PRESS RELEASE

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Blue Earth Therapeutics Announces Results of Early Clinical and Preclinical Studies of Investigational ^{177}Lu-rhPSMA-10.1 in Treatment of Prostate Cancer

– ^{177}Lutetium-labeled radiohybrid (rh) Prostate-Specific Membrane Antigen (^{177}Lu-rhPSMA-10.1) is an optimized, next generation therapeutic radiopharmaceutical –

– Investigational Phase 1/2 clinical trial underway in U.S. –

MONROE TOWNSHIP, NJ and OXFORD, UK, June 28, 2023 – Blue Earth Therapeutics, a Bracco company and emerging leader in the development of innovative next generation therapeutic radiopharmaceuticals, today announced highlights from early clinical and preclinical studies of ^{177}Lu-rhPSMA-10.1 by the Company and a collaborator at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Annual Meeting, June 24 – 27, 2023. ^{177}Lu-rhPSMA-10.1 is an investigational radiohybrid (rh) Prostate-Specific Membrane Antigen-targeted therapeutic radiopharmaceutical for the treatment of prostate cancer. The presentations included results from an independent clinical study conducted by the University of Augsburg that investigated dosimetry and the therapeutic index for ^{177}Lu-rhPSMA-10.1. Also being presented are results of Blue Earth Therapeutics' preclinical studies that examined the therapeutic dose response of ^{177}Lu-rhPSMA-10.1 and the therapeutic efficacy of ^{177}Lu-rhPSMA-10.1 as compared to several other compounds. ^{177}Lu-rhPSMA-10.1 is the first clinical candidate in Blue Earth Therapeutics' oncology development program of advanced targeted therapeutic radiopharmaceuticals. An investigational Phase 1/2 clinical trial (NCT05413850) evaluating the safety, tolerability, dosimetry and anti-tumor activity of ^{177}Lu-rhPSMA-10.1 in eligible men with metastatic castrate-resistant prostate cancer (mCRPC) is underway in the United States.

"We are pleased to share these initial results from Blue Earth Therapeutics' rhPSMA-10.1 program in prostate cancer with the nuclear medicine community at the SNMMI 2023 Annual Meeting," said David E. Gauden, D.Phil., Chief Executive Officer of the Company. "Our goal at Blue Earth Therapeutics is to deliver precise, targeted therapy specific to the patient's condition. The radiohybrid PSMA theranostic technology platform enables molecules within the class to be modified and deployed for either diagnostic PET imaging or therapeutic applications, and can also be developed with both beta- and alpha-emitting therapeutic radioisotopes. Our lead therapeutic compound, ^{177}Lu-rhPSMA-10.1, was carefully optimized during development with the aim of maximizing its therapeutic index by delivering high radiation doses to prostate cancer lesions while sparing normal tissues as far as possible. The preclinical efficacy results in prostate cancer xenografts reported here support a promising therapeutic profile for^{177}Lu-rhPSMA-10.1. They are further supported by the early clinical experience of our collaborators in Augsburg, where the team observed an average 3.3-fold higher tumor absorbed radiation dose compared to PSMA-I&T in a direct intra-patient comparison, without a proportional increase in radiation dose to the kidney.

Highlights of the presentations

Improved therapeutic index with the novel PSMA-ligand ^{177}Lu-rhPSMA-10.1 compared to ^{177}Lu-PSMA I&T – an intrapatient comparison

Results from an independent clinical study by BET collaborators at University Hospital Augsburg, Augsburg, Germany, were presented by Ralph Bundschuh, MD, PhD, Nuclear Medicine, Faculty of Medicine. The study was designed to evaluate and compare dosimetry and therapeutic indices for ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA I&T. It included 4 patients with advanced, histologically confirmed metastatic castrate resistant prostate cancer, each patient received ^{177}Lu-rhPSMA-10.1 (1.06 ± 0.05 GBq) and ^{177}Lu-PSMA-I&T (1.09 ± 0.02 GBq), within 2 subsequent weeks. Dosimetry studies were performed to assess whole body uptake as well as, more specifically, uptake in salivary glands, kidneys, liver, spleen, bone marrow and up to 4 tumor lesions. The therapeutic index (TI), the ratio between mean dose to the metastases and the mean dose to the kidneys, was calculated for each patient.

The effective whole-body dose was found to be (0.038 ± 0.008) Sv/GBq for ^{177}Lu-rhPSMA-10.1 and thus higher than for ^{177}Lu-PSMA-I&T (0.022 ± 0.005) Sv/GBq, mainly due to 50% higher dose to the kidneys with (0.69 ± 0.30) Gy/GBq for ^{177}Lu-rhPSMA-10.1 vs. (0.46 ± 0.11) Gy/GBq for ^{177}Lu-PSMA-I&T. Bone marrow doses were (0.07 ± 0.06) Gy/GBq for ^{177}Lu-rhPSMA-10.1 vs. (0.04 ± 0.04) Gy/GBq for ^{177}Lu-PSMA-I&T, while doses to the salivary glands were (0.43 ± 0.18) Gy/GBq for ^{177}Lu-rhPSMA-10.1 vs. (0.13 ± 0.04) Gy/GBq for ^{177}Lu-PSMA-I&T. Tumor doses were significantly higher with ^{177}Lu-rhPSMA-10.1 than ^{177}Lu-PSMA-I&T. Across each evaluated lesion, ^{177}Lu-rhPSMA-10.1 delivered an average of 3.3 times (1.2-8.3) higher tumor absorbed radiation dose. The TI was higher for ^{177}Lu-rhPSMA-10.1 compared with ^{177}Lu-PSMA-I&T (Patient 1, 43%, Patient 2, 213%, Patient 3, 70%, Patient 4, 6.4%) in all cases. Based on these initial results, the use of ^{177}Lu-rhPSMA-10.1 has the potential to increase the tumor absorbed dose and improve the TI. An improved TI gives the option of maximizing tumor absorbed radiation doses, or, in earlier disease, reducing the radiation exposure to normal organs while still achieving an effective tumor dose. They noted that careful assessment of kidney and salivary gland organ function in prospective clinical trials is necessary.

Enhanced therapeutic response to ^{177}Lu-rhPSMA-10.1 in preclinical models of prostate cancer

Caroline Foxton, Ph.D., Blue Earth Therapeutics, Oxford, UK, presented data from preclinical models of prostate cancer designed to evaluate the therapeutic response to ^{177}Lu-rhPSMA-10.1 using several radiation dose levels, and compare the efficacy of ^{177}Lu-rhPSMA-10.1 to ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T. Results showed that in LNCaP xenografts a single dose of ^{177}Lu-rhPSMA-10.1 significantly suppressed tumor growth (from day 11, $p<0.05$, to day 32, $p<0.0001$) and prolonged survival ($p=0.001$) at all doses tested (15, 30 or 45MBq) compared with controls. Tumor growth was significantly reduced with 30 MBq and 45 MBq compared with 15 MBq of ^{177}Lu-rhPSMA-10.1 (from day 35, $p=0.001$, to day 49, $p<0.0001$), suggesting a dose-response effect. Median survival was 28 days for vehicle control and was not reached for the ^{177}Lu-rhPSMA-10.1 groups at the study endpoint and all dose levels of ^{177}Lu-rhPSMA-10.1 were well-tolerated.

In 22Rv1 xenografts, both ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-617 significantly suppressed tumor growth (from day 18 onwards, $p<0.05$, to day 35, $p<0.0001$) and prolonged survival ($p\leq0.01$) compared with vehicle control. ^{177}Lu-PSMA I&T inhibited tumor growth to a lesser extent (from day 25 onwards, $p<0.05$, to day 35, $p<0.0001$). When compared with ^{177}Lu-PSMA-I&T, ^{177}Lu-rhPSMA-10.1 significantly reduced tumor growth from day 32 onwards ($p<0.05$) to day 49 ($p<0.0001$), whereas ^{177}Lu-PSMA-617 significantly reduced tumor growth on day 49 only ($p<0.05$). Median survival was 33.5 days for vehicle control, 44

days for ^{177}Lu-PSMA-I&T and was not reached for the ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-617 groups. All treatments were well-tolerated. The authors concluded that the analyses demonstrate significant therapeutic efficacy with ^{177}Lu-rhPSMA-10.1 in prostate cancer xenografts, at clinically and sub-clinically equivalent dose levels. They noted that the promising therapeutic profile observed for ^{177}Lu-rhPSMA-10.1 compared with ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T further supports its clinical development.

About Radiohybrid Prostate-Specific Membrane Antigen (rhPSMA)
Radiohybrid Prostate-Specific Membrane Antigen (rhPSMA) compounds consist of a radiohybrid ("rh") Prostate-Specific Membrane Antigen-targeted receptor ligand, which attaches to and is internalized by prostate cancer cells, which can be radiolabeled with imaging isotopes for PET imaging, or with therapeutic isotopes for therapeutic use – providing the potential for creating a true theranostic technology. Radiohybrid technology and rhPSMA originated from the Technical University of Munich, Germany. Blue Earth Diagnostics acquired exclusive, worldwide rights to rhPSMA diagnostic imaging technology from Scintomics GmbH in 2018, and therapeutic rights in 2020, and sublicensed the therapeutic application to its sister company Blue Earth Therapeutics. Blue Earth Diagnostics received U.S. Food and Drug Administration approval for its radiohybrid PSMA PET diagnostic imaging product for use in prostate cancer in 2023. rhPSMA compounds for potential therapeutic use are investigational and have not received regulatory approval.

About Blue Earth Therapeutics
Blue Earth Therapeutics, one of the Bracco family of companies, is a clinical stage company dedicated to advancing next generation targeted radiotherapeutics to treat patients who have cancer. With proven management expertise across the spectrum of radiopharmaceutical and oncology drug development, as well as biotechnology start-up experience, the Company aims to innovate and improve upon current technologies and rapidly advance new targeted therapies for serious diseases. Blue Earth Therapeutics has an emerging pipeline, initially focused on prostate cancer, and with plans to expand into additional disease areas in oncology. Blue Earth Therapeutics is an indirect subsidiary of Bracco Imaging S.p.A, and based in Oxford, UK. For more information, please visit: https://www.blueearththerapeutics.com.

About Bracco Imaging
Bracco Imaging S.p.A., part of the Bracco Group, is a world-leading diagnostic imaging provider. Headquartered in Milan, Italy, Bracco Imaging develops, manufactures and markets diagnostic imaging agents and solutions. It offers a product and solution portfolio for all key diagnostic imaging modalities: X-ray imaging (including Computed Tomography-CT, Interventional Radiology, and Cardiac Catheterization), Magnetic Resonance Imaging (MRI), Contrast Enhanced Ultrasound (CEUS), and Nuclear Medicine through radioactive tracers and novel PET imaging agents to inform clinical management and guide care for cancer patients in areas of unmet medical need. Our continually evolving portfolio is completed by a range of medical devices, advanced administration systems and dose-management software. In 2019 Bracco Imaging enriched its product portfolio by expanding the range of oncology nuclear imaging solutions in the urology segment and other specialties with the acquisition of Blue Earth Diagnostics. In 2021, Bracco Imaging established Blue Earth Therapeutics as a separate, cutting-edge biotechnology vehicle to develop radiopharmaceutical therapies. Visit: www.braccoimaging.com.

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