BC Cancer Protocol Summary of Treatment for Metastatic Castration-Resistant Prostate Cancer using Olaparib with Abiraterone and predniSONE

Protocol Code:	*UGUPAVOABI*
Tumour Group:	*Genitourinary*
Contact Physician:	*Dr. Jean-Michel Lavoie*

ELIGIBILITY:

Patients must:

- Have metastatic castration-resistant prostate cancer (mCRPC),
- Have deleterious or suspected deleterious germline and/or somatic BRCA1 or BRCA2 gene alteration (BRCA mutation must be confirmed before olaparib treatment is initiated),
- Be inappropriate candidate for chemotherapy per provider discretion, and
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:

- Good performance status,
- Serum potassium greater than 3.5 mmol/L

Notes:

- Patients currently being treated with abiraterone per protocol UGUPABI for a maximum of 4 months without progression can transition to UGUPAVOABI if all other eligibility criteria are met
- Prior treatment with UGUPAJABI is permitted if no progression during abiraterone
- This protocol is not funded in combination with anticancer drugs other than androgen deprivation therapy

EXCLUSIONS:

Patients must not have:

- Prior treatment with or progression on poly-(ADP ribose) polymerase (PARP) inhibitor (e.g., olaparib)
- Prior progression during treatment with abiraterone in any setting
- Prior treatment with androgen receptor pathway inhibitor (e.g., apalutamide, enzalutamide, darolutamide, abiraterone) for:
    - Metastatic castrate-sensitive prostate cancer, or
    - Non-metastatic castrate-resistant prostate cancer
- ATM mutation without BRCA mutation (may be eligible for single agent olaparib per UGUPOLAP)

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, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, PSA, testosterone
- Baseline if clinically indicated: total protein, albumin, GGT, LDH, TSH, calcium, INR, MUGA scan or echocardiogram, ECG
- Day 14 (any cycle) if clinically indicated: CBC & Diff
- Cycles 1 to 3, every 2 weeks: potassium, ALT, total bilirubin, alkaline phosphatase, blood pressure
- Every 4 weeks: CBC & Diff, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, blood pressure, PSA
- If clinically indicated: total protein, albumin, GGT, LDH, urea, TSH, calcium, INR, testosterone, blood pressure, MUGA scan or echocardiogram, ECG

PREMEDICATIONS:

- Antiemetic protocol for chemotherapy with low emetogenicity (see SCNAUSEA)

TREATMENT:

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

Drug	Dose	BC Cancer Administration Guideline
olaparib	300 mg twice daily*	PO
abiraterone	1000 mg once daily	
predniSONE**	10 mg once daily or 5 mg twice daily OR 5 mg daily***	

* olaparib tablets must be dispensed in original manufacturer containers with supplied desiccant

** 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

- Treat continuously until disease progression or unacceptable toxicity. One cycle consists of 4 weeks (30 days). Dispense 30 day supply with each physician visit

DOSE MODIFICATIONS:

Olaparib dose levels:

Dose level 0 (100%)	Dose level -1	Dose level -2
300 mg PO BID	250 mg PO BID	200 mg PO BID

1. Hematology

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 100	100% of previous cycle's dose
Less than 1.0	or	Less than 100	Delay until recovery, then re-start at a reduced dose level

2. Renal dysfunction:

- olaparib: If CrCl falls between 31 to 50 mL/min, reduce dose to 200 mg PO twice daily. Treatment with olaparib is not recommended if CrCl is less than or equal to 30 mL/min
- abiraterone/steroid: No dosage adjustment necessary

3. Hepatic dysfunction:

- olaparib: no modifications required for mild to moderate impairment (Child-Pugh A or B). Use in severe impairment (Child-Pugh C) is not recommended as there is no data
- steroid: no modifications required
- abiraterone: adjust based on the following table:

Total bilirubin		ALT	Abiraterone 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

4. Hypokalemia management (abiraterone):

- 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 mmol/L (greater than 4 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)
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	

5. Drug interactions:

- olaparib dose adjustment may be required for concurrent use of CYP3A inhibitors. See BC Cancer Drug Manual

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Anemia**: In patients with hemoglobin less than 90 g/L, consider correction of anemia prior to beginning/continuing olaparib treatment.
3. **Fluid retention:** Fluid retention during abiraterone treatment 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.
4. **Cardiovascular disease**: Caution using abiraterone 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).
5. **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.
6. **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).
7. **Drug interactions**: Olaparib is primarily metabolized by CYP3A. Concurrent use of moderate or strong CYP3A inhibitors and strong CYP3A inducers should be avoided. If concurrent use cannot be avoided, dose modification may be required.
8. **Venous Thromboembolic Events (VTEs)** including fatal pulmonary embolism have been reported in patients receiving olaparib with abiraterone for metastatic castration-resistant prostate cancer. Monitor during treatment and treat as clinically indicated.

Call Dr. Lavoie or tumour group delegate at (250) 519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evid. 2022 Sep;1(9):EVIDoa2200043.
2. Olaparib (Lynparza) Reimbursement Recommendation. Canadian Journal of Health Technologies. Feb 2024
3. CADTH Reimbursement Review. Provisional Funding Algorithm: Prostate cancer. Mar 2024