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

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



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 - NCT03395197³) 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 **Fatique** Moderate (i.e., fatigue not **Severe** (i.e., fatigue not Mild (i.e., fatigue relieved by relieved by rest; limits relieved by rest; limits selfinstrumental activities of daily care ADLs)7 living (ADLs)⁴ Pharmacologic treatment Non-pharmacologic treatmen Non-pharmacologic treatment consistent with NCCN² consistent with NCCN² consistent with NCCN² recommendations recommendations³ and if recommendations and if persistent. persistent. Temporarily hold;⁵ plan to Temporarily hold;⁵ plan to restart at reduced dose⁶ restart at reduced dose⁶ 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 ADL: Activities of daily living; Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy) Restarting therapy depends on the patient's clinical status and relevant test results. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridde Figure 3. Diarrhea Management Diarrhea⁸ **Severe** (i.e., increase Moderate (i.e.. Mild (i.e., increase of of ≥7 stools per day increase of 4-6 stools <4 stools per day from from baseline: per day from baseline; baseline: mild increase incontinence; severe moderate increase in in ostomy output from increase in ostomy ostomy output from output from baseline: baseline) limits self-care ADLs)¹² Antidiarrheal Antidiarrheal Antidiarrheal medication and/or medication and/or medication and/or dietary modifications dietary modifications dietary modifications and if persistent... Intravenous fluids and Temporarily hold; 10 plan electrolyte replacement to restart at reduced and if persistent... 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. O Agent suspected of causing adverse event (e.g., instruction does not apply to Temporarily hold;¹⁰ plan other part of combination therapy). to restart at reduced ¹ Restarting therapy depends on the patient's clinical status and relevant test ¹² Self-care ADL refer to bathing, dressing and undressing, feeding self, using Figure 5. Vomiting Management Vomiting¹³ Moderate (i.e., 3-5 Severe (i.e., ≥6 episodes Mild (i.e., 1-2 episodes episodes separated by 5 separated by 5 minutes separated by 5 minutes minutes in 24 hrs.) in 24 hrs.) in 24 hrs.) Pharmacologic therapy Pharmacologic therapy Pharmacologic therapy consistent with NCCN consistent with NCCN consistent with NCCN and/or ASCO guidelines and/or ASCO guidelines and/or ASCO guidelines for NV¹⁴ and if for NV¹⁴ and if for NV14 and if persistent. persistent. persistent. Temporarily hold;15 plan Temporarily hold;¹⁵ plan Temporarily hold; 15 plan to restart at reduced to restart at reduced to restart at reduced dose¹⁶ dose¹⁶ 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 ⁴NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy). Permanently 6 Restarting therapy depends on the patient's clinical status and relevant test results. discontinue¹ tment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive Figure 7. Neutropenia Management Neutropenia²⁷ $ANC > 1,000 - LLN^{28,29}$ ANC 501-1,000²⁸ ANC $\leq 500^{28}$ Consider temporary No Fever/evidence Fever/evidence fever/evidence hold³⁰ in patients with fever/evidence of infection of infection of infection of infection fever/evidence of infection and individualize treatment Not rapidly Rapidly plan in other Not rapidly Rapidly Temporarily Temporarily circumstances declining³ declining³¹ Declining³ Declining³ hold;32 plan hold;32 plan to to restart at restart at reduced reduced dose³³ dose³³ or consider Temporarily Temporarily Temporarily Temporarily hold;32 plan to hold;32 plan to permanently hold;³² plan t restart at discontinuing³⁴ restart at restart at reduced dose³³ reduced reduced or consider dose³³ dose³³ permanently discontinuing³⁴ 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

Figure 2. Constipation Management Constipation⁸ occasional/intermittent Moderate (i.e., persistent **Severe** (i.e., obstipation symptoms with regular use symptoms; occasional use with manual evacuation of laxatives or enemas: indicated: limits self-care of stool softeners, laxatives, limits instrumental ADLs)9 ADLs)12 dietary modification, or Dietary modifications and/or Dietary modifications Dietary modifications and/or use of osmotic or stimulant and/or use of osmotic or use of osmotic or stimulant laxatives stimulant laxatives laxatives Suppositories and/or Suppositories and/or enemas 8 Severity as defined by CTCAE v4.0 and v5.0. Assume treating physician has enemas and if persistent. and if persistent 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. Agent suspected of causing adverse event (e.g., instruction does not apply to Temporarily hold;¹⁰ plan to Temporarily hold;¹⁰ plan to restart at reduced dose¹¹ restart at reduced dose¹ ¹² Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden Figure 4. Nausea Management Nausea¹³ Mild (i.e., loss of Moderate (i.e., oral Severe (i.e., inadequate intake decreased without appetite without oral caloric or fluid significant dehydration alteration in eating intake, dehydration or weight loss) and/or weight loss) habits) Pharmacologic therapy Pharmacologic therapy Pharmacologic therapy consistent with NCCN consistent with NCCN consistent with NCCN and/or ASCO guidelines and/or ASCO guidelines and/or ASCO guidelines for NV¹⁴ and if for NV¹⁴ for NV¹⁴ persistent... Temporarily hold;¹⁵ plan to restart at reduced dose¹⁶ ³ 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 ⁵Agent 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. Figure 6. Anemia Management Anemia¹⁸ Severe Hgb 8.1-10.0 Hgb 7.1-8.0 Hgb ≤ 7.0 Temporarily hold;²² plan to Unstable²¹ Unstable² Stable¹⁹ AND asymptomatic²⁰ OR symptomatic² restart at reduced dose²³ OR symptomatic² AND asymptomatic²⁰ Temporarily Temporaril No change to Temporarily hold;² Permanently discontinue²⁵ hold;²² plan to hold;22 plan to plan to restart at anticancer restart at reduced restart at reduced medications reduced dose²³ dose²³ or permanently RBC transfusion²⁴ discontinue² No RBC transfusion²⁴ No RBC transfusion²⁴ RBC transfusion^{24,26} ghtheadedness, cold hands and feet, loss of appetite (NCCN Anemia and Neutropenia Guidelines, 2021) ²² Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy 25 Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are ²⁶ Among patients who are asymptomatic with no comorbidities (e.g., cardiac disease, chronic pulmonary disease, cerebral vascular Figure 8. Thrombocytopenia Management Thrombocytopenia³⁵ Platelets <25,000/mm³ (<25.0 x Platelets <75,000 - 25,000 mm³ $(<75.0 \times 109/L - <25.0 \times 109/L)$ Temporarily hold;32 plan to restart at Temporarily hold;³² plan to restart at reduced dose³³ reduced dose³³

Electronic Poster

with BRCA mutated metastatic castration-resistant prostate cancer [Internet]. 2023.

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prostate cancer. FDA [Internet]. 2023 Jun 20. **6.** U.S. Food and Drug Administration. FDA approves niraparib and abiraterone acetate plus prednisone for BRCA-mutated metastatic castration-resistant prostate cancer [Internet]. 2023 Aug. 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

Copyright ©2021. All rights reserved. Presented at 15th European Multidisciplinary Congress on Urological Cancers (EMUC) • November 02-05, 2023 • Marseille, France 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 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.

Elevated ALT/AST³⁶

 $>5 - 20.0 \times ULN^{37}$

Temporarily

hold^{38,39}

>20.0 x ULN³⁷

Permanently

discontinue⁴⁰

²⁹ LLN: Lower limit of normal.

 $>ULN - 3.0 \times ULN^{37}$

Consider temporary

hold³⁸ depending or

individual patient

circumstances³⁹

³⁰ The decision to restart at the same or a reduced dose depends on individual patient circumstances.

³² Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).

Figure 9. Elevated ALT/AST Management

34 Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.

 $>3.0 - 5 \times ULN^{37}$

Temporarily

hold^{38,39}

31 Predicted to decline to ≤500 neutrophils/mcL over the next 48 hours.

33 Restarting therapy depends on the patient's clinical status and relevant test results.



³² Agent suspected of causing adverse event (e.g., instruction does not apply to other part of combination therapy).

³⁴ Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.

33 Restarting therapy depends on the patient's clinical status and relevant test results.

Permanently discontinue³⁴

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.