutamide (GUMCSPENZ),
  - abiraterone (GUMCSPABI), or
  - darolutamide + DOCEtaxel (UGUMCSPDD)
- Patients treated with darolutamide for mCSPC who develop castration resistant disease are NOT eligible to receive abiraterone (UGUPABI, UGUPAVOABI, UGUPAVNABI) or enzalutamide (UGUPENZ)
- Initiation of darolutamide without DOCEtaxel is not funded

**EXCLUSIONS:**

Patients must not have:

- Completed adjuvant treatment (i.e., prior UGUPAJABI) for prostate cancer less than 1 year prior to initiation of UGUMCSPDD

**TESTS:**

- Baseline: CBC & Diff, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, GGT, albumin, INR, PSA, testosterone, blood pressure
- Baseline if clinically indicated: ECG
- Cycles 1 to 6 (DOCEtaxel and darolutamide combination treatment):
  - Before each DOCEtaxel treatment: CBC & Diff, PSA (PSA required every 3 weeks, but results do not have to be available to proceed with treatment)
  - Before DOCEtaxel Cycle 4 and anytime if clinically indicated: total bilirubin, ALT, alkaline phosphatase, LDH, testosterone (see Precaution #5 for guidelines)
- Cycles 7 onward (darolutamide treatment):
  - Each time seen by physician: PSA, blood pressure
  - If clinically indicated: ECG, calcium, albumin, total bilirubin, ALT, random glucose, HbA1c, creatinine, sodium, potassium, TSH, INR, testosterone

**PREMEDICATIONS**:

- Cycles 1 to 6 (DOCEtaxel and darolutamide combination treatment):
  - dexamethasone 8 mg PO bid for 3 days, starting one day prior to each DOCEtaxel administration; patient must receive minimum of 3 doses pre-treatment
  - Additional antiemetics not usually required.
  - DOCEtaxel-induced onycholysis and cutaneous toxicity of the hands may be prevented by wearing frozen gloves starting 15 minutes before DOCEtaxel infusion until 15 minutes after end of DOCEtaxel infusion; gloves should be changed after 45 minutes of wearing to ensure they remain cold during the entire DOCEtaxel infusion
- Cycles 7 onward (darolutamide treatment):
  - No premedications or antiemetics required

**TREATMENT:**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| darolutamide | 600 mg | PO twice daily |

**PLUS:**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| DOCEtaxel | 75 mg/m² | IV in 250 to 500 mL NS over 1 hour<br>(see Precaution #2) (use non-DEHP equipment) |

**PLUS:**

| **Androgen Deprivation Therapy (unless previous bilateral orchiectomy):** | |
|---|---|
| LHRH agonist<br>(e.g. goserelin or leuprolide) | Per protocol GUPADT |
| **or** | |
| LHRH antagonist<br>(degarelix) | |

- Discontinue antiandrogen (e.g., bicalutamide), prior to initiation of darolutamide

- DOCEtaxel: repeat every 21 days x 6 cycles
- darolutamide: continue treatment until disease progression or unacceptable toxicity
- Patients who are unable to tolerate DOCEtaxel are eligible to continue with darolutamide and ADT

## DOSE MODIFICATIONS:

- **Darolutamide:** For toxicities greater than or equal to Grade 3, reduce dose to 300 mg twice daily or withhold dose until symptoms improve. Dose reduction below 300 mg twice daily is not recommended. Dose may be escalated back to 600 mg twice daily based on tolerance

### 1. Hematological

#### A. DOCEtaxel:

| ANC (x $10^9$/L) | Platelets (x $10^9$/L) | DOCEtaxel Dose | DOCEtaxel Dose after Neutropenic Sepsis on DOCEtaxel |
|---|---|---|---|
| Greater than or equal to 1.5 | Greater than 90 | 100% | 75% |
| 1.0 to less than 1.5 | 70 to 90 | 75% | 75% |
| Less than 1.0 | Less than 70 | Delay | Delay |

#### B. Darolutamide:

| ANC (x $10^9$/L) | Platelets (x $10^9$/L) | Darolutamide Dose |
|---|---|---|
| Greater than or equal to 1.5 | Greater than or equal to 75 | 100% |
| 1.0 to less than 1.5 | 50 to less than 75 | 100% |
| 0.5 to less than 1.0 | 25 to less than 50 | Reduce to 300 mg twice daily or hold until resolution per provider discretion. Dose may be escalated back to 600 mg twice daily based on tolerance at provider discretion. |
| Less than 0.5 | Less than 25 | |

2. **Hepatic dysfunction**

**A. DOCEtaxel:**

| Total Bilirubin | | Alkaline Phosphatase* | | AST and/or ALT | DOCEtaxel Dose |
|---|---|---|---|---|---|
| Less than or equal to ULN | and | Less than 2.5 x ULN | and | Less than or equal to 1.5 x ULN | 100% |
| Less than or equal to ULN | and | 2.5 to 5 x ULN | and | 1.6 to 5 x ULN | 75% |
| Greater than ULN | or | Greater than 5 x ULN | or | Greater than 5 x ULN | Discuss with contact provider |

*except in the case of bony metastases and no known hepatic dysfunction

**B. Darolutamide:**

| Hepatic Impairment | Darolutamide Dose |
|---|---|
| Mild (Child-Pugh A) | No adjustment |
| Moderate (Child-Pugh B) | 300 mg twice daily |
| Severe (Child-Pugh C) | Not recommended |

3. **Renal Impairment**

**A. DOCEtaxel:** no dose adjustment required

**B. Darolutamide:**

| Creatinine Clearance (mL/min) | Darolutamide Dose |
|---|---|
| Greater than 30 | No adjustment |
| 15 to 29 | 300 mg twice daily |
| Less than 15 | Not recommended |

**PRECAUTIONS**:

1. **Fluid retention**: Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.
2. **Hypersensitivity** reactions to DOCEtaxel are common but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Systemic Therapy Agents (SCDRUGRX).
3. **Extravasation**: DOCEtaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction. Baseline bilirubin and liver enzymes are recommended before Cycle 1 and then if clinically indicated (e.g., repeat bilirubin and liver enzymes prior to each treatment if liver enzymes are elevated, liver metastases are present or there is severe toxicity such as neutropenia). If bilirubin and liver enzymes are normal and there is no evidence of liver metastases or severe toxicity, check bilirubin and liver enzymes after 3 cycles (i.e., at cycle 4). Note: this information is intended to provide guidance but physicians must use their clinical judgement when making decisions regarding monitoring and dose adjustments.
6. **Rash:** Rash has been reported in patients treated with darolutamide. It is mostly Grade 1 to 2 with less than 1% reported as Grade 3 to 4. Corticosteroids and antihistamines may be used to treat the rash.
7. **Drug interactions**: Darolutamide is primarily metabolized by CYP3A4. Concomitant administration of darolutamide with strong inducers (e.g., rifampin) or strong inhibitors (e.g., itraconazole) of CYP3A4 may result in change in serum level of darolutamide. See BC Cancer Drug Manual.

**Call Dr. Krista Noonan or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

**References**:


1. Smith MR, Hussain M, Saad F, et al; ARASENS Trial Investigators. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med. 2022 Mar 24;386(12):1132-1142.
2. Darolutamide (Nubeqa) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2023; 3(1): 1-19.
3. CADTH Reimbursement Review. Provisional Funding Algorithm. Prostate Cancer. Oct 2023.