PRESS RELEASE

Blue Earth Therapeutics Announces Promising Results of Preclinical Biodistribution and Efficacy Evaluation of ^{177}Lu-rhPSMA-10.1 in Treatment of Prostate Cancer

– ^{177}Lutetium-labelled radiohybrid Prostate-Specific Membrane Antigen (^{177}Lu-rhPSMA-10.1) is in development as a highly optimized, next generation therapeutic radiopharmaceutical –

– ^{177}Lu-rhPSMA-10.1 demonstrated favorable tumor:kidney ratio and statistically significant tumor growth suppression in preclinical studies –

– Phase 1/2 clinical trial of ^{177}Lu-rhPSMA-10.1 in men with metastatic castrate-resistant prostate cancer recently cleared to proceed in United States –

OXFORD, UK and BURLINGTON, Mass., June 14, 2022 – Blue Earth Therapeutics, a Bracco company and emerging leader in the development of innovative next generation therapeutic radiopharmaceuticals, today announced results from a series of preclinical analyses designed to evaluate the biodistribution and potential therapeutic efficacy of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T in the treatment of prostate cancer preclinical models. Results from preclinical biodistribution studies demonstrated that ^{177}Lu-rhPSMA-10.1 performed favorably when compared with ^{177}Lu-PSMA-I&T, with an improved tumor:kidney uptake ratio. Therapeutic efficacy was evaluated in a preclinical prostate cancer xenograft model which showed that ^{177}Lu-rhPSMA-10.1 significantly suppressed tumor growth relative to control, and to a greater extent than ^{177}Lu-PSMA-I&T. The data were presented in an oral presentation at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Annual Meeting. ^{177}Lu-rhPSMA-10.1 is an investigational radiohybrid (rh) Prostate-Specific Membrane Antigen-targeted therapeutic radiopharmaceutical, and the lead candidate in Blue Earth Therapeutics' oncology development program of next generation therapeutic radiopharmaceuticals.

"Radioligand therapy targeting prostate-specific membrane antigen (PSMA) has been shown to be an effective therapy in men with metastatic castration-resistant prostate cancer," said Caroline Foxton, Ph.D., Vice President R&D Strategy and Collaboration at the Blue Earth Group. "However, optimizing tumor uptake and accelerating renal clearance for this class of compounds could improve the therapeutic index, achieve better clinical outcomes and effectively manage radiation exposure to patients. Blue Earth Therapeutics' next generation therapeutic rhPSMA compound has been optimized for favorable biodistribution properties to enhance delivery of therapeutic radiation to tumors while minimizing kidney uptake and retention. Supported by these preclinical data, ^{177}Lu-rhPSMA-10.1 was selected as our lead therapeutic candidate for progression to the clinic."

"We are pleased that the first presentation of preclinical results from Blue Earth Therapeutics' rhPSMA-10.1 program in prostate cancer is being made to the nuclear medicine community at the SNMMI 2022 Annual Meeting," said David E. Gauden, D.Phil., Chief Executive Officer of the Company. "Radiohybrid PSMA technology enables utility as a theranostic because the molecule may be modified and deployed for either diagnostic PET imaging or therapeutic applications. This optimized rhPSMA technology can also be developed with both beta- and alpha-emitting therapeutic radioisotopes, with the potential to deliver personalized, targeted therapy specific to each patient's condition. We are closely collaborating

in the development of ^{177}Lu-rhPSMA-10.1 with our sister company, Blue Earth Diagnostics, by incorporating its investigational ^{18}F-rhPSMA-7.3 PET agent into our clinical development program. ”

Dr. Gauden continued, “Results from these analyses demonstrate the attractive preclinical biodistribution and potential therapeutic efficacy profile of ^{177}Lu-rhPSMA-10.1, and were included in our Investigational New Drug application to the U.S. Food and Drug Administration. Blue Earth Therapeutics’ Phase 1/2 clinical trial for ^{177}Lu-rhPSMA-10.1 in treating men with metastatic castrate-resistant prostate cancer was recently cleared to proceed, and we expect patient enrollment to commence shortly.”

Results

The findings presented at SNMMI included biodistribution data from preclinical models which evaluated ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T uptake and tumor:kidney ratio, and therapeutic efficacy analysis in preclinical prostate cancer xenograft models.

Biodistribution

Data from longitudinal biodistribution analyses in preclinical models showed that the most significant organ uptake for both ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T was observed in the kidney; however, kidney retention was lower for ^{177}Lu-rhPSMA-10.1 than ^{177}Lu-PSMA-I&T at all timepoints, and 6.5-fold lower than that for ^{177}Lu-PSMA-I&T at 12 hours. No other organ (including the brain) showed any significant uptake of ^{177}Lu-rhPSMA-10.1. A single-timepoint biodistribution study using a PSMA-expressing prostate cancer xenograft model examined the tumor:kidney uptake ratio for both compounds. It also showed lower kidney uptake of ^{177}Lu-rhPSMA-10.1, with kidney uptake being 6.4-fold lower for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T at 15 hours post-injection. Higher tumor uptake was seen with ^{177}Lu-rhPSMA-10.1 than ^{177}Lu-PSMA-I&T at this timepoint (2.3-fold), resulting in an improved tumor:kidney ratio for ^{177}Lu-rhPSMA-10.1 (2.3±1.14) compared to ^{177}Lu-PSMA-I&T (0.1±0.03).

Efficacy

The potential therapeutic efficacy of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T was compared in a PSMA-expressing prostate cancer xenograft model. Tumor volume was significantly reduced by ^{177}Lu-rhPSMA-10.1 compared with the vehicle control ($p=0.045$ at 35 days after treatment). When measuring fold-change in tumor volume relative to volume at inclusion, ^{177}Lu-rhPSMA-10.1 showed a statistically significant suppression of tumor growth compared to both non-radiolabeled rhPSMA-10.1 and vehicle control at both 14 days after treatment ($p<0.01$ both comparisons) and 35 days after treatment ($p<0.01$ vs non-radiolabeled rhPSMA-10.1 and $p<0.001$ vs vehicle). ^{177}Lu-PSMA-I&T also reduced tumor growth compared with vehicle control ($p<0.05$), but to a lesser extent than ^{177}Lu-rhPSMA-10.1. No significant effects were noted on any hematological parameters or body weight.

The results were discussed in an oral presentation, “Preclinical evaluation of a novel radioligand therapy for patients with prostate cancer: biodistribution and efficacy of ^{177}Lu-rhPSMA-10.1 in comparison with ^{177}Lu-PSMA-I&T,” by Caroline Foxton, Ph.D., Blue Earth Group, Oxford, UK, at the SNMMI 2022 Annual Meeting on June 13, 2022. Full session details and the abstract are available in the SNMMI online program HERE.

About Radiohybrid Prostate-Specific Membrane Antigen (rhPSMA)

rhPSMA compounds are referred to as radiohybrid (“rh”), as each molecule possesses three distinct domains. The first consists of a Prostate-Specific Membrane Antigen-targeted receptor ligand which attaches to and is internalized by prostate cancer cells. It is attached to two labelling moieties which may be radiolabeled with either ^{18}F for PET imaging, or with isotopes such as ^{177}Lu or ^{225}Ac for

therapeutic use – creating a true theranostic technology. They may play an important role in patient management in the future, and offer the potential for precision medicine for men with prostate cancer. 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 has sublicensed the therapeutic application to its sister company Blue Earth Therapeutics. Blue Earth Therapeutics and Blue Earth Diagnostics work closely on the development of ^{177}Lu-rhPSMA-10.1. Currently, rhPSMA compounds 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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