# Analysis of the Safety, Efficacy, and Time Interval of Xofigo and Pluvicto Combination Therapy in Metastatic Castration-Resistant Prostate Cancer

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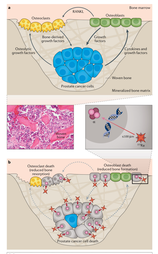
## INTRODUCTION

**Teaching Points:**

- To review mechanisms of and indications for Radium-223 Dichloride (Xofigo) and 177Lu-PSMA-617 (Pluvicto) treatments in Metastatic Castration-Resistant Prostate Cancer (MCRPC).
- To analyze the effects of Xofigo and Pluvicto combination therapy in MCRPC.
- To evaluate the safety of and time interval necessary for successful Xofigo and Pluvicto combination therapy.

### Xogifo Therapy:

- First developed targeted alpha therapy for MCRPC.
- Acts on cancer cells by delivering alpha radiation, while minimizing damage/toxicity to surrounding tissues.
- Radium-223 acts as calcium mimetic, which induces apoptosis through dsDNA breaks in areas of increased bone turnover.
- Administered via IV line and three-way tap with Luer Lock connections, and typically involves 6 total injections.
- Does not require positive prostate-specific membrane antigen (PSMA).
- Does not affect soft tissue.

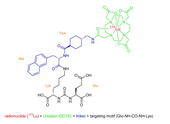



Morris MJ, Corey E, Guise TA, Gulley JL, Kevin Kelly W, Quinn DI, Scholz A, Sgouros G. Radium-223 mechanism of action: implications for use in treatment combinations. Nat Rev Urol. 2019 Dec;16(12):745-756.

### Pluvicto Therapy:

- Radioligand therapy that acts by delivering beta-particle radiation to PSMA-expressing cells and the surrounding environment.
- Indicated for male adult patients with PSMA-positive MCRPC.
- Administered via IV injection of infusion.
- Effective on both bone and soft tissue.

Chemical Structure of Pluvicto



radionuclide (177Lu) + chelator (DOTA) + linker + targeting motif (Glu-NH-CO-NH-Lys)

Hennrich U, Eder M. [177Lu]Lu-PSMA-617 (Pluvicto™): The First FDA-Approved Radiotherapeutical for Treatment of Prostate Cancer. Pharmaceuticals (Basel). 2022 Oct 20;15(10):1292.

### Metastatic Castration-Resistant Prostate Cancer:

- Prostate cancer is one of the most commonly diagnosed cancers in men worldwide (1.3 million new cases per year).
- MCRPC describes prostate cancer encompassing a wide range of molecular tumor behavior and a high risk of progression, leading to a poor long-term prognosis and a short overall survival.
- Typically don't respond to initial treatments, such as surgery or hormone therapy.

## METHODS

- Databases Medical Literature Analysis and Retrieval System Online (MEDLINE)/PubMed and Google Scholar were used for the literature search between 2017 and 2023.
- Key words: "Radium-223 Therapy," "177Lu-PSMA," "Time Interval," "Prostate Cancer," "Pluvicto," "Xofigo," and "MCRPC."
- Editorial, commentaries, and unpublished works were excluded.

## RESULTS

### Effects of Xofigo Therapy:

- Advantageous compared to other radiopharmaceutical agents due to short half-life (11.4 days) and use of alpha-emission.
- FDA approved for men with MCRPC, symptomatic bone metastases, and no visceral disease, but studies have shown that Xofigo is effective in men with asymptomatic bone disease, as well.
- Compared to placebo (11.3 months), Xofigo has demonstrated increased median overall survival (14.9 months) in MCRPC patients.
- Typically, patients who have undergone Xofigo therapy have fewer hospitalization days in the first year after treatment and less pain compared to the placebo group.
- Pitfalls of Xofigo:
  - An increase in PSA levels is commonly seen during treatment
  - Potential for decreased neutrophil and platelet counts exist while using Xofigo

| $^{223}RaCl_2$ | | | |
|---|---|---|---|
| Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer (ALSYMPCA) [7] | $^{223}RaCl_2$ vs. placebo in mCRPC with bone metastasis | Phase III | $^{223}RaCl_2$ improved overall survival vs. placebo (median, 14.0 months vs. 11.2 months). |
| Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223) [8] | Abiraterone acetate + prednisone/prednisolone with $^{223}RaCl_2$ vs. placebo | Phase III | Addition of $^{223}RaCl_2$ did not improve symptomatic skeletal event-free survival and was associated with increasing frequency of fractures (9% vs. 3%). |
| Prospective Evaluation of Bone Metabolic Markers as Surrogate Markers of Response to Radium-223 Therapy in Metastatic Castration-resistant Prostate Cancer [9,10] | Enzalutamide + $^{223}RaCl_2$ vs. enzalutamide alone | Phase II | Combination Enzalutamide + $^{223}RaCl_2$ did not show increase in fractures or other adverse events and showed improved bone metabolic markers. |
| Radium-223 Safety, Efficacy, and Concurrent Use with Abiraterone or Enzalutamide: First U.S. Experience from an Expanded Access Program [11] | $^{223}RaCl_2$ + concurrent abiraterone acetate or enzalutamide | Phase II | Patients with less advanced disease (<3 prior therapies) were more likely to benefit from $^{223}RaCl_2$ |

Adapted from Parent EE, Kase AM. A Treatment Paradigm Shift: Targeted Radionuclide Therapies for Metastatic Castrate Resistant Prostate Cancer. Cancers (Basel). 2022 Sep 1;14(17):4276.

### Effects of Pluvicto Therapy:

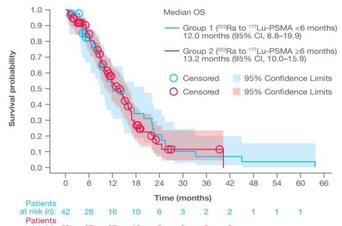
- Compared to best standard of care (SOC) for MCRPC, Pluvicto has proven to be more effective.
- Compared to cabazitaxel, pluvicto caused a greater PSA response (reduction of PSA >50% from baseline), delayed disease progression, and delayed radiographic progression.
- Pluvicto administered with SOC has led to increased overall survival compared to SOC alone (15.3 months vs 11.3 months), displaying potential for effective treatment alongside other radiotherapeutic agents, such as Xofigo.
- Pitfalls of Pluvicto:
  - Increased duration of exposure during treatment (>3 times longer than SOC)
  - Increased chance of certain adverse effects -> fatigue, dry mouth, nausea, decreased leukocytes, etc.
  - Serious adverse reactions occurred in 36% of patients in VISION trial.
  - Adverse effects have potential to lead to dose interruption.

| $^{177}$ Lu PSMA-617 | | | |
|---|---|---|---|
| Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer [12] | $^{177}$ Lu PSMA-617 +SOC vs. SOC alone | Phase III | $^{177}$Lu PSMA-617 +SOC (compared to SOC alone) improved rPFS (median, 8.7 vs. 3.4 months) and OS (median, 15.3 vs. 11.3 months). |
| [$^{177}$Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomized, open-label, phase 2 trial [13]. | $^{177}$ Lu PSMA-617 vs. cabazitaxel | Phase II | $^{177}$Lu PSMA-617 arm had greater PSA response (66%) vs. cabazitaxel (37%) Grade 3–4 adverse events occurred in (33%) of 98 men in the $^{177}$Lu PSMA-617 v 45 (53%) of 85 men in the cabazitaxel group. |

Adapted from Keam SJ. Lutetium Lu 177 Vipivotide Tetraxetan: First Approval. Mol Diagn Ther. 2022 Jul;26(4):467-475.

### Effects of Xofigo and Pluvicto Combination Therapy Across Varying Time Intervals:

**Figure 3. Overall survival from start of $^{177}$Lu-PSMA**




Adapted from Rahbar K et al. Safety and Survival Outcomes of $^{177}$Lu-Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer with Prior $^{223}$Ra treatment: The RALU Study. J Nucl Med. 2023 Apr;64(4):574-578.

- As displayed above, Rahbar et al discovered that starting Pluvicto <6 months after the last dose of Xofigo therapy or >6 months afterward yielded similar median overall survival at 12.0 months and 13.2 months, respectively.
- During Pluvicto, 39% of patients experienced a 30% decline in prostate-specific antigen (PSA), and 29% of them experienced a 50% decline in PSA.
- Undergoing chemotherapy prior to or during Pluvicto led to no significant impact on the study, bolstering the case for an acceptable safety profile for this combination therapy.

- Both the most commonly experienced serious treatment-emergent adverse effect (TEAE) and Grade 3-4 TEAE for patients in this study was anemia.
- The incidence of TEAEs in patients who began Pluvicto <6 months after completing Xofigo did not significantly vary from that of patients who began Pluvicto >6 months later.

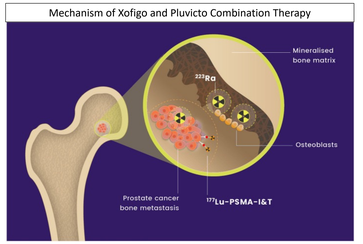
**Table 3. Incidence of treatment-emergent adverse events**

| | Group 1: $^{223}$Ra to $^{177}$Lu-PSMA <6 months (N=42) | | Group 2: $^{223}$Ra to $^{177}$Lu-PSMA ≥6 months (N 90) | |
|---|---|---|---|---|
| **TEAEs** | | | | |
| Any-grade TEAE | 30 (71) | | 74 (82) | |
| Serious TEAE | 14 (33) | | 25 (28) | |
| Grade 3–4 TEAE | 15 (36) | | 22 (24) | |
| **TEAEs in ≥10% of patients[a]** | **Any grade** | **Grade 3–4** | **Any grade** | **Grade 3–4** |
| Dry mouth | 3 (7) | 0 (0) | 16 (18) | 0 (0) |
| Nausea | 5 (12) | 0 (0) | 7 (8) | 0 (0) |
| Fatigue | 5 (12) | 0 (0) | 6 (7) | 0 (0) |

Data are *n* (%) and reported for during $^{177}$Lu-PSMA therapy up to 30 days of follow-up
[a]MedDRA preferred terms by CTCAE grading. Categories selected based on incidence of any-grade TEAEs in any group.
Excludes laboratory abnormalities
CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Adapted from Rahbar K et al. Safety and Survival Outcomes of $^{177}$Lu-Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer with Prior $^{223}$Ra treatment: The RALU Study. J Nucl Med. 2023 Apr;64(4):574-578.

Mechanism of Xofigo and Pluvicto Combination Therapy




Kostos L et al. AlphaBet: Combination of Radium-223 and [177Lu]Lu-PSMA-I&T in men with metastatic castration-resistant prostate cancer (clinical trial protocol). Front Med (Lausanne). 2022 Nov 18;9:1059122.

- Further studies involving Xofigo and Pluvicto combination therapy are currently ongoing, such as the AlphaBet trial by Kostos et al.
- Both Xofigo and Pluvicto therapies have been studied in combination with numerous anti-cancer agents, such as chemotherapy, anti-androgen therapy, immunotherapy, and PARP inhibitors, but the combination of Xofigo and Pluvicto is an extremely recent innovation, and, according to recent studies, has displayed potential to be more effective than its predecessors.

## CONCLUSIONS

- Treatment of MCRPC using Pluvicto within 6 months of completing Xofigo was determined to be clinically feasible, efficacious, and well-tolerated amongst most patients.
- As this is still a novel treatment, more research is necessary to determine exactly how effective it will be, but the existing literature has demonstrated an impressive potential to drastically improve MCRPC outcomes.

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