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MEDIA & INVESTOR RELEASE

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

- *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*

Basel, October 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 (^{177}Lu) 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 (^{177}Lu) 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.

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.

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