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Novartis Pluvicto® shows clinically meaningful and highly statistically significant rPFS benefit in patients with PSMA-positive metastatic castration-resistant prostate cancer in the pre-taxane setting

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- Phase III PSMAfore trial with Pluvicto® met its primary endpoint of radiographic progression-free survival (rPFS) with a HR of 0.41[1]; Pluvicto more than doubled median rPFS to 12.0 months per updated analysis*[1]
- Pluvicto also showed improved quality of life compared to daily oral ARPI, along with improvements in other clinically meaningful efficacy endpoints[1]
- Overall survival (OS) data interpretation at second interim analysis was confounded by 84% crossover[1]; PSMAfore continues to collect OS data
- Novartis is investigating a broad portfolio of RLTs in advanced cancers including breast, colon, neuroendocrine, lung, pancreatic and prostate and is investing in production capacity to continue meeting global patient needs

EAST HANOVER, N.J., Oct. 23, 2023 -- Novartis today presents data from the Phase III PSMAfore trial at the 2023 European Society for Medical Oncology (ESMO) Congress. Data presented at the Presidential Symposium showed that Pluvicto® (lutetium Lu 177 vipivotide tetraxetan) met its primary endpoint with a clinically meaningful and statistically significant benefit in radiographic progression-free survival (rPFS) in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) after treatment with androgen receptor pathway inhibitor (ARPI) therapy, compared to a change in ARPI[1].

Efficacy endpoint	Pluvicto vs. change in ARPI
Radiographic progression-free survival *[a]	HR 0.41 (95% CI: 0.29, 0.56; p<0.0001)
Median rPFS*	12.0 vs. 5.6 months
≥50% decline in prostate-specific antigen levels	57.6% vs. 20.4%
Time to symptomatic skeletal event (SSE)[a]	HR 0.35 (95% CI: 0.22, 0.57)
Objective response rate (ORR)[b]	50.7% vs. 14.9%
Duration of response (DOR)[b]	13.6 vs. 10.1 months
FACT-P score[a]	HR 0.59 (95% CI: 0.47, 0.72)
Brief Pain Inventory-Short Form (BPI-SF)[a]	HR 0.69 (95% CI: 0.56, 0.85)
Prespecified crossover-adjusted overall survival[a]	HR 0.80 (95% CI: 0.48, 1.33)
Unadjusted OS[a] (84% crossover)	HR 1.16 (95% CI: 0.83, 1.64)

[a] Hazard Ratio (95% Confidence Interval). Functional Assessment of Cancer Therapy-Prostate

[b] In patients with measurable disease at baseline in soft tissue per RECIST v1.1.

"The rPFS data are impressive and the treatment effect is comparable with what was observed in the VISION trial," said Dr. Oliver Sartor, PSMAfore Co-Principal Investigator, Chairman of the Trial Steering Committee and adjunct professor in the Department of Urology at Tulane University School of Medicine, New Orleans, LA, one of the many sites where the trial was conducted. "We look forward to a future where Pluvicto may be a viable therapy for patients in need of alternative, earlier options."

"These promising results from PSMAfore could change the treatment paradigm for advanced prostate cancer by allowing patients to potentially avoid or delay taxane-based chemotherapy, which carries a heavy burden of side effects," said Jeff Legos, Executive Vice President, Global Head of Oncology Development at Novartis. "While data collection for overall survival continues, the consistency of the benefit observed on other clinically meaningful efficacy endpoints, together with improved quality of life and favorable safety profile, show the potential of Pluvicto for taxane-naïve patients with mCRPC."

The trial met its primary endpoint of rPFS[2] with a 59% reduction in the risk of radiographic disease progression in patients with Pluvicto versus a change of ARPI[1]. Using a data cut off with a median of 8.6 months longer study follow-up, an updated rPFS analysis (HR 0.43; 95% CI: 0.33, 0.54) demonstrated a consistent clinical benefit in patients with Pluvicto versus a change in ARPI, more than doubling time to radiographic disease progression (12.0 months vs. 5.6 median

months)[1].

Patients on Pluvicto also showed improved quality of life, maintaining their FACT-P total score for 3 months longer than a change in ARPI (7.5 vs. 4.3 months), with a delay in worsening pain (BPI-SF) of 5.0 versus 3.7 months[1]. Other clinically meaningful efficacy endpoints also favored Pluvicto, with a PSA decline of at least 50% being >2.5X more frequent with Pluvicto than with a change in ARPI[1].

At the second interim OS analysis with 45% of events, the pre-specified crossover-adjusted OS analysis demonstrated a hazard ratio of 0.80 (95% CI: 0.48, 1.33)[1]. The unadjusted intent-to-treat OS analysis was confounded as 84% of patients who discontinued ARPI due to radiographic progression crossed over to receive Pluvicto[1]. The trial will continue to assess OS, with the next interim OS analysis expected in 2024.

The trial demonstrated a favorable safety profile with 6 cycles of Pluvicto[1]:

Adverse events (AEs)	Pluvicto vs. change in ARPI[a]
Grade 3–4	33.9% vs. 43.1%
Serious	20.3% vs. 28.0%
Leading to dose-adjustment	3.5% vs. 15.1%
Leading to discontinuation	5.7% vs. 5.2%

[a] In patients who experienced ≥1 adverse event.

The most frequently reported all-grade AEs for Pluvicto were primarily Grade 1–2 and included dry mouth (57.3%), asthenia (31.7%), nausea (31.3%), anemia (24.2%) and fatigue (22.9%)[1].

Currently, patients diagnosed with metastatic prostate cancer have a 5-year survival rate of approximately 30%[3] and there remains an urgent need for treatment options for patients who have disease progression despite the current standard of care[4-7].

*Pluvicto met its primary endpoint of rPFS at the primary analysis based on centrally confirmed rPFS events with an October 2022 data cut off[1]. The updated exploratory rPFS analysis was based on the latest data cut off of June 2023 and only nominally significant[1].

About the PSMAfore Study
PSMAfore (NCT04689828) is a Phase III, open-label, multi-center, 1:1 randomized study comparing the efficacy and safety of Pluvicto to a change in ARPI (abiraterone or enzalutamide) in patients with PSMA-positive mCRPC who have not been exposed to a taxane-containing regimen[8]. Patients enrolled must have progressed only once after receiving a second-generation ARPI (abiraterone, enzalutamide, darolutamide or apalutamide)[8].

Patients randomized to the change in the ARPI arm were allowed to crossover to receive Pluvicto upon confirmation of radiographic progression by blinded independent central review (BICR). There were 469 participants enrolled in the study[8].

The primary endpoint is rPFS, defined as the time from randomization to radiographic progression by PCWG3-modified RECIST v1.1 (as assessed by BICR) or death[8]. The key secondary endpoint of OS is defined as the time from date of randomization until the date of death due to any cause[8]. The pre-specified crossover-adjusted OS analysis was performed using the rank-preserving structural failure time (RPSFT) model to adjust for crossover[8].

About Pluvicto® (lutetium Lu 177 vipivotide tetraxetan)
Pluvicto is an intravenous radioligand therapy (RLT) combining a targeting compound (a ligand) with a therapeutic radionuclide (a radioactive particle, in this case lutetium-177)[9,10]. After administration into the bloodstream, Pluvicto binds to target cells, including prostate cancer cells that express PSMA, a transmembrane protein[9,10]. Once bound, energy emissions from the radioisotope damage the target cells and nearby cells, disrupting their ability to replicate and/or triggering cell death[10].

Pluvicto is approved in the U.S., the E.U. and other countries to treat adults with a type of advanced cancer called PSMA-positive mCRPC and who have already been treated with other anticancer treatments (ARPI and taxane-based chemotherapy)[11-15]. These regulatory decisions are supported by the results from the pivotal Phase III VISION trial, where Pluvicto met both primary endpoints of OS and rPFS, reducing the risk of death by 38% and the risk of radiographic progression or death by 60% compared to standard of care[9].

As part of our goal to move into earlier stages of disease, we have two additional Phase III studies to evaluate Pluvicto in earlier lines of treatment for PSMA-positive prostate cancer: PSMAddition (NCT04720157) is ongoing in the metastatic hormone-sensitive setting and PSMA-DC (NCT05939414) in the oligometastatic setting is in preparation. More information on these studies may be found at www.clinicaltrials.gov.

Novartis and Prostate Cancer
With more than 1.4 million new cases and 375,000 deaths in 2020 alone, prostate cancer is the most frequently diagnosed cancer in men in 112 countries – more than half the world[16].

At Novartis, we are harnessing the innovation of our world-class scientists, strategic partnerships and one of the industry's most competitive pipelines to explore the potential of new, targeted therapies and precision medicine platforms to address the greatest unmet needs in prostate cancer.

Our goal is to reduce the global disease burden, extend the lives of patients with prostate cancer and elevate current standards of care.

Novartis and Radioligand Therapy (RLT)

Novartis is reimagining cancer care with RLT for patients with advanced cancers. By harnessing the power of radioactive atoms and applying it to advanced cancers, RLT is theoretically able to deliver radiation to target cells anywhere in the body[17,18].

Novartis is investigating a broad portfolio of RLTs, exploring new isotopes, ligands and combination therapies to look beyond gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and prostate cancer and into breast, colon, lung and pancreatic cancer.

Novartis has established global expertise, specialized supply chain and manufacturing capabilities across its network of RLT production sites. In order to support growing demand for our RLT platform, we have expanded our production capabilities in Millburn, New Jersey (U.S.), Zaragoza (Spain) and Ivrea (Italy) and have a new-state-of-the art facility in Indianapolis, Indiana (U.S.), which is expected to open in the coming months, pending approval from the U.S. Food and Drug Administration (FDA) approval. We are continually evaluating additional opportunities to expand capacity around the world.

Important Safety Information

Use of PLUVICTO involves exposure to radioactivity. Long-term, accruing radiation exposure is associated with increased risk for cancer. To minimize radiation exposure to others following administration of PLUVICTO, patients are advised 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.

PLUVICTO may cause low level of blood cell counts. Patients should tell their doctor right away if they develop any new or worsening symptoms, including tiredness or weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty to stop bleeding, or frequent infections with signs such as fever, chills, sore throat, or mouth ulcers. PLUVICTO may also cause problems with kidneys. Patients should tell their doctor right away if they develop any new or worsening symptoms, including passing urine less often or passing much smaller amounts of urine than usual.

Before receiving PLUVICTO, patients should tell their doctor if they have low level of blood cell counts (hemoglobin, white blood cell count, absolute neutrophil count, platelet count); if they have or have had tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty stopping bleeding, or frequent infections with signs such as fever, chills, sore throat, or mouth ulcers (possible signs of myelosuppression); if they have or have had kidney problems; if they have or have had any other type of cancer or treatment for cancer, as PLUVICTO contributes to long-term cumulative radiation exposure; and if they are sexually active, as all radiopharmaceuticals, including PLUVICTO, have the potential to cause harm to an unborn baby. Patients should use effective contraception for intercourse during treatment with PLUVICTO and for 14 weeks after the last dose. PLUVICTO may cause temporary or permanent infertility.

Before administration of PLUVICTO patients should drink plenty of water in order to urinate as often as possible during the first hours after administration.

The most common side effects of PLUVICTO include tiredness, dry mouth, nausea, low red blood cell count, loss of appetite, changes in bowel movements (constipation or diarrhea), vomiting, low blood platelet count, urinary tract infection, weight loss, and abdominal pain.

Please see full Prescribing Information for PLUVICTO at https://www.novartis.us/sites/www.novartis.us/files/pluvicto.pdf.

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "may," "could," "would," "expect," "anticipate," "seek," "look forward," "believe," "committed," "investigational," "pipeline," "launch," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is a focused innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

Reimagine medicine with us: Visit us at https://www.novartis.com and connect with us on LinkedIn, Facebook, X/Twitter and Instagram.

References

1. Novartis Data on File.
2. Novartis. Press release. Novartis Pluvicto™ shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA-positive metastatic castration-resistant prostate cancer. December 5, 2022. https://www.novartis.com/news/media-releases/novartis-pluvictotm-shows-statistically-significant-and-clinically-meaningful-radiographic-progression-free-survival-benefit-patients-psma-positive-metastatic-castration-resistant-prostate-cancer
3. American Cancer Society (ACS). Survival Rates for Prostate Cancer. Accessed October 2022. https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-stagi….
4. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(22):2091-2102. doi:10.1056/NEJMoa1911440.
5. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019;381(26):2506-

2518. doi:10.1056/NEJMoa1911206.
6. Komura K, Fujiwara Y, Uchimoto T, et al. Comparison of Radiographic Progression-Free Survival and PSA Response on Sequential Treatment Using Abiraterone and Enzalutamide for Newly Diagnosed Castration-Resistant Prostate Cancer: A Propensity Score Matched Analysis from Multicenter Cohort. J Clin Med. 2019;8(8):1251. Published 2019 Aug 19. doi:10.3390/jcm8081251.
7. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-1512. doi:10.1056/NEJMoa040720.
8. Novartis Pharmaceuticals. ^{177}Lu-PSMA-617 vs. Androgen Receptor-directed Therapy in the Treatment of Progressive Metastatic Castrate Resistant Prostate Cancer (PSMAfore). U.S. National Library of Medicine: Clinical Trials. 2020; NCT04689828.
9. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385(12):1091-1103. doi:10.1056/NEJMoa2107322.
10. University of Chicago Medicine. Lutetium-177 PSMA Therapy for Prostate Cancer (Pluvicto). Accessed October 3, 2023. https://www.uchicagomedicine.org/cancer/types-treatments/prostate-cance…
11. Pluvicto [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; 2022.
12. Pluvicto [Summary of Product Characteristics]. EMA. 2022
13. Advanced Accelerator Applications USA, Inc. PLUVICTO™ Canadian Product Monograph. August 25, 2022.
14. Pluvicto [Summary of Product Characteristics]. Great Britain. 2022.
15. Swissmedic. Pluvicto® und Pluvicto® CA Injektions-/Infusionslösung i.v. (Lutetium(^{177}Lu)-vipivotid-Tetraxetan). Accessed October 3, 2023. https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authoris…
16. Sung H, Ferlay J, Siegel RL, Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660.
17. Jadvar H. Targeted Radionuclide Therapy: An Evolution Toward Precision Cancer Treatment [published correction appears in AJR Am J Roentgenol. 2017 Oct;209(4):949]. AJR Am J Roentgenol. 2017;209(2):277-288. doi:10.2214/AJR.17.18264
18. Jurcic JG, Wong JYC, Knoc SJ, et al. Targeted radionuclide therapy. In: Tepper JE, Foote RE, Michalski JM, eds. Gunderson & Tepper's Clinical Radiation Oncology. 5th ed. Elsevier, Inc. 2021;71(3):209-249.

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Novartis Media Relations

E-mail: media.relations@novartis.com

Central		North America	
Richard Jarvis	+41 79 584 2326	Julie Masow	+1 862 579 8456
Anja von Treskow	+41 79 392 9697	Michael Meo	+1 862 274 5414
Anna Schäfers	+41 79 801 7267	Marlena Abdinoor	+1 617 335 9525
Switzerland Satoshi Sugimoto	+41 79 619 2035		

Novartis Investor Relations

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 345 4440
Nicole Zinsli-Somm	+41 61 324 3809	Parag Mahanti	+1 973 876 4912
Isabella Zinck	+41 61 324 7188	Jonathan Graham	+1 201 602 9921
Imke Kappes	+41 61 324 8269		
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10. https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html
11. https://www.uchicagomedicine.org/cancer/types-treatments/prostate-cancer/treatment/lutetium-177-psma-therapy-for-prostate-cancer
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