The Bullseye

THE VISION STUDY

ISSUE #1
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In this issue, four experts provide their perspectives on mCRPC and PLUVICTO in the VISION study.

THIS ISSUE'S EXPERTS

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The perspectives provided within this newsletter by Dr Shore, Dr Fleming, Dr Brown, and Dr Gejerman 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.

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 (AR) pathway inhibition and taxane-based chemotherapy.

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Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection.

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PLUVICTO®
lutetium Lu 177 vipivotide tetraxetan
INJECTION FOR INTRAVENOUS USE

Patients with mCRPC urgently need therapeutic options.

- More than half of patients die within **2 years** of an mCRPC diagnosis[1]
- With every line of therapy, fewer patients are treated. Of all treated first-line patients, only **55%** are treated second-line and only **30%** are treated in third-line[1]
- Despite availability of ARPIs and chemotherapy, as patients progress through lines of therapy, unique treatment options become increasingly limited[2,3]

mCRPC is a lethal disease. Patients and their caregivers are always wanting to know, do I have **other tools in my armamentarium** that I can avail myself of when I progress on an ARPI and when I progress on a taxane-based therapy?

Dr Shore

PLUVICTO was studied in the VISION trial, the largest phase 3 trial of a PSMA-targeted radioligand therapy.[4,5]

The VISION trial was a randomized, multicenter, active-control study comparing PLUVICTO + BSOC vs BSOC alone in 831 men with PSMA+ mCRPC.

I refer to this as a **"plus one" trial**, where patients were going to get the **best standard of care**, plus a **novel therapy**.

Dr Fleming

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.

To minimize radiation exposure to others, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days, to refrain from sexual activity for 7 days, and to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

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Scan this QR code to be directed to a video of Dr Shore providing an overview of the VISION trial

https://www.pluvicto-hcp.com/me-perspectives-pluvicto-hcp#4541

VISION enrolled men with PSMA+ mCRPC who had progressed on an ARPI and taxane therapy.[4,5]

Baseline patient characteristics were well balanced across the treatment and control arms.

Across both treatment and control arms, 58% of patients received only 1 prior taxane.

"When I sit down with a patient now and say, "Look, here's your PSMA scan, it's lighting up. And while that's very disconcerting, that shows us that we can have a **therapeutic option that we did not have before**."

Dr Gejerman

IMPORTANT SAFETY INFORMATION (continued)

Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression. In the VISION study, grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥3 pancytopenia occurred in 1.1% of patients (including 2 fatal events). Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed. One death due to sepsis and concurrent neutropenia was observed.

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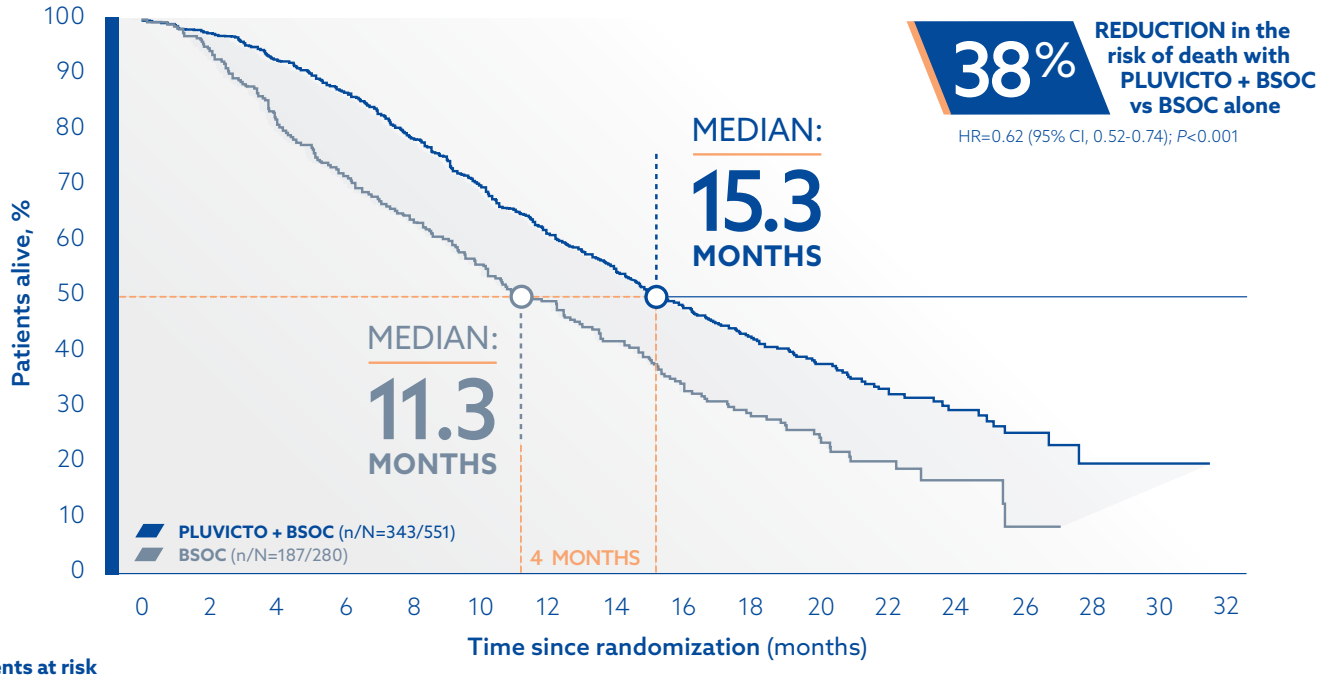
PLUVICTO is the first and only PSMA-targeted radioligand therapy to significantly improve overall survival (OS) in a phase 3 mCRPC trial.[4,5]

> Many of these **patients are asking** for another form of therapy that's different, and then I can have the **conversation with them about PLUVICTO**. It's an RLT, it has a novel mechanism of action and has a **life-prolonging benefit**.
>
> **Dr Shore**

Median OS (alternate primary end point)



No. of patients at risk

PLUVICTO + BSOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
BSOC	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

IMPORTANT SAFETY INFORMATION (continued)

Myelosuppression (continued)

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

Please see additional Important Safety Information throughout and on page 10.

A post hoc exploratory subgroup analysis of OS by number of prior taxanes was conducted in VISION.[6]

	PLUVICTO + BSOC median OS (months)	BSOC alone median OS (months)
1 prior taxane	16.2 (n/N=206/342)	11.8 (n/N=108/165)
2 prior taxanes[a]	13.6 (n/N=113/170)	10.6 (n/N=70/99)

Patients treated with PLUVICTO who had 1 prior taxane showed a greater median OS than those who had 2 prior taxane therapies.

Limitations: No formal statistical testing was planned for this exploratory subgroup analysis; therefore, there was no prespecified statistical procedure controlling for type 1 error. These results should be interpreted with caution.

[a]Of the 831 patients, 8 had received more than 2 taxanes previously.[7]

> The data from the VISION trial are **compelling**. We have improvements in overall survival, we have improvements in radiographic progression-free survival, and some improvements in important secondary end points. Furthermore, we know that treatment options in the "third-line" space can be sometimes limited, and these patients can oftentimes progress rapidly. I think it's important that we try to **identify these patients robustly, start them on therapy quickly,** and **try to support them through their course** and get the intended benefits seen in the VISION trial.
>
> **Dr Brown**

IMPORTANT SAFETY INFORMATION (continued)

Renal Toxicity

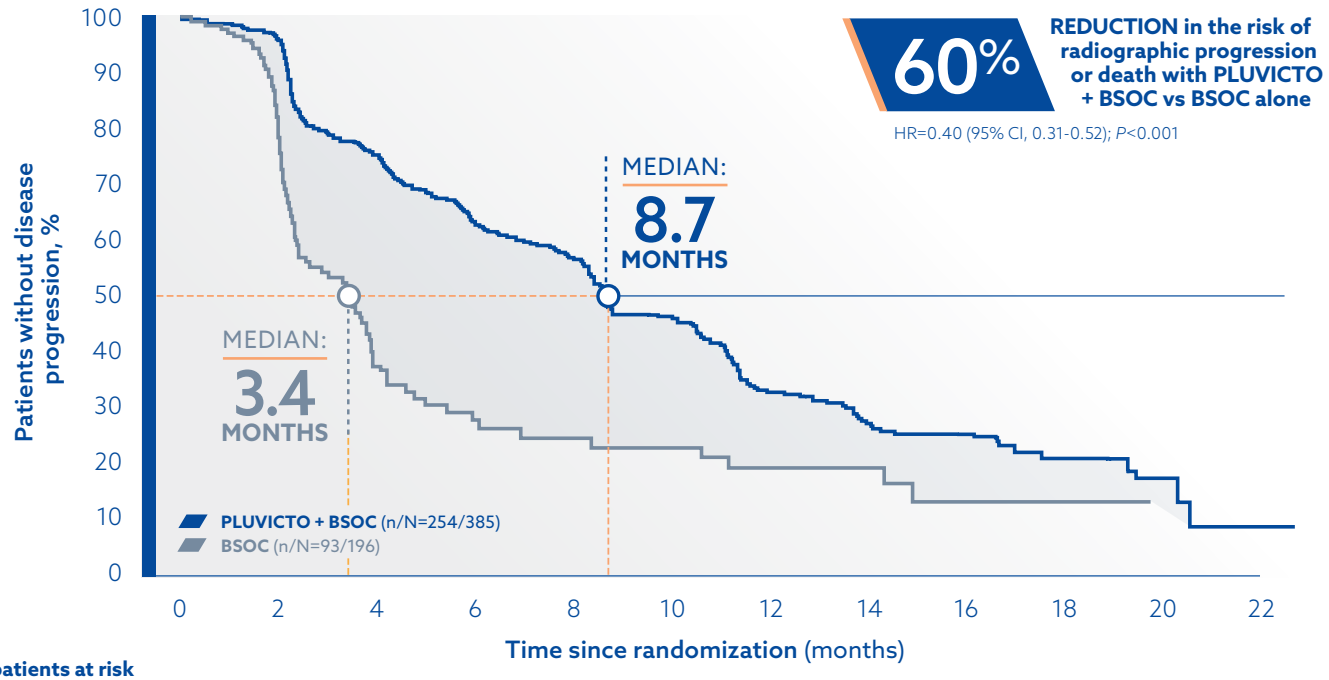
PLUVICTO can cause severe renal toxicity. In the VISION study, grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with PLUVICTO.

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated creatinine clearance (CrCl), before and during treatment. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity of renal toxicity.

Please see additional Important Safety Information throughout and on page 10.

rPFS was significantly longer with PLUVICTO + BSOC vs BSOC alone.[5,6]

Median rPFS (alternate primary end point)



No. of patients at risk

PLUVICTO + BSOC	385	362	272	215	182	137	88	71	49	21	6	1
BSOC	196	119	36	19	14	13	7	7	3	2	0	0

Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early dropout in the control arm.

Significantly more patients achieved a response with PLUVICTO + BSOC vs patients treated with BSOC alone.[4,8]

- PLUVICTO + BSOC achieved a **30%** ORR (n=95; 95% CI, 25-35)*,†
- BSOC alone achieved a **2%** ORR (n=2; 95% CI, 0-6)*,†

*ORR is reported as a measure of response in soft tissue, lymph node, or visceral lesions.
†Stratified Wald's Chi-Square test 2-sided *P* value.

IMPORTANT SAFETY INFORMATION (continued)

Embryo-Fetal Toxicity

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose.

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Patient-reported outcomes for PLUVICTO were assessed by FACT-P and BPI-SF.[8]

> We've all experienced patients where we really pull out of the fire: patients that were not doing well, just felt very fatigued or in pain.
>
> **Dr Gejerman**

Median time to worsening **FACT-P total score**[8]

5.7 MONTHS with PLUVICTO + BSOC

VS

2.2 MONTHS with BSOC alone

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 quality of life. FACT-P measures physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer subscale[5,9]

Median time to worsening **BPI-SF pain intensity**[8]

5.9 MONTHS with PLUVICTO + BSOC

VS

2.2 MONTHS with BSOC alone

BPI-SF assessed the severity of patients' pain and its impact on daily function through a 9-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 (on 7 HRQOL dimensions of general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life)[5,9]

- Both time to worsening FACT-P total score and time to worsening BPI-SF pain intensity were preplanned secondary end points. Data are from patients who were randomized after enhanced study site education measures who had a baseline assessment and at least 1 postbaseline assessment[5,8]
- For analysis of each outcome, only patients with a baseline assessment and ≥1 postbaseline time point were included. Main models were adjusted for randomization stratification factors[9]
- Type 1 error was not controlled in the quality-of-life analyses. There was no hypothesis testing for patient-reported outcomes and no α control was applied[9]

IMPORTANT SAFETY INFORMATION (continued)

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.

Please see additional Important Safety Information throughout and on page 10.

PLUVICTO has an established safety profile.[4]

Adverse reactions occurring at a ≥5% incidence in patients who received PLUVICTO + BSOC[4,7,8,*]

	PLUVICTO + BSOC (n=529)		BSOC (n=205)	
Adverse Reactions	All grades (%)	Grades 3 to 4 (%)	All grades (%)	Grades 3 to 4 (%)
General disorders				
Fatigue	43	6	23	1.5
Decreased appetite	21	1.9	15	0.5
Weight decreased	11	0.4	9	0
Peripheral edema[a]	10	0.4	7	0.5
Pyrexia	7	0.4	3.4	0
Gastrointestinal disorders				
Dry mouth[b]	39	0	0.5	0
Nausea	35	1.3	17	0.5
Constipation	20	1.1	11	0.5
Vomiting[c]	19	0.9	6	0.5
Diarrhea	19	0.8	2.9	0.5
Abdominal pain[d]	11	1.1	6	0.5
Blood and lymphatic system disorders				
Anemia	32	13	13	4.9
Thrombocytopenia	17	8	4.4	1
Renal and urinary disorders				
Urinary tract infection[e]	12	3.8	1	0.5
Acute kidney injury[f]	9	3.2	6	2.9
Nervous system disorders				
Dizziness	8	0.9	4.4	0
Headache	7	0.8	2	0
Dysgeusia[g]	7	0	1.5	0

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. [a]Peripheral edema includes peripheral edema, fluid retention, and fluid overload. [b]Dry mouth includes dry mouth, aptyalism, and dry throat. [c]Vomiting includes vomiting and retching. [d]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain. [e]Urinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial. [f]Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased. [g]Dysgeusia includes dysgeusia and taste disorder.

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions

The most common adverse reactions (≥20%) occurring at a higher incidence in patients who received PLUVICTO plus best standard of care (BSoC) were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. Clinically relevant adverse reactions in <5% of patients included dry eye, vertigo, and pancytopenia (including bicytopenia).

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PLUVICTO has an established safety profile.[4]

- 12% of patients discontinued PLUVICTO + BSOC due to any treatment-related adverse events vs 8% with BSOC alone
- Clinically relevant adverse reactions in <5% of patients who received PLUVICTO + BSOC included dry eye, vertigo, and pancytopenia (including bicytopenia)

No unexpected laboratory abnormalities were reported.

Scan this QR code to be directed to a video of a multidisciplinary team providing an overview of the efficacy and safety of PLUVICTO

https://www.pluvicto-hcp.com/me-perspectives-pluvicto-hcp#4516

IMPORTANT SAFETY INFORMATION (continued)

Laboratory Abnormalities

The most common laboratory abnormalities that worsened from baseline in ≥30% of patients who received PLUVICTO plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

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PLUVICTO Indication and Important Safety Information

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Please see full Prescribing Information at www.pluvicto.com.

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Notes

PLUVICTO –
A radioligand therapy for patients with PSMA+ mCRPC

> What's especially **hopeful** about PLUVICTO is it's another mechanism of action where we combine a diagnostic test, where patients can see where their disease is, **with a treatment that targets that directly**.
>
> **Dr Fleming**

- **PLUVICTO targets PSMA, a biomarker overexpressed in more than 80% of men with prostate cancer**
- **PLUVICTO significantly improves OS**
  - Median OS was 15.3 months with PLUVICTO + BSOC vs 11.3 months with BSOC alone (HR=0.62; 95% CI, 0.52-0.74; *P*<.001)
- **PLUVICTO has an established safety profile**
  - Most common ARs (≥20%) with PLUVICTO + BSOC were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation
- **PLUVICTO can be used after only 1 ARPI, 1 taxane, and PSMA+ PET scan**

Consider PLUVICTO when your patients are starting on their first chemotherapy.

> It's nice to look to a therapy with a **different mechanism of action, imparting an overall survival benefit** in a multidisciplinary care setting.
>
> **Dr Brown**

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