REVIEW

# *Side effect management algorithms for niraparib/abiraterone acetate in prostate cancer*

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***Introduction:*** *Niraparib, a PARP1/2 inhibitor, is newly approved in combination with abiraterone acetate (AA) plus prednisone or prednisolone (niraparib/AA+P) for the treatment of adult patients with BRCA-mutated, treatment-naïve metastatic castration resistant prostate cancer (mCRPC). Detailed guidance beyond the prescribing information may be helpful in managing the side effect profile and dosing practicalities of this combination therapy.*

***Materials and methods:*** *A panel of specialists convened to design management algorithms for four common niraparib/AA+P treatment-related adverse events (AEs) in mCRPC; anemia, thrombocytopenia, hypertension, and nausea. The algorithms build on Health Canada-approved prescribing information to highlight practical considerations related to monitoring, treatment adjustment, and specialist referral to support clinical practice.*

***Results:*** *The panel's recommendations were largely aligned with the niraparib/AA+P product monograph. Single agent AA+P followed by reintroduction niraparib/AA+P using the low dose formulation of niraparib/AA were common strategies for managing higher grade AE's. Recommendations for hypertension management were expanded to include a sequence of anti-hypertensive medication trials prior to a change in anti-cancer therapy, where feasible.*

***Conclusion:*** *These algorithms are intended to provide practical assistance to Canadian clinicians managing the most common AEs encountered with the novel combination, niraparib/AA+P, for mCRPC.*

**Key Words:** PARP inhibitor, niraparib, adverse events, prostatic neoplasms, castration-resistant, thrombocytopenia, hypertension, anemia, nausea, algorithms

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## Introduction

Prostate cancer is the most common cancer among men in Canada and metastatic castration-resistant prostate cancer (mCRPC), an advanced stage, has a real world median survival of ~29 months.[1,2] In mCRPC, approximately 20%-30% of tumors harbor germline or somatic alterations in homologous recombination repair (HRR)-associated genes, including BRCA1/2,[3-5] leading to poor prognosis and resistance to standard systemic therapies.[6-13]

Poly (ADP-ribose) polymerase inhibitors (PARPi's) were designed to inhibit DNA repair and promote accumulation of unrepaired DNA double-strand breaks in HRR deficient cells, leading to cancer cell apoptosis and have been used for the treatment of mCRPC for several years.[9,14,15]

Next generation mCRPC systemic treatment involves the simultaneous targeting of DNA repair and androgen receptor (AR) signalling.[16-19] Recently, two PARP inhibitors, first niraparib and later olaparib, have been approved by Health Canada in combination with abiraterone acetate plus prednisone or prednisolone (AA+P), an AR signaling inhibitor for adult patients with deleterious or suspected deleterious BRCA-mutated, treatment-naïve mCRPC.[15,18-20] Niraparib/AA is available in a combination 100 mg/500 mg tablet for standard dosing (2 tablets/day) and a low strength 50 mg/500 mg tablet for dose reductions (2 tablets/day), administered with 10 mg of P daily.[20]

While the types of treatment-related adverse effects (AEs) are generally similar between PARPis, the frequency and severity can differ between agents and across tumor types.[15,20] Furthermore, combination with an AR inhibitor and P can impact AE frequency and complicate the attribution of cause for AEs.[15,20] In the MAGNITUDE study, anemia, hypertension, constipation, fatigue, nausea, and thrombocytopenia were experienced by > 20% of patients with mCRPC receiving niraparib/AA+P.[18,19] Anemia, hypertension, thrombocytopenia and neutropenia were the most frequently observed Grade (G) ≥ 3 AEs.[18,19] AEs during treatment with niraparib/AA+P led to dose interruptions in 49.1%, reductions in 20.3%, and permanent discontinuation in 15.1% of patients.[19] Similar patterns were observed with olaparib/AA and talazoparib/enzalutamide.[16,17]

AE management is critical to maximizing the potential benefits of targeted therapy and optimizing patient quality of life (QoL).[21] While the product monograph (PM) provides recommendations regarding AE management,[20] clinical implementation is often more nuanced, considering patient/disease characteristics and preferences, practicalities of clinic visits, and access to specialty consult.

This guidance aims to provide practical recommendations that build on to the niraparib/AA PM to assist Canadian clinicians in managing four AEs (anemia, thrombocytopenia, hypertension, and nausea) common with this novel combination in mCRPC.

## Methods

### *Organization, panel composition, planning and coordination*

A team of three medical and urologic oncologists convened in 2022 to review clinical data for the combination of niraparib/AA+P and discuss AE management. Draft algorithms were developed for the management of four treatment-related AEs: anemia, thrombocytopenia, hypertension, and nausea. These AEs were identified, from the first interim analysis of the MAGNITUDE study and clinical experience, as the most common and commonly treatment-limiting.[18]

Each algorithm was developed to align with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 definitions of severity (Grade 1-5, see Table 1.[22] Following the release of the Health Canada-approved PM, a broader group of subject matter experts was convened to adapt the algorithms to align with the PM (August 2023).[20] This group, "the panel", included the authors; a medical oncologist (Dr. Ko), two urologic oncologists (Dr. Lattouf and Dr. Gotto), and two cardiologists (Dr. Davis and Dr. Constance). The panel then proceeded independently to refine and finalize the algorithms.

### *Review and development of recommendations*

For each selected AE, the draft algorithm was reviewed alongside the PM recommendation before, during, and after the online meeting and the algorithms were refined to include detailed monitoring and niraparib/AA+P dose adjustment guidance, as well as identify triggers for specialist consultation. Ancillary guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology / Hematology (ASCO/ASH), European Society for Medical Oncology (ESMO), Association for the Advancement of Blood & Biotherapies (AABB), Choosing Wisely Canada, and Hypertension Canada were reviewed by the panel and referenced where appropriate.

The panel reached consensus on each algorithm with a population (i.e., Canadian patients with mCRPC) perspective in mind. If needed, consensus was achieved by voting (an 80% majority required for a strong recommendation) and is noted in the text. The algorithms were finalized in November 2023. Notable variances from the PM are noted where applicable. It was assumed that patients would have access to all mentioned medications and that the proprietary niraparib/AA combination (in either regular dose: two 100 mg/500 mg tablets/day, or low dose: two 50 mg/500 mg tablets/day) would be used, according to its label.[20]

TABLE 1. **NCI CTCAE v5.0 event/measure description by grade**[22]

| Event / Measure | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 | GRADE 5 |
|---|---|---|---|---|---|
| **Anemia** | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated | Life-threatening consequences; urgent intervention indicated | Death |
| **Platelet count decreased (Thrombocytopenia)** | <LLN - 75,000/mm$^3$; <LLN - 75.0 x 10e9 /L | <75,000 - 50,000/mm$^3$; <75.0 - 50.0 x 10e9 /L | <50,000 - 25,000/mm$^3$; <50.0 - 25.0 x 10e9 /L | <25,000/mm$^3$; <25.0 x 10e9 /L | - |
| **Hypertension** | **Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; | **Adult:** Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated; | **Adult:** Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; | **Adult:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | Death |
| **Nausea** | Loss of appetite without alteration in eating habits | Oral intake decreased without significant weight loss, dehydration or malnutrition | Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated | - | - |

Consideration of outcomes, interventions, values, preferences and their relative importance to patients with mCRPC was gathered indirectly from published literature. In addition, feasibility within the current Canadian healthcare system was considered (e.g., ease of specialist consultation for a community oncologist). The panel formulated the management algorithms based on patient outcomes of importance and practical feasibility of implementation. This report was structured based on the RIGHT-Ad@pt guideline checklist.[23]

### *How to use these recommendations*

This guidance is intended to supplement the niraparib/AA PM and help clinicians make decisions about AE management.

## Results/recommendations

The panel rated anemia, thrombocytopenia, hypertension, and nausea as critical AEs that could impact treatment delivery and the optimization of outcomes for patients with mCRPC treated with niraparib/AA. Prioritized outcomes were maximized survival benefit, followed by QoL and delay in symptoms, in alignment with national guidelines for the treatment of mCRPC and a patient-related survey.[24] The panel developed algorithms outlining the treatment, monitoring, and consultation recommendations for each of the four prioritized AEs: anemia, Figure 1, thrombocytopenia, Figure 2, hypertension, Figure 3, and nausea, Figure 4.

## Anemia

Anemia is a common occurrence for cancer patients and its effects can be far reaching, including detriments to performance status, QoL, and worsened comorbid conditions.[25] Guidelines recommend prompt evaluation (including iron, nutritional, and hemolysis studies) for possible causes of anemia when hemoglobin (Hgb) level is ≤ 110 g/L.[26,27] Importantly, Hgb levels are not the only indicators of anemia severity, since age and comorbid conditions can influence a patient's sensitivity to anemia and its resulting symptoms.[25] Red blood cell (RBC) transfusion, iron or other micronutrient supplementation, and use of erythropoietic agents may be indicated depending on the etiology.[26,28]

The MAGNITUDE study excluded patients with baseline Hgb counts < 90 g/L.[18] Anemia was the most frequent AE (46.2% G1-4; and 28.3% G3) observed in mCRPC patients with HRR gene mutations receiving niraparib/AA+P, but was rarely severe (1.4% G4).[18,20] Median time from first dose to first onset of anemia was 57 days; however, 50% of those patients had ongoing, low-grade, persistent anemia.[20] Anemia led to drug discontinuation in 2.4% of patients receiving niraparib/AA+P.[18] The PM thus recommends complete blood count (CBC) tests weekly for the first month, weekly to bi-weekly for the next two months, then monthly for the first year, and then every other month for the remainder of treatment.[20] Approximately 22% and 13% of patients in the MAGNITUDE study had dose interruptions and dose reductions of niraparib/AA due to anemia.[20] Twenty-six percent of patients received at least one anemia-related transfusion.[20] All-grade anemia occurred in 11% of patients receiving AA+P.[29]

### *Anemia guidance, Figure 1*

G1/2 anemia: Clinicians are advised to implement weekly monitoring upon findings of G1/2 anemia, with no change in treatment (dose interruption/

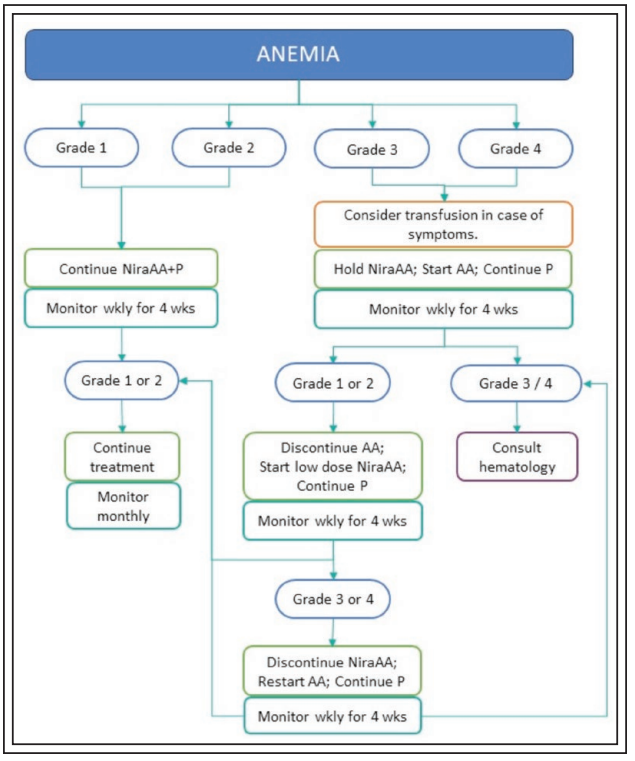


**Figure 1.** Suggested management algorithm for the occurrence of anemia during niraparib/AA+P treatment in mCRPC. These recommendations are based on common clinical scenarios and should be followed at the clinician's discretion, with the individual patient contemplated.

AA = abiraterone acetate single agent; NiraAA = niraparib/AA combination agent; P = prednisone or prednisolone; wkly = weekly; wks = weeks.

reduction). After four weeks of stability or decrease in severity of anemia, monitoring can be extended to monthly intervals.

G3/4 anemia: The panel recommends RBC transfusion in symptomatic patients, in line with current management guidelines, while adhering to guidance on limiting blood product use.[26,30,31] In addition, some guidelines (AABB, ESMO)[28,32] indicate transfusion for a specific Hgb level (< 70-80 g/L) and/or comorbidity (e.g., cardiovascular disease), whereas NCCN[26] highlights that no single target is appropriate for all cases and that transfusion risk/benefit should be balanced on an individual basis. In tandem with the decision to transfuse, niraparib/AA should be held, AA started, and P continued. Treatment-induced anemia is expected to resolve or improve within four weeks, after which a decision can be made: if G2 or better, to stop AA and introduce low dose niraparib/AA with continued weekly monitoring. If unresolved, consultation with hematology is recommended. If anemia progresses to G3 or worse following introduction of low dose niraparib/AA, the panel recommends discontinuation of niraparib/AA and a retrial of AA+P with weekly monitoring for 4 weeks (and hematology consultation if G3/4 anemia persists).

These recommendations largely align with the niraparib/AA PM,[20] with increased detail regarding supportive care provision and monitoring duration.

## Thrombocytopenia

Thrombocytopenia is a common AE experienced by cancer patients. It is typically associated with chemotherapy, but can also be caused by marrow infiltration, infection, liver dysfunction, or other drugs.[33,34] Low platelet count, particularly < 25.0 x $10^9$ /L, increases the risk of major bleeding events.[35] Drug-related thrombocytopenia can be managed by modifying cancer treatment dose/regimen or platelet transfusion, as indicated.[34] Importantly, modification of existing antithrombotic therapy must be undertaken with careful consideration and guidelines should be followed with care in patients on concomitant antithrombotic or anticoagulant therapies.[35]

In the MAGNITUDE study, which excluded patients with baseline platelet counts < 100.0 x $10^9$ cells/L, the incidence of G3 and G4 thrombocytopenia was 2.8% and 3.8%, respectively, in mCRPC patients with HRR gene mutations receiving niraparib/AA+P.[18] Median time from first dose to first onset was 43 days.[20] The PM thus recommends frequent CBC testing as outlined for anemia surveillance.[20] Furthermore, the use of medicinal products known to reduce platelet counts are cautioned with niraparib/AA.[20] In the MAGNITUDE study, thrombocytopenia was managed with dose modification (interruption 9.4% and reduction in 2.8%) and platelet transfusion (2.4%), with discontinuation occurring in 0.5% of patients.[18,20] A concurrent bleeding event occurred in 1.4% of patients.[20] Thrombocytopenia is not a common AE associated with AA+P.[29]

### *Thrombocytopenia guidance, Figure 2*

G1 thrombocytopenia: Clinicians are advised to implement weekly monitoring with no change in treatment. After four weeks of stability or resolution, monitoring can be extended to monthly intervals.

G2/3 thrombocytopenia: Niraparib/AA should be held, AA started, and P continued. Thrombocytopenia is expected to resolve or improve within 2-4 weeks. If it resolves to G1, stop AA and introduce low dose niraparib/AA with continued weekly monitoring. If

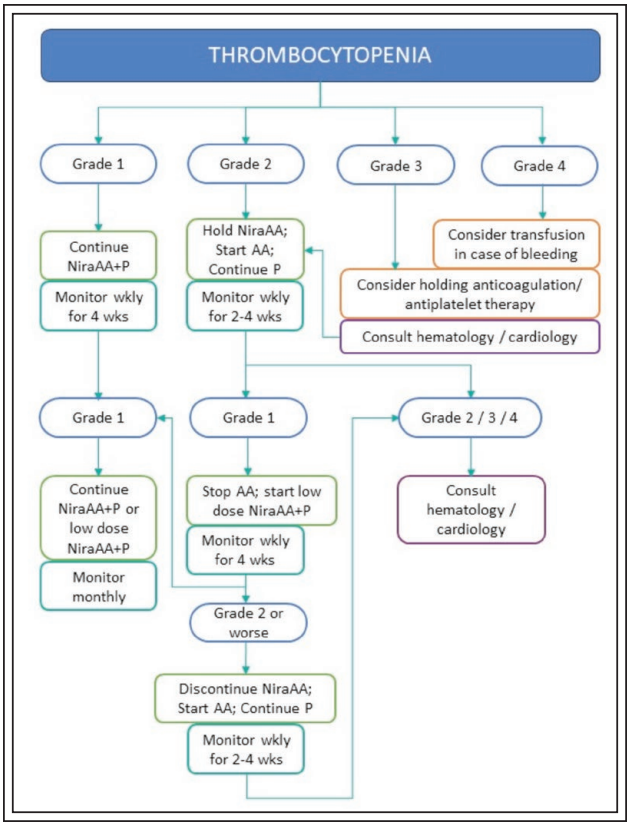


**Figure 2.** Suggested management algorithm for the occurrence of thrombocytopenia during niraparib/AA+P treatment in mCRPC. These recommendations are based on common clinical scenarios and should be followed at the clinician's discretion, with the individual patient contemplated.

AA = abiraterone acetate single agent; NiraAA = niraparib/AA combination agent; P = prednisone or prednisolone; wkly = weekly; wks = weeks.

thrombocytopenia progresses to G2 or worse following low dose niraparib/AA, the panel recommends discontinuation of niraparib/AA+P and retrial of AA+P. If thrombocytopenia continues at G ≥ 2 four weeks after a trial with AA+P, hematology consult is recommended.

In the case of G4 thrombocytopenia, the panel recommends transfusion if bleeding or if platelet count falls to < 10.0 x $10^9$ /L, aligned with recent management guidelines,[36,37] and then treatment modification and monitoring aligned with G2/3 recommendations. Consideration should be given to modifying concomitant anticoagulation/antiplatelet therapy, in consultation with hematology and/or cardiology, for G3/4 thrombocytopenia.

In contrast to the niraparib/AA PM, the panel advises against restarting niraparib/AA at full dose in the event of resolved G ≥ 2 thrombocytopenia. Since there is no reasonable intervention to support platelet recovery, restarting full dose niraparib/AA is expected to lead to a recurrence of treatment-related thrombocytopenia. In line with the PM, niraparib/AA discontinuation is recommended after a trial of low dose niraparib/AA and recurrence of G ≥ 3 thrombocytopenia.

## Hypertension

Hypertension is an AE that may be related to both niraparib/AA and AA.[18,29] In the pivotal phase III trial of niraparib/AA+P, mCRPC patients with uncontrolled hypertension (persistent systolic blood pressure [BP] ≥ 160 mmHg or diastolic BP ≥ 100 mmHg) at baseline were excluded.[18] Still, 31.1% and 14.6% of patients experienced G1-3 and G3 hypertension, respectively.[18] The median time to onset was 56 days.[20] There were no hypertensive crises or posterior reversible encephalopathy syndrome events in the MAGNITUDE study, and no patients discontinued treatment due to hypertension.[20] In adults with uncomplicated hypertension, first-line treatment may include angiotensin converting enzyme inhibitors (ACEi's), angiotensin receptor blockers, calcium channel blockers (CCBs), and longer-acting thiazide-like diuretics.[38]

### *Hypertension guidance, Figure 3*

Management of hypertension begins with a confirmation of measurement/diagnosis. In all cases of suspected or in-office elevated BP measures (systolic BP ≥ 120 mmHg or diastolic BP ≥ 80 mmHg), out-of-office measurement (either 24-hour ambulatory or home BP monitoring) is recommended to confirm true elevation.[38] Grading in this guidance refers to the absolute BP measurements noted by CTCAE for each grade (not the associated management). The algorithm

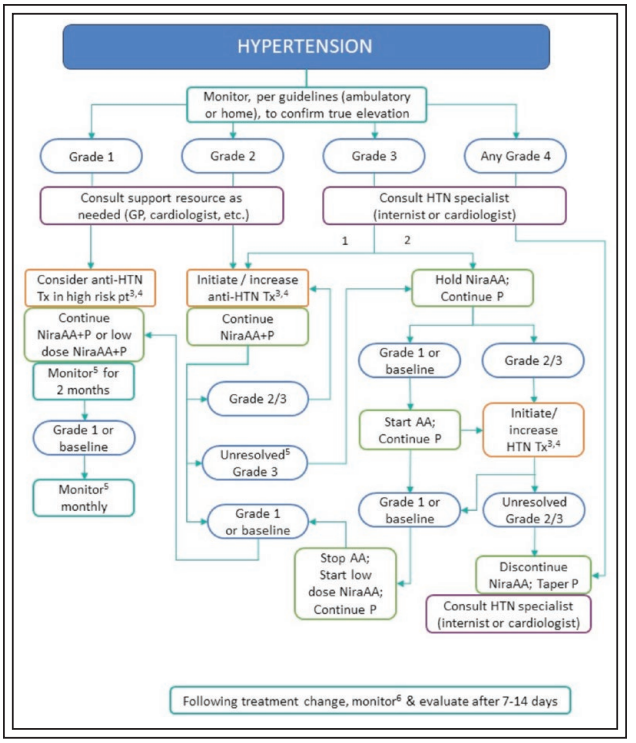


**Figure 3.** Suggested management algorithm for the occurrence of hypertension during niraparib/AA+P treatment in mCRPC. These recommendations are based on common clinical scenarios and should be followed at the clinician's discretion, with the individual patient contemplated.

[1]this arm assumes intervention with hypertension medications can begin immediately (i.e., expertise/support are available).
[2]this arm assumes intervention with hypertension medications would be delayed (i.e., expertise/support are not available).
[3]per guidelines, caution re: drug-drug interactions (CCB first, ACEi next).
[4]refer to hypertension specialist if already on ≥ 4 agents.
[5]considered unresolved following two attempted HTN agent initiations / dose increases without improvement.
[6]per guidelines; ambulatory or at home at least 2x/wk; target Grade 1 (consider target SBP <120 in patients at high CV risk).
AA = abiraterone acetate single agent; HTN = hypertension; GP = general practitioner; NiraAA = niraparib/AA combination agent; P = prednisone or prednisolone; pt = patient; Tx = treatment; wkly = weekly; wks = weeks.

for hypertension management is both complicated and relieved by the available, effective, and relatively low risk antihypertensive treatment options. In addition, cancer and its treatment are complicating factors for hypertension management with polypharmacy and competing risks relevant considerations. As such, the panel recommends CCBs first, followed by ACEi's for hypertension control, unless there are compelling indications for another agent.[38] Following any treatment

change, monitoring should continue, per guidelines, allowing for 7-14 days of observation before further adjustments are made. The target for all interventions is achievement of G1 or better (consider target SBP < 120 mm Hg in patients at high risk and over 50 years of age).[38]

The panel assumed that most medical oncologists would have capacity to manage, or time to obtain specialist consultation on, G1/2 hypertension according to national guidelines.[38] In more urgent cases (i.e., some G3 or all G4 hypertension), the panel offers two scenarios. The panel recommends the first line of intervention for G1-3 events be the initiation or up-titration of antihypertensive therapy before a change to the niraparib/AA+P treatment. Importantly, if it is not within the capacity of the clinician to treat the hypertension, G3 hypertension should be addressed by the temporary discontinuation of niraparib/AA.

G1 hypertension: Clinicians are advised to consider antihypertensive treatment for high-risk patients, per guideline recommendations,[38] while continuing niraparib/AA+P and monitoring biweekly for two months. If G1 is stable or improved, monitoring can extend to monthly intervals.

G2/3 hypertension: Niraparib/AA+P can be continued alongside intensified antihypertensive therapy, according to guideline recommendations.[38] G2/3 hypertension would be considered unresolved following two attempted hypertension agent initiations / dose increases without improvement. In the case of unresolved hypertension, the panel recommends holding niraparib/AA and continuing P. If hypertension resolves to G1 or baseline, a trial with AA+P should be undertaken. If this improvement is maintained, an attempt to introduce low dose niraparib/AA can be made. If niraparib/AA was held immediately following G3 hypertension, an attempt should be made to initiate or up-titrate antihypertensive medications as soon as possible and then reintroduce AA or low dose niraparib/AA, depending on sequence, if hypertension can be controlled.

In the case of G4 hypertension, immediate discontinuation of niraparib/AA is warranted and consultation with a hypertension specialist (internist or cardiologist) should occur urgently. Discontinuation and consultation are also suggested for cases that are resistant to treatment interventions.

## Nausea

Nausea and vomiting are common side effects of cytotoxic cancer therapies and significantly impact patient QoL.[39] They are among the most feared of cancer treatment side effects and may decrease treatment adherence.[39] Recommendations for emesis treatment concurrent with the use of low or moderate emetic risk anti-cancer therapies vary by guideline, from prophylactic to as-needed prescription of 5-HT3 (serotonin) receptor antagonists and/or dexamethasone, metoclopramide, prochlorperazine, and dopamine receptor antagonist.[39,40] Therapies with a moderate to high emetic risk, per NCCN guidelines,[40] have a frequency of occurrence ≥ 30%, which is higher than the observed rate of all grade nausea in the niraparib/AA+P arm of the MAGNITUDE trial (23.6%).[18] The occurrence of G3 nausea in mCRPC patients treated with niraparib/AA+P was 0.5%.[18]

### *Nausea guidance, Figure 4*

For all grades of nausea, clinicians are encouraged to offer supportive care aligned with NCCN guidelines.[40]

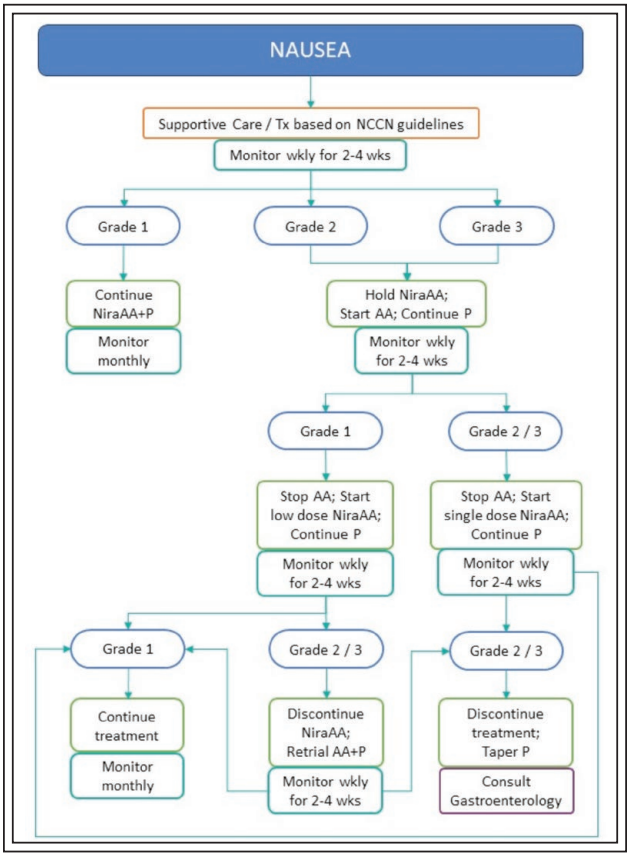


**Figure 4.** Suggested management algorithm for the occurrence of nausea during niraparib/AA+P treatment in mCRPC. These recommendations are based on common clinical scenarios and should be followed at the clinician's discretion, with the individual patient contemplated.

AA = abiraterone acetate single agent; NiraAA = niraparib/AA combination agent; P = prednisone or prednisolone; Tx = treatment; wks = weeks.

Since the risk category for niraparib/AA-induced nausea is unclear, the panel recommends serious consideration of prior experience with antiemetics and patient risk factors when deciding how aggressive antiemetic management should be.[40]

For G1 nausea: Monitor for symptoms monthly with no change to anticancer treatment.

G2/3 nausea: Niraparib/AA should be held, AA started, and P continued. Treatment-induced nausea is expected to resolve or improve within 4 weeks, after which: if G1 or resolved, stop AA and trial low dose niraparib/AA. If the patient experiences G2/3 nausea following low dose niraparib/AA, the panel recommends discontinuation of low dose niraparib/AA and a retrial of AA. Alternatively, if unresolved (G2/3), after starting AA, stop AA and trial single dose (50/500 mg) niraparib/AA.

Persistent G2/3 nausea warrants treatment discontinuation (taper P) and consultation with gastroenterology.

These recommendations are more conservative than the PM, which simply recommends discontinuation of niraparib/AA after a G ≥ 3 event persists for more than 28 days.[20] This likely reflects the generalized nature of recommendations for non-hematologic AEs in the PM (not specific to nausea), and the severity of G3 and lack of G4 nausea according to CTCAE categorizations.[22] The panel recognizes that anti-emetic management can be critical to anticancer treatment success, but that if all interventions are unsuccessful, continued nausea at even a G2 level is expected to impact patient QoL, treatment compliance, and, consequently, long term efficacy.

## Discussion/summary

After a thorough review of the niraparib/AA+P PM and management guidelines related to four key AEs associated with its use in mCRPC, the panel detailed management considerations for each CTCAE event grade and anticipated outcome. These recommendations generally aligned with those in the PM, but provided increased guidance on their implementation by highlighting relevant guidelines as well as points at which specialist consultation might be practical or warranted.

### *Limitations*

The algorithms outlined cannot account for the nuance of each patient scenario. In addition, real world experience with niraparib/AA+P and emerging knowledge or advances in care may impact the recommendations made here. The algorithms were not shared for external review, so their content is subject to any inherent biases of the panel and assumptions made based on published literature (e.g., patient values). Finally, while some practicalities of the healthcare system and clinician capacity were considered, assumptions were made regarding unrestricted access to monitoring and treatments.

## Conclusion

Niraparib/AA+P is a novel first line treatment option for patients with HRR-mutated mCRPC. This unique combination of PARP and androgen biosynthesis inhibition for cancer control demonstrates improved efficacy versus current standard of care but may entail more complex side effect management. This guidance supplements the niraparib/AA+P prescribing information to provide practical recommendations on the monitoring, treatment adjustments, and specialty consultations required to minimize key adverse effects and optimize treatment exposure and outcomes.

## Disclosures

J-BL: Sits on advisory boards for: Pfizer, Janssen, Novartis, BMS, Merck, Abvie, Knights Therapeutics, Roche. Conducts research for: BMS; Astellas; AstraZeneca. Janssen support for manuscript writing and revisions. JJK: Sits on advisory boards for: Pfizer, Janssen, Novartis, BMS, Merck, Roche, AstraZeneca, Astellas, Bayer, Seagen and Takeda. Received research funding from Janssen, Bayer, AstraZeneca, and Astellas. Janssen support for manuscript writing and revisions. MKD: Consulting and speaking honoraria from Pfizer, Janssen, AstraZeneca, Ionis, Alnylam, Beigene, Bayer, Novo Nordisk, Abbott, HLS, BI-Lilly, Jazz Pharmaceuticals. Research support from Pfizer. Janssen support for manuscript writing and revisions. CC: Janssen support for manuscript writing and revisions. GG: Has received honoraria from Astellas Pharma, AstraZeneca, Bayer, EMD Serono, Ferring, Janssen, McKesson, Merck, Pfizer, Sanofi, and Tolmar. Janssen support for manuscript writing and revisions. □

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