FDA APPROVED FOR PATIENTS WITHOUT PRIOR CHEMOTHERAPY*

The Bullseye

THE **PSMAFORE** STUDY IN REVIEW

ISSUE #2

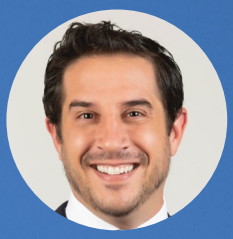
Indication

PLUVICTO® (lutetium Lu 177 vipivotide tetraxetan) is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor inhibition (ARPI) therapy, and

- are considered appropriate to delay taxane-based chemotherapy, or
- have received prior taxane-based chemotherapy

In this issue, 3 experts provide their perspectives on mCRPC and PLUVICTO in the PSMAfore study.

THIS ISSUE'S EXPERTS



Jason Hafron, MD
Urologist
from Michigan

Phillip Koo, MD
Nuclear Medicine Physician
and Radiologist
from Arizona

Scott Tagawa, MD
Medical Oncologist
from New York

The perspectives provided within this newsletter by Dr Hafron, Dr Koo, and Dr Tagawa are their own and not reflective of their affiliations. The medical experts in this newsletter have been paid by Novartis to provide their perspectives. This newsletter is not intended to be and does not serve as medical advice, guidance, or recommendations from Novartis.

FDA, US Food and Drug Administration.
*For patients considered appropriate to delay taxane-based chemotherapy.[1]

IMPORTANT SAFETY INFORMATION

Risk From Radiation Exposure

PLUVICTO contributes to a patient's long-term cumulative radiation exposure, which is associated with an increased risk for cancer.

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Patients with mCRPC need effective and tolerable treatments earlier

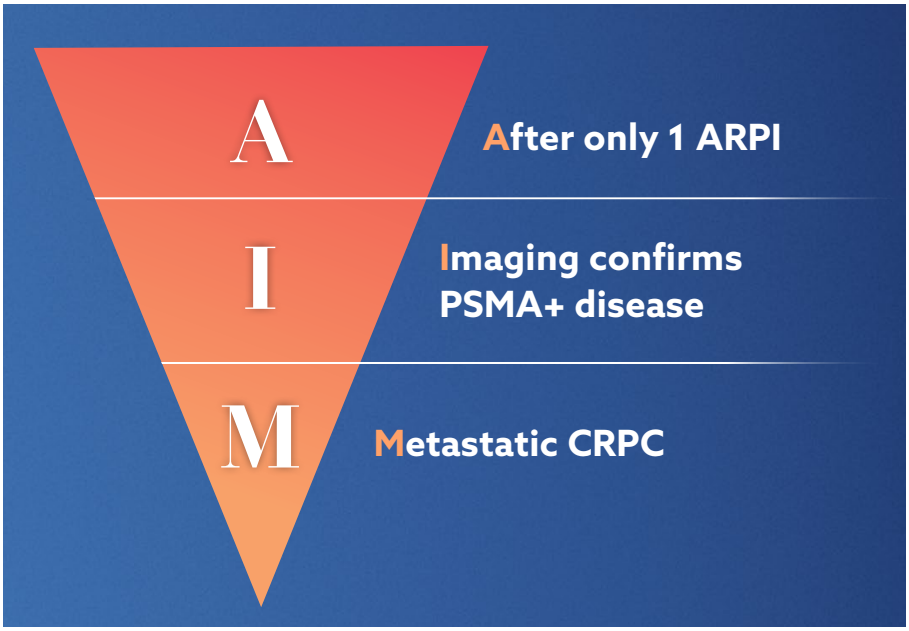
> I think that what we really want to have are more treatment options... Another mechanism of action I think would be great for the provider as well as for our patients.
>
> **Dr Tagawa**

Dr Tagawa has been compensated for his time by Novartis Pharmaceuticals Corporation.

- Prostate cancer is the **second** leading cause of cancer deaths in males, with 19 per 100,000 men dying per year[2,3]
- **A majority of patients die within 2 years** of an mCRPC diagnosis[4]
- More than half of patients with mCRPC will receive **only 1 life-prolonging therapy**[5]
- mCRPC is associated with **fast progression**, which can disrupt patients' lives[5,6]

PLUVICTO is the first and only PSMA-targeted RLT approved after only 1 ARPI

After your patients with PSMA+ mCRPC receive their 1st ARPI, be ready for what's next



AIM for PLUVICTO even earlier in mCRPC[1,7]

1 ARPI could have been received at **any** point in your patient's prostate cancer journey, including in the castration-sensitive setting[1,7]

PSMA+, PSMA-positive; RLT, radioligand therapy.

IMPORTANT SAFETY INFORMATION (continued)

Risk From Radiation Exposure (continued)

Ensure patients increase oral fluid intake and advise them to void as often as possible to reduce bladder radiation.

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Patients in your practice may be eligible for PLUVICTO

Scan this QR code to hear about medical expert perspectives on a patient with mCRPC after progression on an ARPI

https://www.pluvicto-hcp.com/psma-positive-mcrpc/medical-expert-perspectives

PSMAfore was a phase 3 trial comparing PLUVICTO vs a change in ARPI for chemo-naive patients*

PSMAfore was a randomized, multicenter, open-label, active-controlled study that compared PLUVICTO vs a change in ARPI[1,7]

> It's always very challenging to design a trial that is perfect, but I think the takeaway is PSMAfore really addresses that pre-chemotherapy space.
>
> **Dr Koo**

Dr Koo has been compensated for his time by Novartis Pharmaceuticals Corporation.

PSMAfore enrolled 468 men with PSMA+ mCRPC who had progressed on 1 prior ARPI[1]

- Patient characteristics in the PSMAfore trial were well balanced[1,7]

*For patients considered appropriate to delay taxane-based chemotherapy.[1]

IMPORTANT SAFETY INFORMATION (continued)

Myelosuppression

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Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity of myelosuppression.

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Primary end point

rPFS: In the primary analysis, PLUVICTO achieved statistically significant rPFS[1]

- Median rPFS was 9.3 months with PLUVICTO vs 5.6 months with a change in ARPI (HR=0.41 [95% CI, 0.29-0.56]; *P*<0.0001)

> In PSMAfore, rPFS was very strong. You see a true benefit in treating these patients as opposed to just flipping it to another ARPI.
>
> **Dr Hafron**

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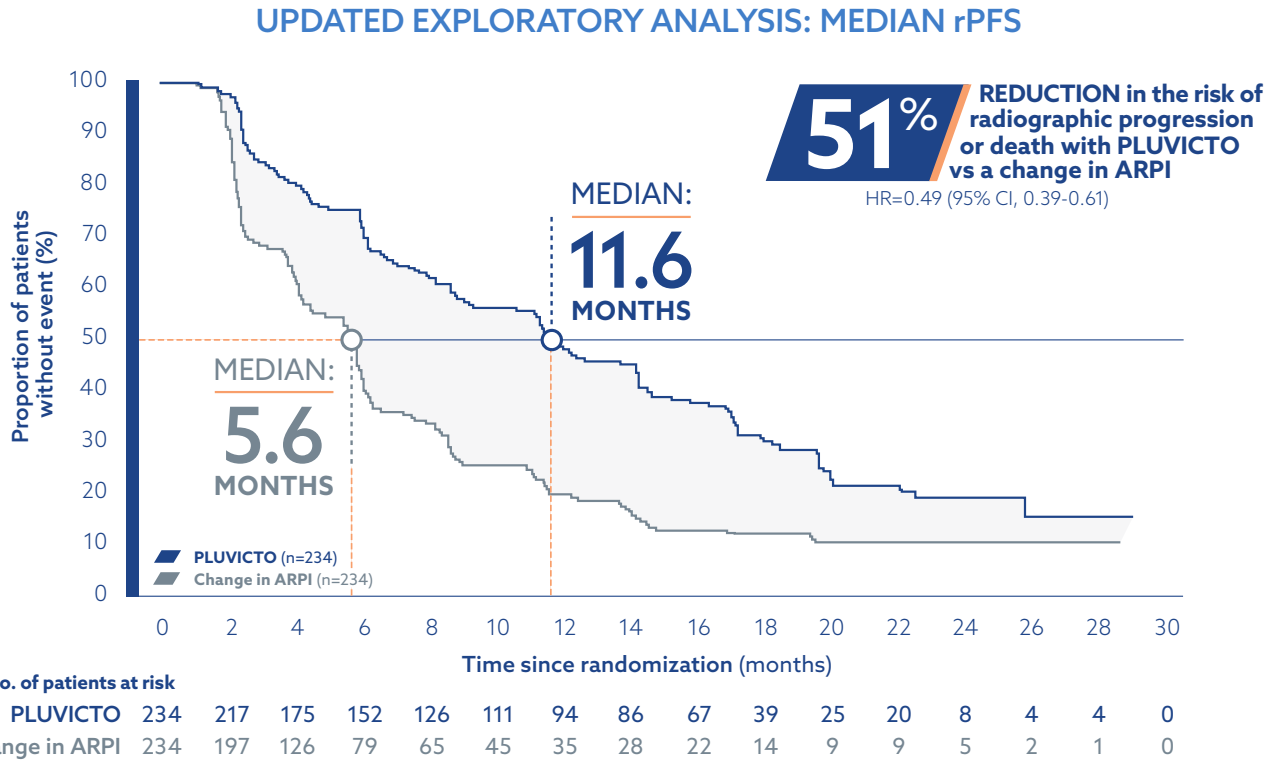
In the updated exploratory analysis

PLUVICTO more than doubled median rPFS vs a change in ARPI[7]



Exploratory rPFS analysis was performed with a median follow-up period of 24 months vs the primary analysis at 7 months. This analysis was not controlled for Type-I error.[7]

HR, hazard ratio; rPFS, radiographic progression-free survival.

IMPORTANT SAFETY INFORMATION (continued)

Renal Toxicity

PLUVICTO can cause severe renal toxicity. In the PSMAfore study, grade 3 or 4 acute kidney injury (1.3%) occurred in patients treated with PLUVICTO.

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Key secondary end point

OS: Numerically favored PLUVICTO but was not statistically significant; high crossover rate may have confounded OS analysis[1,7]

- At the preplanned final analysis,* **HR = 0.91** (95% CI: 0.72-1.14); median OS was 24.5 months with PLUVICTO and 23.1 months with a change in ARPI[1,8]
- **60.3%** of patients randomized to the change in ARPI arm subsequently crossed over to receive PLUVICTO following confirmed radiographic progression[8]
- In addition to the final OS analysis in PSMAfore, a **cross-adjusted OS analysis** based on the inverse probability of censoring weights (IPCW) was performed, which yielded a lower **HR of 0.59** (95% CI: 0.38-0.91)[8]

> There was crossover there, but there was not a deterioration. Essentially every single end point was positive, without deterioration in OS. I think it's a great option to have.
>
> **Dr Tagawa**

Dr Tagawa has been compensated for his time by Novartis Pharmaceuticals Corporation.

OS, overall survival.

*Data cutoff for the final analysis was January 1, 2025, with a total of 299 events occurring.[9]

IMPORTANT SAFETY INFORMATION (continued)

Embryo-Fetal Toxicity

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Infertility

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation-absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

Adverse Reactions and Laboratory Abnormalities

In the pooled safety population for the PSMAfore and VISION studies (N=756), the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased lymphocytes (83%), decreased hemoglobin (65%), fatigue (49%), dry mouth (46%), decreased platelets (40%), decreased estimated glomerular filtration rate (37%), nausea (35%),decreased neutrophils (31%), decreased calcium (29%), decreased sodium (27%), increased aspartate aminotransferase (26%), increased alkaline phosphatase (24%), arthralgia (22%), decreased appetite (21%), increased potassium (21%), constipation (21%), and back pain (21%).

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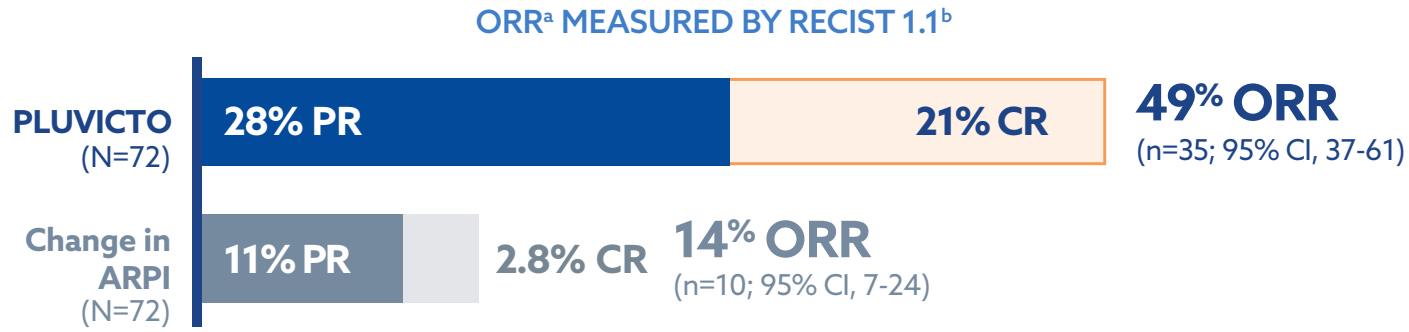
Additional end points

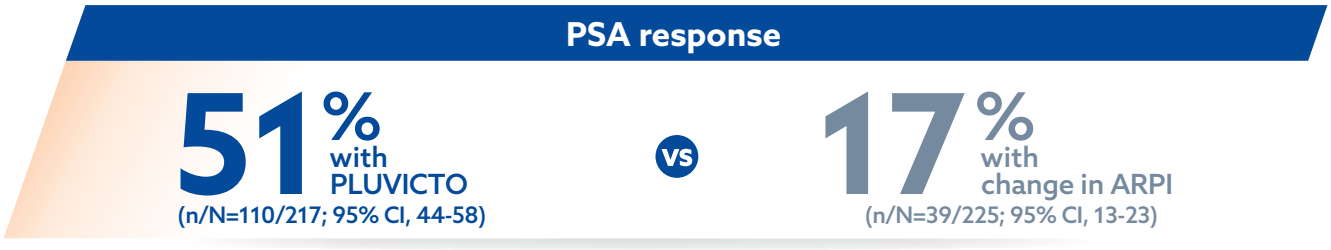
ORR: More patients had a response to PLUVICTO, with >7× more CRs seen with PLUVICTO vs a change in ARPI[1,*]



ORR=CR+PR.

[a]Responses are based on soft tissue and bone lesion assessment.
[b]Patients with measurable disease baseline.

PSA: More patients had a PSA decline with PLUVICTO vs a change in ARPI[7,*]



- Data are from patients with available PSA measurements at the time of the third data cutoff
- PSA50 response was defined as a confirmed PSA decrease of 50% or more

> Reductions in PSA, prolongation in time [to progression], just outcomes in quality of life — essentially everything was positive and demonstrated improvements in reduction of measurable disease.
>
> **Dr Tagawa**

Dr Tagawa has been compensated for his time by Novartis Pharmaceuticals Corporation.

CR, complete response; ORR, overall response rate; PR, partial response; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

*Not powered for statistical significance.

IMPORTANT SAFETY INFORMATION (continued)

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Additional end points

Patient-reported outcomes for PLUVICTO[7]

> For someone who walks in the door with minimal symptoms of the cancer, I want to maintain that good quality of life.
>
> **Dr Tagawa**

Dr Tagawa has been compensated for his time by Novartis Pharmaceuticals Corporation.

PSMAfore: PLUVICTO TIME TO WORSENING OF HRQOL vs A CHANGE IN ARPI

Median time to worsening FACT-P total score

7.5 MONTHS with PLUVICTO

VS

4.3 MONTHS with change in ARPI

The **FACT-P** total score is the sum of the scores of 39 items of the questionnaire and ranges from 1 to 156, with higher scores indicating better QOL. FACT-P measures physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer specific symptoms.

Median time to worsening BPI-SF pain intensity

5.0 MONTHS with PLUVICTO

VS

3.7 MONTHS with change in ARPI

BPI-SF assesses the severity of patients' pain and its impact on daily function through a 13-question form, with scores ranging from 0 to 10 and lower scores representing lower levels of pain intensity. BPI-SF measures pain intensity (worst, least, average, current), pain relief, and interference of pain.

- Both time to worsening FACT-P total score and time to worsening BPI-SF pain intensity were preplanned secondary end points
- Type-I error was not controlled in the QOL analyses. There was no hypothesis testing for patient-reported outcomes, and no control was applied. These results are not statistically significant and should be interpreted with caution

BPI-SF, Brief Pain Inventory-Short Form; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HRQOL, health-related quality of life; QOL, quality of life.

IMPORTANT SAFETY INFORMATION (continued)

Risk From Radiation Exposure (continued)

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PLUVICTO has a favorable safety profile[7]

> In the treated arm, the grade ≥3 AEs are less compared to the placebo or the change in ARPI arm. That's a pretty compelling signal that shows up in the trial.
>
> **Dr Hafron**

Dr Hafron has been compensated for his time by Novartis Pharmaceuticals Corporation.

Grade ≥3 AE rates were lower in the PLUVICTO group with a longer median duration of exposure[7]

- Incidence of grade ≥3 TEAEs: 36% with PLUVICTO (n = 81) vs 48% with a change in ARPI (n = 112)
- Median duration of exposure: 8.4 months with PLUVICTO vs 6.5 months with a change in ARPI

PSMAfore: ADVERSE REACTIONS OCCURRING AT ≥10% INCIDENCE IN PATIENTS WHO RECEIVED PLUVICTO[7,a]

	PLUVICTO (n=227)		Change in ARPI (n=232)	
Adverse reactions	All grades (%)	Grades 3 or 4 (%)	All grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders				
Dry mouth[b]	61	0.9	2.6	0
Nausea	32	0	12	0.4
Constipation	22	0.4	14	0
Diarrhea	17	0	9	0.4
Vomiting	11	0	4.7	0
General disorders				
Fatigue[b]	53	1.3	53	5
Metabolism and nutrition disorders				
Decreased appetite	22	0	19	0.4
Musculoskeletal and connective tissue disorders				
Arthralgia	20	0	23	0.4
Back pain	14	1.3	20	2.6

Clinically relevant ARs in <10% of patients who received PLUVICTO included dysgeusia, abdominal pain, peripheral edema, headache, acute kidney injury, weight decreased, urinary tract infection, dry eye, dizziness, dry skin, oral fungal infection, gastroesophageal reflux disease, pyrexia, vertigo, stomatitis, dysphagia, esophagitis, pancytopenia, and bone marrow failure.[1]

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.[7]

[b]Includes multiple similar terms.

AE, adverse event; AR, adverse reaction; TEAE, treatment-emergent adverse event.

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PLUVICTO has proven tolerability

> We're seeing good tolerability, so as urologists we're getting very comfortable with this radioligand therapy.
>
> **Dr Hafron**

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Permanent discontinuation rate due to an AE[7]

6% with PLUVICTO (n=13) vs **5%** with change in ARPI (n=12)

ARs leading to permanent discontinuation of PLUVICTO in ≥1% of patients who received PLUVICTO were thrombocytopenia (1.8%) and dry mouth (1.3%)[1]

Dose modification due to an AE[7]

4% with PLUVICTO (n=8) vs **16%** with change in ARPI (n=36)

The most frequent (≥0.5%) AR leading to a dose reduction of PLUVICTO in patients who received PLUVICTO was dry mouth (0.9%)[1]

Dose interruption due to an AE[7]

12% with PLUVICTO (n=28) vs **19%** with change in ARPI (n=45)

The most frequent (≥1%) ARs leading to a dose interruption of PLUVICTO in patients who received PLUVICTO were COVID-19 (3.1%) and anemia (1.8%)[1]

Scan this QR code to view resources about PLUVICTO available for your practice and your patients

https://www.pluvicto-hcp.com/psma-positive-mcrpc/resources

IMPORTANT SAFETY INFORMATION (continued)

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PLUVICTO Indication and ISI

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Embryo-Fetal Toxicity

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In the PSMAfore trial after only 1 ARPI,[1,7]

> Efficacy is strong. We're seeing a good hazard ratio. So I think it will be a very impactful tool for our patients.
>
> **Dr Hafron**

PLUVICTO more than doubled median rPFS vs a change in ARPI

- Updated exploratory analysis: Median rPFS was 11.6 months with PLUVICTO vs 5.6 months with a change in ARPI (HR=0.49 [95% CI, 0.39-0.61])*

PLUVICTO has a favorable safety profile

- Grade ≥3 AE rates were lower in the PLUVICTO group with a longer median duration of exposure

> [Treatment selection is a] nuanced decision, but I think there's a large group of patients that could benefit from this drug in the space.
>
> **Dr Koo**

> It's nice to have that combination of the molecular selection and targeting in one kind of overall package with a different mechanism of action than many of the other drugs.
>
> **Dr Tagawa**

Drs Hafron, Koo, and Tagawa have been compensated for their time by Novartis Pharmaceuticals Corporation.

CHOOSE PLUVICTO AFTER ONLY 1 ARPI[1]

*Exploratory rPFS analysis was performed with a median follow-up period of 24 months vs the primary analysis at 7 months. This analysis was not controlled for type-I error.[7]

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