BC Cancer Protocol Summary of Treatment for Metastatic Castration-Resistant Prostate Cancer using niraparib-abiraterone and predniSONE

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

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 niraparib-abiraterone 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
- Blood pressure optimized prior to starting treatment
  Adequate hematological, renal and hepatic function

Notes:

- Patients currently being treated with abiraterone per protocol UGUPABI for a maximum of 4 months without progression can transition to UGUPAVNABI if all other eligibility criteria are met
- Prior treatment with UGUPAJABI is permitted if no progression during abiraterone, and if 6 months or more from completion of UGUPAJABI
- This protocol is not funded in combination with anticancer drugs other than androgen deprivation therapy

EXCLUSIONS:

Patients must not have:

- Clinical suspicion of myelodysplasia,
- Prior treatment with or progression on poly-(ADP ribose) polymerase (PARP) inhibitor for mCRPC (e.g., olaparib or niraparib)
- 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 100 mmHg)

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, PSA, testosterone, blood pressure
- Baseline if clinically indicated: total protein, albumin, GGT, LDH, TSH, calcium, INR, MUGA scan or echocardiogram, ECG
- Prior to each cycle: CBC & Diff, total bilirubin, ALT, alkaline phosphatase, creatinine, random glucose, sodium, potassium, blood pressure, PSA
- Cycle 1, Days 8 and 22: CBC & Diff
- Cycles 1 to 3, Day 15: CBC & Diff, total bilirubin, ALT, alkaline phosphatase, potassium
- Cycles 1 and 2: Weekly blood pressure*
- If clinically indicated (any cycle):
    - Weekly CBC & Diff
    - Day 15 total bilirubin, ALT, and alkaline phosphatase
- If clinically indicated: total protein, albumin, GGT, LDH, TSH, calcium, INR, testosterone, triglycerides, total cholesterol, blood pressure, MUGA scan or echocardiogram, ECG

* Self-monitoring by patient is acceptable. See Precautions.

PREMEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
niraparib-abiraterone	200 mg-1000 mg once daily	PO
predniSONE**	10 mg once daily OR 5 mg twice daily OR 5 mg once daily***	

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

** 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:

- Note: niraparib-abiraterone tablets are available in two strengths. Dose levels vary depending on toxicity. Use correct tablet strength for respective dose modifications
  - niraparib-abiraterone 100 mg-500 mg tablet
  - niraparib-abiraterone 50 mg-500 mg tablet

1. Hematological (anemia, neutropenia, and thrombocytopenia):

- Dose levels are different for hematological than for hepatotoxicity toxicity
- Dose levels for hematological toxicity:

Dose level 0 niraparib-abiraterone	Dose level -1 hematological toxicity niraparib-abiraterone
200 mg-1000 mg once daily (Each dose = TWO tablets of niraparib-abiraterone 100mg - 500mg tablet)	100 mg-1000 mg once daily (Each dose = TWO tablets of niraparib-abiraterone 50mg - 500mg tablet)

- Note: predniSONE or dexamethasone no dose modifications required
- Discontinue niraparib-abiraterone if severe persistent hematological toxicity has not resolved within 28 days of interruption

Anemia:

- Cycle 1: may initiate treatment if Hgb 90 g/L or greater
- During treatment:

<table>
<tr><th>Grade</th><th>Description</th><th colspan="2">Niraparib-abiraterone Dose/Management</th></tr>
<tr><td>1</td><td>Hgb lower level of normal to 100 g/L</td><td colspan="2">• Continue at same dose
• Consider weekly CBC & Diff</td></tr>
<tr><td rowspan="2">2</td><td rowspan="2">Hgb less than 100 to 80 g/L</td><td colspan="2">If baseline Hgb was 100 g/L or greater:
• Continue at same dose
• Weekly CBC & Diff for 4 weeks</td></tr>
<tr><td colspan="2">If baseline Hgb was less than 100 g/L:
• Continue at same dose
• No weekly CBC & Diff required</td></tr>
<tr><td>3 or greater, first occurrence</td><td>Hgb less than 80 g/L; transfusion indicated</td><td colspan="2">• Hold niraparib-abiraterone
• CBC & Diff at least weekly until Hgb 80 or greater, then
• Restart at same dose
• Consider dose reduction to Dose level - 1 (100 mg-1000 mg once daily) if anemia recurs after restarting</td></tr>
<tr><td rowspan="2">3 or greater, second occurrence</td><td rowspan="2">Hgb less than 80 g/L; transfusion indicated</td><td>Current Dose level: 0</td><td>• Hold niraparib-abiraterone
• CBC & Diff at least weekly until Hgb 80 or greater, then
• Restart at Dose level -1 (100 mg-1000 mg once daily)
• Weekly CBC & Diff for 4 weeks after restarting</td></tr>
<tr><td>Current Dose level: -1 (100 mg-1000 mg once daily)</td><td>Consider discontinuation</td></tr>
<tr><td>3 or greater, third occurrence</td><td>Hgb less than 80 g/L; transfusion indicated</td><td colspan="2">Discontinue</td></tr>
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Neutropenia and Thrombocytopenia:

Grade	Description			Management	
	ANC (x 10^9/L)		Platelets (x 10^9/L)		
1	1.5 or greater	and	75 or greater	• Continue niraparib-abiraterone at same dose • Consider weekly CBC & Diff	
2	1.0 to less than 1.5	or	50 to less than 75	• Consider holding niraparib-abiraterone • CBC & Diff at least weekly until ANC 1.5 and platelets 75, then • Restart niraparib-abiraterone at same dose • Weekly CBC & Diff for 4 weeks	
3 or greater, first occurrence	0.5 to less than 1.0	or	25 to less than 50	• Hold niraparib-abiraterone • CBC & Diff at least weekly until ANC 1.5 and platelets 75, then • Restart niraparib-abiraterone at either same dose or Dose level -1 (100 mg-1000 mg once daily) per provider discretion* • Weekly CBC & Diff for 4 weeks	
3 or greater, second occurrence	0.5 to less than 1.0	or	25 to less than 50	Current Dose level: 0	• Hold niraparib-abiraterone • CBC & Diff at least weekly until ANC 1.5 and platelets 75, then • Restart niraparib-abiraterone at Dose level -1 • Weekly CBC & Diff for 4 weeks
				Current Dose level: -1 (100 mg-1000 mg once daily)	Consider discontinuation of niraparib-abiraterone
3 or greater, third occurrence	0.5 to less than 1.0	or	25 to less than 50	Discontinue niraparib-abiraterone	

* e.g., consider dose reduction if platelet transfusion required, or for febrile neutropenia

2. Hepatotoxicity during treatment:

- Dose levels are different for hepatotoxicity than for hematological toxicity
- Dose levels for hepatotoxicity:

Dose level 0 niraparib-abiraterone	Dose level -1 hepatotoxicity niraparib-abiraterone
200 mg-1000 mg once daily (Each dose = TWO tablets of niraparib-abiraterone 100mg – 500mg tablet)	100 mg-500 mg once daily (Each dose = ONE tablet of niraparib-abiraterone 100mg – 500mg tablet)

- predniSONE or dexamethasone: no dose modifications required
- niraparib-abiraterone:

ALT and/or AST		Total bilirubin	Management
Greater than 5 x ULN	or	Greater than 3 x ULN	• Hold niraparib-abiraterone until recovery to ALT (and AST, if ordered) 2.5 x ULN or less and total bilirubin 1.5 x ULN or less, then • Restart at Dose level -1 (100 mg-500 mg once daily), with monitoring of liver function tests every 2 weeks minimum for 3 months, then monthly thereafter • If hepatotoxicity recurs at lower dose, discontinue
20 x ULN or greater	-	-	Discontinue niraparib-abiraterone
ALT greater than 3 x ULN	and	Greater than 2 X ULN	If no biliary obstruction or other cause for elevation, discontinue niraparib-abiraterone

3. Hypokalemia:

- 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	Hold 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	Hold until potassium corrected. Initiate oral or IV potassium and cardiac monitoring. Consider monitoring magnesium and replacement if needed.	
Less than 2.5	Grade 4	Hold until potassium corrected. Initiate oral or IV potassium and cardiac monitoring. Consider monitoring magnesium and replacement if needed	

PRECAUTIONS:

1. **Hematologic toxicities** including **anemia, neutropenia, and thrombocytopenia** may occur during treatment with niraparib-abiraterone. Most events occur during the first two months of treatment. In patients with hemoglobin less than 90 g/L, consider correction of anemia prior to initiating niraparib-abiraterone treatment. Use caution when combining with other drugs that can reduce platelet counts, due to risk of thrombocytopenia. Monitor for hematologic toxicity throughout treatment. Permanently discontinue niraparib-abiraterone if severe hematologic toxicity does not resolve within four weeks of treatment interruption. Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. Abiraterone can cause **mineralocorticoid** and **cardiovascular effects** such as **hypertension, hypokalemia,** and **fluid retention.** Patients with pre-existing cardiovascular disease (e.g., myocardial infarction, thrombosis, unstable angina or arrythmia) are at increased risk while on treatment with niraparib-abiraterone. QTc prolongation has been reported in patients with hypokalemia during niraparib-abiraterone treatment. Mineralocorticoid effects are driven by compensatory adrenocorticotropic hormone (ACTH) increases. Concomitant use of corticosteroids during treatment suppresses ACTH drive, which reduces the incidence and severity of mineralocorticoid effects. Hypokalemia should be corrected prior to treatment. Monitor for adrenal insufficiency during and after infection or stress; increased doses of corticosteroids may be required. Monitor for adrenal insufficiency if corticosteroids are withdrawn.
3. **Hypertension** is a side effect of both niraparib and abiraterone and may occur early in treatment. Hypertension should be controlled prior to starting treatment. Monitor blood pressure during treatment. Blood pressure monitoring can be done by self-monitoring or by primary care provider, provided it is reviewed by treating clinician at each visit. Patients with history of cardiovascular disease may require more frequent monitoring.

   Temporary suspension of niraparib-abiraterone is recommended for patients with hypertension greater than 160 mmHg systolic or greater than 100 mmHg diastolic. Permanently discontinue niraparib-abiraterone for hypertensive crisis.
4. **Hepatic Dysfunction:** Severe hepatotoxicity with marked increases in liver enzymes has been reported with niraparib-abiraterone. Abiraterone monotherapy has been associated with serious hepatotoxicity such as fulminant hepatitis and active liver failure, including fatal cases. There are no data on the use of niraparib-abiraterone in patients with moderate or severe hepatic impairment. Do not use in patients with Child-Pugh Class C liver impairment. Regular monitoring of serum transaminases and bilirubin during treatment is recommended.
5. **Drug interactions** can occur during treatment with niraparib-abiraterone. Levels of niraparib-abiraterone or medications given concurrently with niraparib-abiraterone may be impacted. Action may be required. See BC Cancer Drug Manual.
6. **Venous Thromboembolic Events** (VTEs) including pulmonary embolism have been reported in patients receiving niraparib-abiraterone for metastatic castration-resistant prostate cancer. Monitor during treatment and treat as clinically indicated.
7. **Posterior Reversible Encephalopathy Syndrome** (PRES) has been reported in patients receiving niraparib. Symptoms of PRES may include seizures, headache, altered mental status, visual disturbance, and cortical blindness. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. If PRES is confirmed during treatment, permanently discontinue niraparib-abiraterone.
8. **Secondary malignancies** including **myelodysplastic syndrome/acute myeloid leukemia** (MDS/AML) have been reported with PARP inhibitor treatment. For suspected MDS/AML or prolonged hematological toxicities, referral to hematologist is recommended. Permanently discontinue niraparib-abiraterone if MDS/AML is confirmed.

Call Dr. Krista Noonan or tumour group delegate at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

References:

1. Chi KN, Rathkopf D, Smith MR, et al; MAGNITUDE Principal Investigators. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2023 Jun 20;41(18):3339-3351.
2. Niraparib and Abiraterone Acetate (Akeega) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies. Feb 2024; 4(2):1-24
3. Canada's Drug Agency (CDA-AMC) Provisional Funding Algorithm: Prostate Cancer (Draft). 5 Dec 2024