

MEDIA & INVESTOR RELEASE

Novartis ¹⁷⁷Lu-PSMA-617 significantly improves overall survival and radiographic progression-free survival for men with metastatic castration-resistant prostate cancer in Phase III VISION study

- *Men who received ¹⁷⁷Lu-PSMA-617 plus best standard of care had a 38% reduction in risk of death (median OS benefit of 4 months) and a 60% reduction in the risk of radiographic disease progression or death (median rPFS benefit of 5 months) compared to best standard of care alone¹*
- *Significant improvement demonstrated in all key secondary endpoints, including time to first symptomatic skeletal event, overall response rate and disease control rate¹*
- *VISION study findings to be presented during 2021 ASCO plenary; regulatory submissions to US and EU Health Authorities on track for 2H21; two additional pivotal studies in earlier lines of treatment for metastatic prostate cancer to start 1H21, goal to move into earlier stages of disease*
- *Novartis commitment to leadership in radioligand therapy (RLT) further strengthened by recent partnerships and investments; more than 15 ongoing research and discovery programs to identify and accelerate next wave of RLTs for cancer*

Basel, June 3, 2021 — Novartis today announced that results of the Phase III VISION study evaluating ¹⁷⁷Lu-PSMA-617, a targeted radioligand therapy, plus best standard of care (SOC) demonstrated significant improvement in overall survival (OS) compared to SOC alone, in patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)¹. The difference in OS between study arms was statistically significant (one-sided $p < 0.001$), with an estimated 38% reduction in risk of death in the ¹⁷⁷Lu-PSMA-617 arm (n=551) compared to the best standard of care only arm (n=280) (hazard ratio: 0.62 with 95% confidence interval (CI): (0.52, 0.74))¹. These results will be presented during the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting plenary session on June 6.

Patients receiving ¹⁷⁷Lu-PSMA-617 also demonstrated a statistically significant (one-sided $p < 0.001$) 60% risk reduction for radiographic progression-free survival or death (rPFS), compared to the best standard of care only arm (hazard ratio: 0.40 with 99.2% CI: (0.29, 0.57))¹. There was a higher rate of drug-related treatment emergent adverse events reported in the ¹⁷⁷Lu-PSMA-617 treatment arm (85.3%) compared to standard of care alone (28.8%)¹.

Across both arms of the study, rates of treatment discontinuation associated with treatment-emergent adverse events occurred as follows: In the ¹⁷⁷Lu-PSMA-617 plus standard of care (SOC) arm, 11.9% of patients discontinued ¹⁷⁷Lu-PSMA-617 and 8.5% discontinued SOC; while in the SOC alone arm 7.8% of patients discontinued treatment¹.

“Patients suffering from metastatic CRPC who have progressed through contemporary hormonal treatments and chemotherapy have few meaningful therapeutic options,” said Michael J. Morris, MD, who chaired the study’s Scientific Committee and is the Prostate Cancer Section Head, Genitourinary Oncology Service, Division of Solid Tumor Oncology at Memorial Sloan Kettering Cancer Center. “The study demonstrated that ¹⁷⁷Lu-PSMA-617 improves disease progression and prolongs survival, which are key measures of clinical benefit in the mCRPC population. I am grateful to be a part of this study that may lead to additional therapeutic options for these patients.”

“Men with metastatic prostate cancer have an approximately 3 in 10 chance of surviving 5 years². These data from the first Phase III study of a radioligand therapy in this advanced prostate cancer setting confirm the potential of ¹⁷⁷Lu-PSMA-617 targeted therapy to improve clinical outcomes,” said John Tsai, Head of Global Drug Development and Chief Medical Officer for Novartis. “Our comprehensive development program for this targeted therapy seeks to reach eligible patients with advanced prostate cancer, who express the PSMA biomarker^{1,3-6}. And, we won’t stop with prostate cancer, our team is exploring next generation RLT across a number of tumor types.”

Two additional studies with ¹⁷⁷Lu-PSMA-617 radioligand therapy in earlier lines of treatment for metastatic prostate cancer are planned to start in the first half of 2021, investigating potential clinical utility in the mCRPC pre-taxane setting (PSMAfore) and in the metastatic hormone-sensitive setting (PSMAddition).

Additional VISION data

Median OS (95% CI) for the ¹⁷⁷Lu-PSMA-617 plus best standard of care arm in the VISION study was 15.3 months (14.2, 16.9), compared to 11.3 months (9.8, 13.5) in the best standard of care arm only¹. The median rPFS (99.2% CI) was 8.7 months (7.9, 10.8) for the ¹⁷⁷Lu-PSMA-617 arm compared to 3.4 months (2.4, 4.0) for the best standard of care only arm¹.

Key secondary endpoints were also met. The median time to first symptomatic skeletal event was 11.5 months (95% CI: 10.3, 13.2) in ¹⁷⁷Lu-PSMA-617 arm compared to 6.8 months (95% CI: 5.2, 8.5) in the best standard of care only arm (hazard ratio: 0.50 (95%CI: 0.40, 0.62)); two-sided p-value: <0.001¹. Significant differences were also seen in overall response rate in patients with measurable or non-measurable disease at baseline (29.8% partial or complete response in the ¹⁷⁷Lu-PSMA-617 arm compared to 1.7% partial response in the best standard of care only arm (two-sided p-value: <0.001)) and disease control rate (89.0% in ¹⁷⁷Lu-PSMA-617 arm compared to 66.7% in the best standard of care only arm (two-sided p-value: <0.001))¹.

Grade ≥3 drug-related treatment emergent adverse events occurred in 28.4% of the ¹⁷⁷Lu-PSMA-617 arm compared to 3.9% in the best standard of care only arm¹. The most common treatment emergent adverse events regardless of drug relatedness (above 2% respectively for the ¹⁷⁷Lu-PSMA-617 and best standard of care arm) were anemia (12.9% vs. 4.9%), thrombocytopenia (7.9% vs. 1%), lymphopenia (7.8% vs. 0.5%), fatigue (5.9% vs. 1.5%), urinary tract infection (3.8% vs 0.5%), neutropenia (3.4% vs 0.5%), hypertension (3.2% vs 1.5%), back pain (3.2% vs. 3.4%), acute kidney injury (3.0% vs 2.4%), leukopenia (2.5% vs. 0.5%), bone pain (2.5% vs. 2.4%), hematuria (2.5% vs 0.5%), and spinal cord compression (1.3% vs. 5.4%)¹.

Serious drug-related treatment emergent adverse events occurred in 9.3% of patients in the ¹⁷⁷Lu-PSMA-617 arm compared to 2.4% in the best standard of care only arm¹.

Visit <https://www.hcp.novartis.com/virtual-congress/a-2021/> for the latest information from Novartis, including our commitment to the Oncology community, and access to our ASCO21 Virtual Scientific Program data presentations (for registered participants).

About Advanced Prostate Cancer

Prostate cancer is a form of cancer that develops in the prostate gland, a small walnut shaped gland in the pelvis of men. In castration resistant prostate cancer (CRPC), the tumor shows signs of growth, such as rising Prostate Specific Antigen (PSA) levels, despite the use of hormone treatments that lower testosterone⁷. In metastatic CRPC (mCRPC), the tumor spreads to other parts of the body, such as neighboring organs or bones and remains unresponsive to hormone treatment⁷. The five-year survival rate for patients with metastatic prostate cancer is approximately 30%².

About Phenotypic Precision Medicine in Advanced Prostate Cancer

Despite advances in prostate cancer care, there is a high unmet need for new targeted treatment options to improve outcomes for patients with mCRPC. More than 80% of prostate cancer tumors highly express a phenotypic biomarker⁶ called Prostate Specific Membrane Antigen (PSMA)^{3-5,8-9}, making it a promising diagnostic (through positron emission tomography (PET) scan imaging) and potential therapeutic target for radioligand therapy¹⁰. This differs from 'genotypic' precision medicine which targets specific genetic alterations in cancer cells⁶.

About ¹⁷⁷Lu-PSMA-617

¹⁷⁷Lu-PSMA-617 is an investigational PSMA-targeted radioligand therapy for metastatic castration-resistant prostate cancer. It is a type of precision cancer treatment combining a targeting compound (ligand) with a therapeutic radioisotope (a radioactive particle)¹¹⁻¹³. After administration into the bloodstream, ¹⁷⁷Lu-PSMA-617 binds to prostate cancer cells that express PSMA¹⁴, a transmembrane protein, with high tumor-to-normal tissue uptake^{11,15,16}. Once bound, emissions from the radioisotope damage tumor cells, disrupting their ability to replicate and/or triggering cell death¹⁷⁻¹⁹. The radiation from the radioisotope works over very short distances to limit damage to surrounding cells^{10,11,15}.

About VISION

VISION is an international, prospective, randomized, open-label, multicenter, phase III study to assess the efficacy and safety of ¹⁷⁷Lu-PSMA-617 (7.4 GBq administered by intravenous infusion every 6 weeks for a maximum of 6 cycles) plus investigator-chosen best standard of care in the investigational arm, versus best standard of care in the control arm²⁰. Patients with PSMA PET-scan positive mCRPC, and progression after prior taxane and androgen receptor pathway inhibitors, were randomized in a 2:1 ratio in favor of the investigational arm²⁰. The alternate primary endpoints were rPFS and OS²⁰. The study enrolled 831 patients¹.

Disclaimer

This media update 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," "will," "would," "anticipated," "believe," "committed," "commitment," "investigational," "evaluating," "promising," "ambition," "opportunity," "upcoming," "pursuing," "underway," "to ensure," "intend," "to submit," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for ¹⁷⁷Lu-PSMA-617, or regarding potential future revenues from ¹⁷⁷Lu-PSMA-617. 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 ¹⁷⁷Lu-PSMA-617 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 ¹⁷⁷Lu-PSMA-617 will be commercially successful in the future. In

particular, our expectations regarding ¹⁷⁷Lu-PSMA-617 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 such as COVID-19; 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 media update as of this date and does not undertake any obligation to update any forward-looking statements contained in this media update as a result of new information, future events or otherwise.

About Novartis

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 110,000 people of more than 140 nationalities work at Novartis around the world. Find out more at <https://www.novartis.com>.

Novartis is on Twitter. Sign up to follow @Novartis at <https://twitter.com/novartisnews>
For Novartis multimedia content, please visit <https://www.novartis.com/news/media-library>
For questions about the site or required registration, please contact media.relations@novartis.com

References

1. Novartis Data on File
2. SEER. Cancer stat facts: prostate cancer April 2021. [<https://seer.cancer.gov/statfacts/html/prost.html>]
3. Hupe MC, Philippi C, Roth D, et al. Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis. *Front Oncol* 2018;8:623
4. Bostwick DG, Pacelli A, Blute M, et al. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer* 1998;82(11):2256–61
5. Pomykala KL, Czernin J, Grogan TR, et al. Total-body ⁶⁸Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients: potential impact on bone scan guidelines. *J Nucl Med* 2020;61(3):405–11
6. Sant GR, Knopf KB, Albala DM. Live-single-cell phenotypic cancer biomarkers-future role in precision oncology? *NPJ Precision Oncology* 2017;1(1):21
7. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011;65(11):1180–92
8. Minner S, Wittmer C, Graefen M, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. *Prostate* 2011;71(3):281–8
9. Hope TA, Aggarwal R, Chee B, et al. Impact of ⁶⁸Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. *J Nucl Med* 2017;58(12):1956–61
10. Hofman MS, Violet J, Hicks RJ et al. [¹⁷⁷Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol* 2018;19(6):825–33
11. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. *J Nucl Med* 2016;57(8):1170–6 [<https://pubmed.ncbi.nlm.nih.gov/26985056/>]
12. Eder M, Schäfer M, Bauder-Wüst U, et al. ⁶⁸Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. *Bioconj Chem* 2012;23(4):688–97.
13. Benešová M, Schäfer M, Bauder-Wüst U, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med* 2015;56(6):914–20

14. Haberkorn U, Eder M, Kopka K, et al. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. *Clin Cancer Res* 22(1):9-15.2016
15. Violet J, Jackson P, Ferdinandus J et al. Dosimetry of (177)Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med* 2019;60(4):517–23
16. Current K, Meyer C, Magyar CE et al. Investigating PSMA-targeted radioligand therapy efficacy as a function of cellular PSMA levels and intra-tumoral PSMA heterogeneity. *Clin Cancer Res* 2020;26(12):2946–55.
17. Kassis A. Therapeutic Radionuclides: Biophysical and Radiobiologic Principles. *Semin Nucl Med.* 2008; 38(5): 358–366
18. Fendler W, Stuparu A, et al. Establishing 177Lu-PSMA-617 Radioligand Therapy in a Syngeneic Model of Murine Prostate Cancer. *J Nucl Med* 2017; 58: 1786–1792
19. Ruigrok E, van Vliet N, et al. Extensive preclinical evaluation of lutetium-177-labeled PSMA-specific tracers for prostate cancer radionuclide therapy. *Eur J Nucl Med Mol Imaging.* 2020; 48: 1339-1350
20. Sartor AO, Morris MJ, Krause BJ. VISION: an international, prospective, open-label, multicenter, randomized phase 3 study of ¹⁷⁷Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2019;37(15 suppl):TPS5099

###

Novartis Media Relations

E-mail: media.relations@novartis.com

Anja von Treskow
 Novartis Global Media Relations
 +41 79 392 8697
anja.von_treskow@novartis.com

Rachel Levine
 Advanced Accelerator Applications, a Novartis
 Company
 +1 917 375 2935
rachel.levine@novartis.com

Julie Masow
 Novartis US External Engagement
 +1 862 579 8456
julie.masow@novartis.com

Novartis Investor Relations

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

Central
 Samir Shah +41 61 324 7944
 Thomas Hungerbuehler +41 61 324 8425
 Isabella Zinck +41 61 324 7188

North America
 Sloan Simpson +1 862 778 5052