BC Cancer Protocol Summary of Therapy for Castration Sensitive Very High-Risk Non-Metastatic Prostate Cancer using Abiraterone and predniSONE

Protocol Code: *UGUPAJABI*

Tumour Group: *Genitourinary*

Contact Physician: *Dr. Scott Tyldesley*

ELIGIBILITY:

Patients must have:
- Castration sensitive non-metastatic histologically confirmed prostate adenocarcinoma,
- Planned for curative intent radiotherapy,
- No prior systemic therapy*,
- Very high-risk disease:
  - Clinical or pathologic pelvic node positive, or
  - Node negative with at least 2 of the following:
    - Clinical stage T3 or T4,
    - Gleason score 8 to 10,
    - Prostate-specific antigen (PSA) 40 ng/mL or greater
- BC Cancer “Compassionate Access Program” request approval prior to treatment

* up to 6 months of prior androgen deprivation therapy permissible

Patients should have:
- Good performance status,
- Serum potassium greater than 3.5 mmol/L

Note:
- Combination with enzalutamide, apalutamide or darolutamide is not funded

EXCLUSIONS:

Patients must not have:
- Biochemical recurrence (relapsed disease after prior treatment)

CAUTIONS:

- Uncontrolled hypertension (systolic blood pressure greater than 160 mmHg or diastolic greater than 95 mmHg)
- Total bilirubin greater than 1.5 x ULN, ALT greater than 2.5 x ULN

TESTS:

- Baseline: CBC & Diff, platelets, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, PSA, testosterone
- Baseline if clinically indicated: total protein, albumin, GGT, LDH, TSH, calcium, MUGA scan or echocardiogram
- Cycles 1 to 3, every 4 weeks: CBC & Diff, platelets, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, blood pressure*, PSA
- Cycles 1 to 3, every 2 weeks: potassium, ALT, total bilirubin, alkaline phosphatase, blood pressure*
- Cycles 4 onward, before each physician visit: CBC & Diff, platelets, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, testosterone, PSA, blood pressure*
- If clinically indicated: total protein, albumin, GGT, LDH, TSH, calcium, MUGA scan or echocardiogram

* See Hypertension in Precautions

TREATMENT:

Androgen deprivation therapy (e.g., LHRH agonist, LHRH antagonist) should be maintained unless prior bilateral orchiectomy.

Drug	Dose	BC Cancer Administration Guideline
abiraterone	1000 mg	PO daily
predniSONE*	10 mg daily or 5 mg twice daily OR 5 mg daily**	PO daily

* Dexamethasone may be substituted for patient or physician preference, based upon toxicity and patient tolerance. When substituting dexamethasone for predniSONE, the dose is:

- PredniSONE 10 mg PO daily: dexamethasone 1.5 mg PO daily
- PredniSONE 5 mg PO daily: dexamethasone 0.5 mg PO daily

**More mineralocorticoid side effects were observed with the lower dose of predniSONE

- One cycle consists of 4 weeks (30 days).
  - For cycles 1 to 3: Dispense 30 day supply with each physician visit.
  - For cycles 4 onwards: Dispense 90 day supply with each physician visit.
- Treat for a maximum of **25 cycles or 2 years** of treatment, unless disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. Hepatic dysfunction:

Total bilirubin		ALT	Dose
Less than or equal to ULN to 1.5 x ULN	and	Less than or equal to ULN to 2.5 x ULN	100%
Greater than 1.5 to 3 x ULN	and	Greater than 2.5 to 5 x ULN	100% ▪ Monitor liver tests at least weekly until Grade 1 (Total bilirubin less than 1.5 x ULN, ALT less than 2.5 x ULN)
Greater than 3 x ULN	or	Greater than 5 x ULN	▪ Hold abiraterone. ▪ Monitor liver tests at least weekly until Grade 1 (Total bilirubin less than 1.5 x ULN, ALT less than 2.5 x ULN) ▪ Reduce dose of abiraterone by 250 mg and resume only after liver tests less than or equal to Grade 1

ULN = upper limit of normal

2. Hypokalemia Management:

Hypokalemia has been observed and should be aggressively managed. Serum potassium should be monitored closely in patients who develop hypokalemia.

Serum potassium (mmol/L)	Grade of Hypokalemia	Action	Further Action or Maintenance
Low potassium or History of hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations.	Titrate dose to maintain potassium greater than 3.5 mmol/L and less than 5.0 mmol/L (greater than 4.0 mmol/L recommended)
Less than 3.5 to 3	Grade 1	Initiate oral or IV potassium supplementation. Consider monitoring magnesium and replacement if needed.	Titrate dose to maintain potassium greater than 3.5 mmol/L and less than 5 mmol/L (greater than 4 mmol/L recommended)

Serum potassium (mmol/L)	Grade of Hypokalemia	Action	Further Action or Maintenance
Less than 3.5 to 3 Symptomatic	Grade 2	Withhold abiraterone until potassium corrected. Initiate oral or IV potassium supplementation. Consider monitoring magnesium and replacement if needed.	Titrate dose to maintain potassium greater than 3.5 mmol/L and less than 5 mmol/L (greater than 4 mmol/L recommended)
Less than 3 to 2.5	Grade 3	Withhold abiraterone until potassium corrected. Initiate oral or IV potassium and cardiac monitoring. Consider monitoring magnesium and replacement if needed.	
Less than 2.5	Grade 4	Withhold abiraterone until potassium corrected. Initiate oral or IV potassium and cardiac monitoring. Consider monitoring magnesium and replacement if needed	

PRECAUTIONS:

1. **Fluid retention:** Fluid retention can occur due to mineralocorticoid excess caused by compensatory adrenocorticotropic hormone (ACTH) drive. The administration of predniSONE will help reduce incidence and severity of fluid retention.
2. **Cardiovascular disease**: Caution in patients with clinically significant cardiovascular disease (e.g., severe angina, myocardial infarction within 6 months, a history of class 2 congestive heart failure or greater, arterial thrombotic event within 6 months, stroke or transient ischemic attack within 6 months.
3. **Hypertension:** Patients with hypertension should exercise caution while on abiraterone. Rigorous treatment of blood pressure is necessary, since abiraterone can cause a rapid onset of high blood pressure. Blood pressure will need to be monitored once every 2 weeks for the first three months of abiraterone therapy. Temporary suspension of abiraterone is recommended for patients with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment with abiraterone may be resumed once hypertension is controlled (see also http://www.hypertension.ca). Blood pressure monitoring can be done by self-monitoring or by primary care provider, provided it is reviewed by treating clinician at each visit.
4. **Renal impairment:** No dosage adjustment is necessary for patients with renal impairment.

5. **Hepatic Dysfunction:** Abiraterone undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST and ALT) may occur during the first 3 months after starting treatment so a more frequent monitoring of liver function tests is required (every 2 weeks in the first three months and monthly thereafter).

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

References:

1. Attard G, Murphy L, Clarke NW, et al; Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet. 2022 Jan 29;399(10323):447-460.
2. Abiraterone Acetate and Prednisone CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Sep 2023
3. CADTH Reimbursement Review. Provisional Funding Algorithm: Prostate cancer. October 2023.