# Expert consensus recommendations for managing adverse events in patients with metastatic prostate cancer treated with poly (ADP-ribose) polymerase inhibitor (PARPi) + novel hormonal therapy (NHT) combination therapy

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## Objective

Develop expert consensus on the management of adverse events (AEs) in patients with mPC treated with a combination of PARPi + NHT.

## Conclusions

These expert recommendations can help guide management of AEs in patients with mPC receiving combination PARPi + NHT therapy.

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## Background

- Recent clinical trials (PROpel - NCT03732820,[1] MAGNITUDE - NCT03748641,[2] and TALAPRO-2 - NCT03395197[3]) have shown a significant improvement in radiographic progression-free survival in men with metastatic prostate cancer (mPC) treated with combination PARPi and NHT treatment.
- Between May 2023 and August 2023, the Food and Drug Administration approved 3 PARPi + NHT combination therapies for the treatment of patients with mPC in the United States.[4–6] Between November 2022 and August 2023, a PARPi + NHT combination was also approved by European Medicine Agency, Pharmaceuticals and Medical Devices Agency (Japan), and Health Canada.[7-9]
- Across clinical trials, commonly reported adverse events (AEs) associated from this treatment combination include nausea and vomiting, anemia, fatigue, constipation, decreased hemoglobin, neutrophils, platelets, and laboratory abnormalities.[4–6]
- There are currently no available guidelines or consensus for management of AEs induced by combination PARPi + NHT.
- The objective of the multidisciplinary and geographically diverse panel was to develop expert consensus on the management of AEs in patients with mPC treated with a combination of PARPi + NHT.

## Materials and Methods

- The RAND/University of California Los Angeles (UCLA) Appropriateness Method was used to develop AE management guidelines.
- AEs were defined and classified by severity using Common Terminology Criteria for Adverse Events (CTCAE) and National Comprehensive Cancer Network (NCCN) guidelines.
- A panel of 12 experts 1) were provided a literature review of common AEs from PARPi and NHT therapies across cancer types; 2) using a rating form survey, independently rated 419 AE management options for the agent suspected of causing the AE on a 1–9 scale; 3) discussed areas of agreement and disagreement at a professionally-moderated, in-person meeting in March 2023; and 4) repeated the ratings.
- Second-round ratings formed the basis of expert recommendations, approved by all panelists in September 2023.
- Experts included 8 genitourinary-focused healthcare professionals (7 medical oncologists, 1 advanced practice registered nurse), 3 urologists, and 1 patient advocate.
- The advanced practice registered nurse and patient advocate were included to represent non-physician providers who frequently see patients with mPC.
- Panelists had an average of 16 years of clinical experience (range 4-34) and experience treating and/or consulting patients with mPC (mean 179 patients, range 60-325 in the past year at the time of the panel meeting).

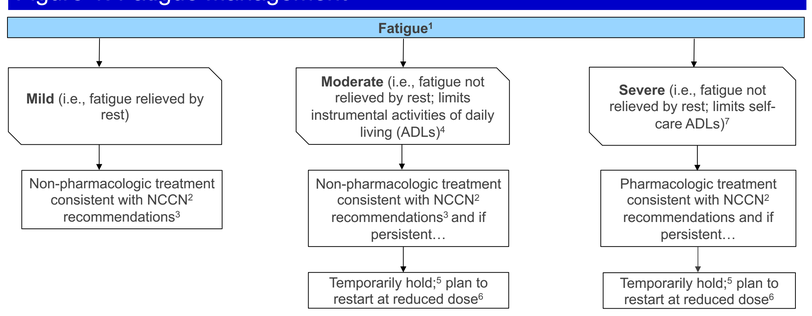
## Results

- Areas of disagreement decreased from 41% to 21% between first and second round ratings.
- Panelists agreed on 59% of ratings in Round 1 and 78% in Round 2.
- There was agreement on at least 1 management strategy for every clinical situation discussed.

## Conclusions

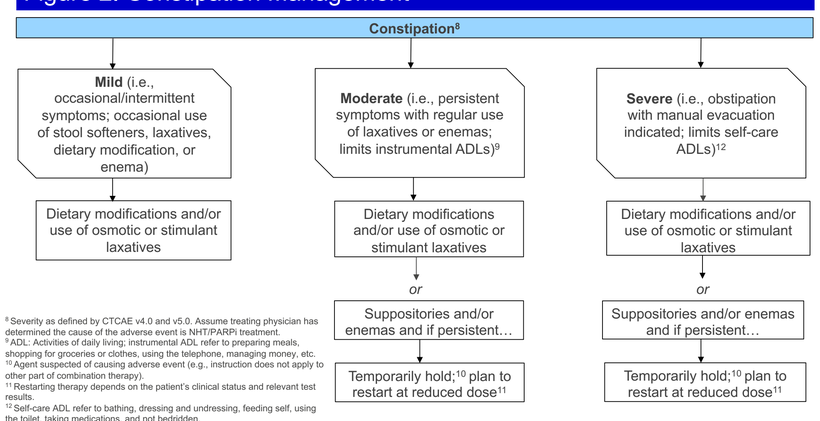
- This expert guidance is based on currently available evidence and the agreement of a multidisciplinary group of medical oncologists, urologists, an advanced practice registered nurse, and a patient advocate.
- These statements are not specific to individual PARPi + NHT agents. The absolute level of dose reduction and the length of time treatment should be held in response to an AE must be individualized and practitioners should refer to individual drug labels for more specific guidance.
- These recommendations can help guide physician management of AEs in patients with mPC receiving combination PARPi + NHT therapy.

### Figure 1. Fatigue Management



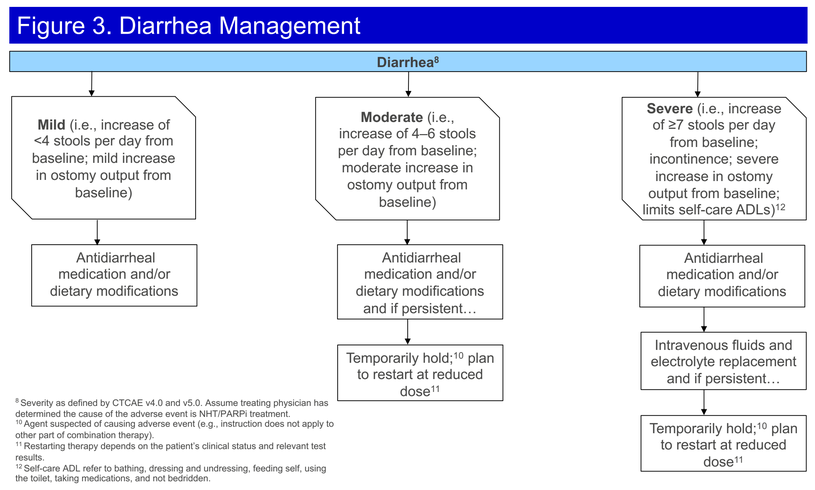

[1] Severity as defined by CTCAE v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[2] NCCN: National Comprehensive Cancer Network.
[3] E.g., physical activity, yoga, massage therapy, CBT, BT, psycho-educational therapies, educational therapies.
[4] ADL: Activities of daily living; Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[5] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[6] Restarting therapy depends on the patient's clinical status and relevant test results.
[7] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### Figure 2. Constipation Management



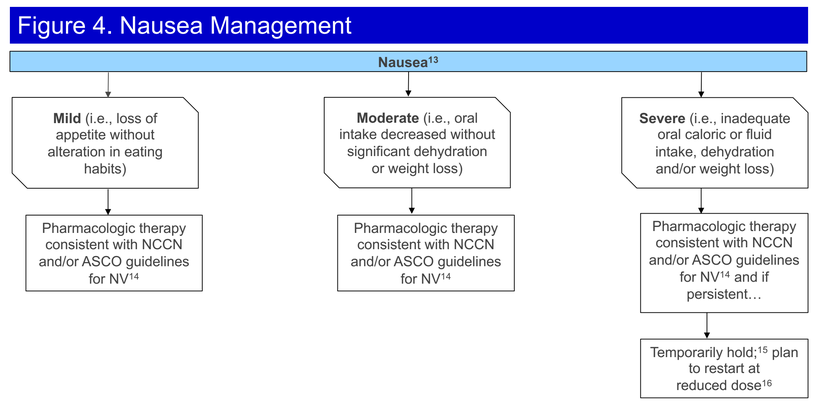

[8] Severity as defined by CTCAE v4.0 and v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[9] ADL: Activities of daily living; instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[10] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[11] Restarting therapy depends on the patient's clinical status and relevant test results.
[12] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### Figure 3. Diarrhea Management



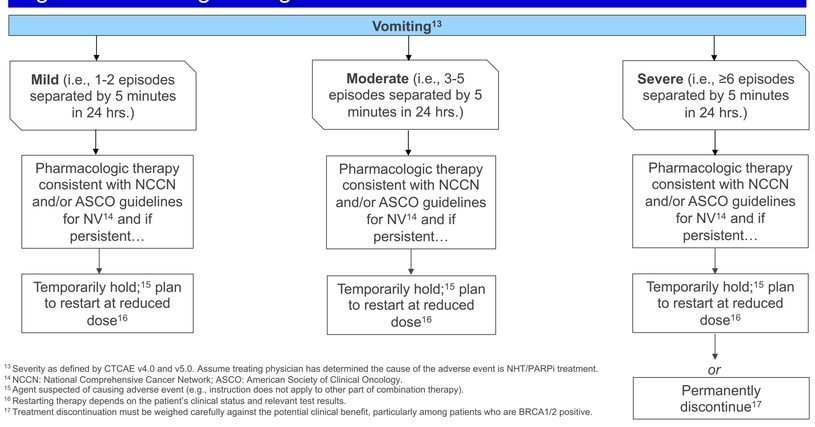

[8] Severity as defined by CTCAE v4.0 and v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[10] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[11] Restarting therapy depends on the patient's clinical status and relevant test results.
[12] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### Figure 4. Nausea Management



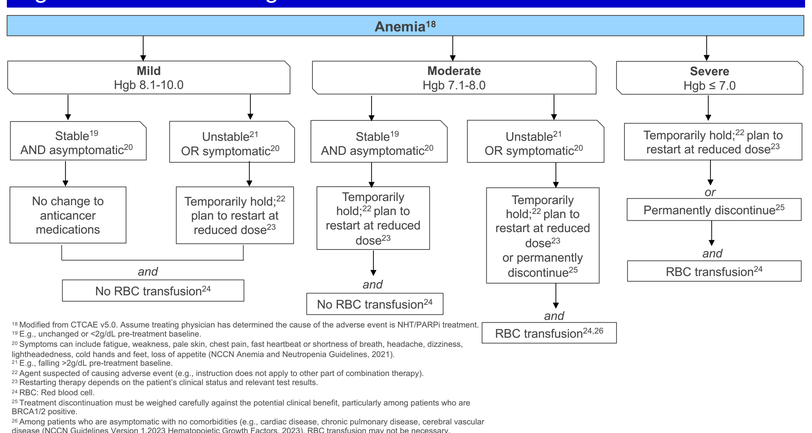

[13] Severity as defined by CTCAE v4.0 and v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[14] NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology.
[15] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[16] Restarting therapy depends on the patient's clinical status and relevant test results.

### Figure 5. Vomiting Management



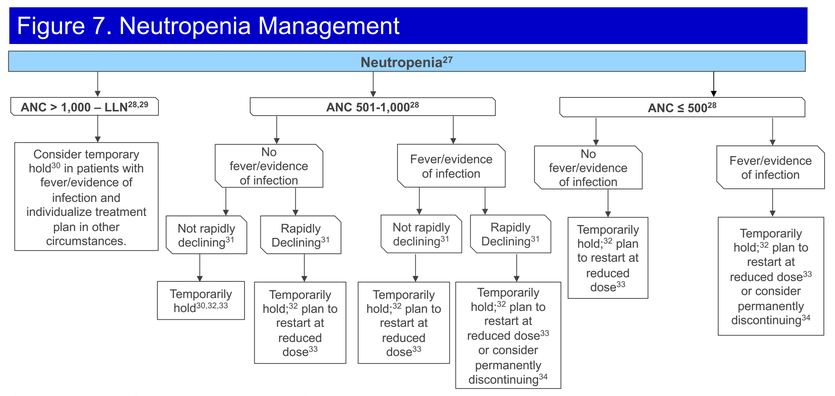

[13] Severity as defined by CTCAE v4.0 and v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[14] NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology.
[15] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[16] Restarting therapy depends on the patient's clinical status and relevant test results.
[17] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.

### Figure 6. Anemia Management



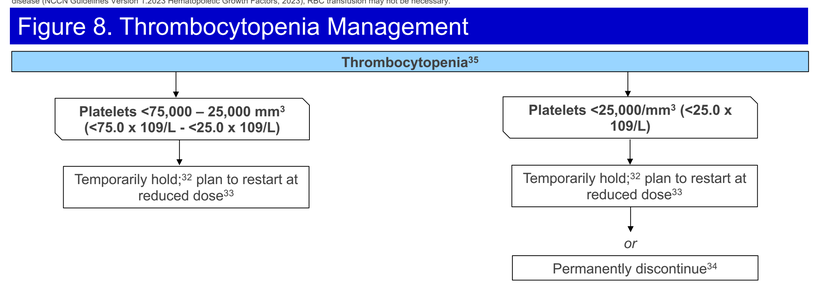

[18] Modified from CTCAE v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[19] E.g., unchanged or <2g/dL pre-treatment baseline.
[20] Symptoms can include fatigue, weakness, pale skin, chest pain, fast heartbeat or shortness of breath, headache, dizziness, lightheadedness, cold hands and feet, loss of appetite (NCCN Anemia and Neutropenia Guidelines, 2021).
[21] E.g., falling >2g/dL pre-treatment baseline.
[22] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[23] Restarting therapy depends on the patient's clinical status and relevant test results.
[24] RBC: Red blood cell.
[25] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.
[26] Among patients who are asymptomatic with no comorbidities (e.g., cardiac disease, chronic pulmonary disease, cerebral vascular disease (NCCN Guidelines Version 1.2023 Hematopoietic Growth Factors, 2023), RBC transfusion may not be necessary.

### Figure 7. Neutropenia Management



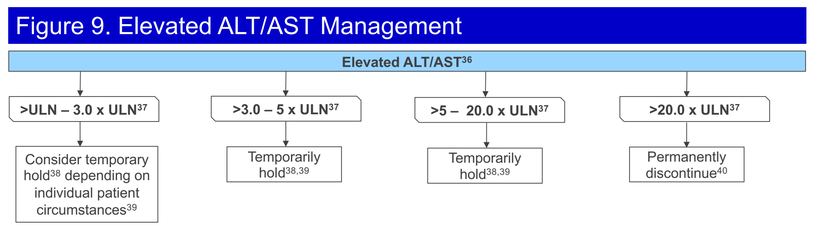

[27] Severity as defined by NCCN Guidelines Version 1.2023 Hematopoietic Growth Factors. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[28] ANC: Absolute neutrophil count.
[29] LLN: Lower limit of normal.
[30] The decision to restart at the same or a reduced dose depends on individual patient circumstances.
[31] Predicted to decline to ≤500 neutrophils/mcL over the next 48 hours.
[32] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[33] Restarting therapy depends on the patient's clinical status and relevant test results.
[34] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.

### Figure 8. Thrombocytopenia Management



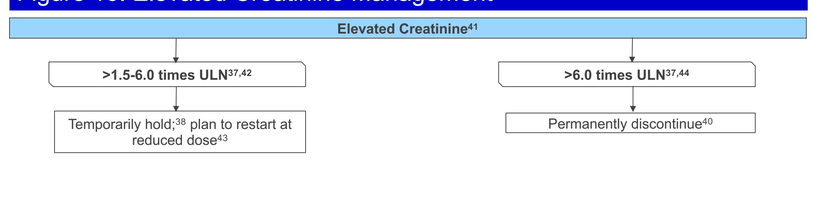

[32] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[33] Restarting therapy depends on the patient's clinical status and relevant test results.
[34] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.
[35] Severity defined by CTCAE v3.0, Blood and Bone Marrow Adverse Events, Platelets. 2006. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.

### Figure 9. Elevated ALT/AST Management




[36] Severity defined by CTCAE v5.0. ALT: alanine transaminase; AST: aspartate aminotransferase Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[37] ULN: Upper limit of normal.
[38] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[39] Restarting therapy depends on the patient's clinical status and relevant test results. The decision to restart at the same or a reduced dose depends on individual patient circumstances.
[40] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.

### Figure 10. Elevated Creatinine Management




[37] ULN: Upper limit of normal.
[38] Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).
[39] Restarting therapy depends on the patient's clinical status and relevant test results. The decision to restart at the same or a reduced dose depends on individual patient circumstances.
[40] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.
[41] Severity defined by CTCAE v5.0. Assume treating physician has determined the cause of the adverse event is NHT/PARPi treatment.
[42] eGFR or CrCl 59 - 15 ml/min/1.73 m²
[43] Restarting therapy depends on the patient's clinical status and relevant test results.
[44] eGFR or CrCl <15 ml/min/1.73 m²; dialysis or renal transplant indicated.

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**7**. Lynparza in combination with abiraterone approved in the EU as 1st-line treatment for patients with metastatic castration-resistant prostate cancer [Internet]. 2022.
**8**. Lynparza plus abiraterone approved in Japan for the treatment of BRCA-mutated metastatic castration-resistant prostate cancer [Internet]. 2023.
**9**. AstraZeneca. Health Canada approves Lynparza in combination with abiraterone and prednisone or prednisolone for patients with BRCA mutated metastatic castration-resistant prostate cancer [Internet]. 2023.



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