BC Cancer Protocol Summary of Therapy for Castration Sensitive High-Risk Non-Metastatic Prostate Cancer using Enzalutamide

Protocol Code:	*UGUPAJENZ*
Tumour Group:	*Genitourinary*
Contact Physician:	*GU Systemic Therapy*

ELIGIBILITY:

Salvage radiation therapy remains a curative treatment for this population after radical prostatectomy (RP) and would typically be considered first before offering enzalutamide, with or without androgen deprivation therapy (ADT), unless the patient is not a candidate for this treatment.

Patients must have:
- Castration sensitive non-metastatic histologically confirmed prostate adenocarcinoma,
- Completed curative intent radical prostatectomy (RP) or radiotherapy (RT),
- Biochemical recurrence:
  - PSA doubling time of 9 months or less, and
- BC Cancer “Compassionate Access Program” request approval prior to treatment

Patients should have:
- Good performance status,
- Screening prostate-specific antigen (PSA) level
  - 1 ng/mL or higher in prior RP (with or without postoperative RT) patients, or
  - At least 2 ng/mL above nadir in prior RT, and
- Testosterone 5.2 nmol/L or higher before treatment initiation

Note:
- Enzalutamide may be given with (preferred) or without androgen deprivation therapy (ADT)
- Upon progression, patients are NOT eligible to receive further androgen receptor axis pathway inhibitors

EXCLUSIONS:

Patients must not:
- Have radiologic evidence of metastases
- Be a candidate for salvage radiation therapy

CAUTION:
- Uncontrolled hypertension

Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/terms-of-use

TESTS:

- Baseline: PSA, testosterone, blood pressure
- Baseline if clinically indicated: ECG, CBC & Diff, creatinine, sodium, potassium
- Each time seen by physician: PSA, blood pressure
- If clinically indicated: creatinine, sodium, potassium, testosterone, ECG

TREATMENT:

Androgen deprivation therapy (e.g., LHRH agonist, LHRH antagonist) should be maintained (unless previous bilateral orchiectomy), however, enzalutamide monotherapy is permitted for patients unable to tolerate the side effects of combination treatment. Discontinue other antiandrogens (e.g., bicalutamide) prior to initiation of enzalutamide.

Drug	Dose	BC Cancer Administration Guideline
enzalutamide	160 daily	PO

Dispense a 90-day supply with each physician visit. Treatment (including LHRH agonist/antagonist) should be held if PSA is less than 0.2 ng/mL after 36 weeks and may be restarted based on appropriate PSA level (reference 1) and on treating physician's discretion and clinical judgement. Treatment should be discontinued if disease progression or unacceptable toxicity.

Dose reduction:
Dose level -1: enzalutamide120 mg PO daily
Dose level -2: enzalutamide 80 mg PO daily

PRECAUTIONS:

1. **QT prolongation:** Enzalutamide is associated with QTc prolongation. It should be used with caution in patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g. hypokalemia) or patients who are taking medications known to prolong the QT interval.
2. **Seizure:** Enzalutamide is associated with an increased risk of seizure, with a greater risk of seizure at daily doses higher than 160 mg. Seizures resolved after treatment cessation.
3. **Hypertension:** Enzalutamide is associated with increased blood pressure in approximately 7% of patients. Hypertension rarely leads to discontinuation or dose modification, but may require antihypertensive treatment. Blood pressure will need to be monitored once every 2 weeks for the first three months of enzalutamide therapy. Temporary suspension of enzalutamide is recommended for patients with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment with enzalutamide may be resumed once hypertension is controlled.

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4. **Drug interactions**: CYP2C8 inhibitors (e.g. gemfibrozil) may increase the serum level of enzalutamide. Reduce enzalutamide dose to 80 mg once daily in patients who must be co-administered with a strong CYP2C8 inhibitor. Enzalutamide is a strong inducer of CYP 3A4. Avoid co-administration with CYP 3A4 substrates with a narrow therapeutic index if possible. Dose adjustment of the substrate to maintain therapeutic concentrations and additional monitoring may be required.
5. **Cognitive function:** Patients are at risk of worsening cognitive function during treatment with enzalutamide. Symptoms may present as memory impairment, cognitive disorder, confusion, somnolence, delirium, dementia, disorientation, speech disturbance, and mental status changes.
6. **Falls and fractures:** Falls and fractures have been associated with enzalutamide. The mechanism is unknown and concomitant neurological symptoms, such as dizziness or syncope, were rarely reported as an adverse event with the falls. Consider initiation of bone-sparing agent or referral to bone health specialist if patient at increased risk of fracture.

Contact the GU Systemic Therapy physician at your regional cancer centre or GU Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. N Engl J Med. 2023 Oct 19;389(16):1453-1465.
2. Enzalutamide (Xtandi) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Nov 2024:1-9.
3. CADTH Reimbursement Review. Provisional Funding Algorithm: Prostate cancer. January 2025.

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