PRESS RELEASE

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Blue Earth Therapeutics Announces Promising Results of Preclinical Evaluation of ^{225}Ac-rhPSMA-10.1 for Potential Targeted Alpha Therapy of Prostate Cancer

– ^{225}Actinium-labeled radiohybrid Prostate-Specific Membrane Antigen (^{225}Ac-rhPSMA-10.1) is in development as a highly optimized, next generation therapeutic radiopharmaceutical –

– ^{225}Ac-rhPSMA-10.1 demonstrated favorable, significant tumor growth reduction in preclinical models –

– Abstract recognized as Top Rated Oral Presentation by European Association of Nuclear Medicine –

–Planned studies using ^{225}Ac radioisotope complement Company's ongoing Phase 1/2 clinical trial of ^{177}Lu-rhPSMA-10.1 in men with metastatic castrate resistant prostate cancer –

MONROE TOWNSHIP, NJ and OXFORD, UK, September 11, 2023 – 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 binding affinity, lipophilicity, cellular internalization and therapeutic efficacy of ^{225}Ac-rhPSMA-10.1 in preclinical models for the treatment of prostate cancer, using ^{177}Lu-rhPSMA-10.1 as a comparator. Results showed that both ^{225}Ac-rhPSMA-10.1 and ^{177}Lu-rhPSMA-10.1 demonstrated excellent PSMA binding affinity, high cellular internalization and similar lipophilicity. Therapeutic response and efficacy were evaluated in a preclinical prostate cancer model which showed that ^{225}Ac-rhPSMA-10.1 significantly suppressed tumor growth relative to control. The data were presented in an oral presentation at the Annual Congress of the European Association of Nuclear Medicine (EANM'23) in Vienna, Austria. ^{225}Ac-rhPSMA-10.1 is an investigational radiohybrid (rh) Prostate-Specific Membrane Antigen-targeted therapeutic radiopharmaceutical, and the lead alpha-emitting candidate in Blue Earth Therapeutics' oncology development program of next generation therapeutic radiopharmaceuticals.

"We are pleased that the first presentation of preclinical results from Blue Earth Therapeutics' prostate cancer program using rhPSMA-10.1 radiolabeled with ^{225}Ac is being made to the nuclear medicine community at the EANM'23 Annual Meeting," said David E. Gauden, D.Phil., Chief Executive Officer of the Company. "Underscoring our commitment to advancing science, we are also honored that the abstract has been recognized as a "Top Rated Oral Presentation" by the Association. ^{225}Ac-rhPSMA-10.1 is our second pipeline compound, and, like our lead Phase 1/2 compound ^{177}Lu-rhPSMA-10.1, it is based on innovative radiohybrid PSMA theranostic technology. The radiohybrid platform enables molecules within the class to be modified and deployed for either diagnostic PET imaging or therapeutic applications, and they can also be developed with both beta- and alpha-emitting therapeutic radioisotopes. The pharmacokinetic profile of rhPSMA-10.1 was carefully optimized during development to deliver high radiation doses to prostate cancer lesions while sparing normal tissues as far as possible, and we are building on that work by radiolabeling it with the powerful alpha-emitting radioisotope, ^{225}Ac.

Dr. Gauden continued, "Results from these preclinical analyses demonstrate a promising therapeutic profile for ^{225}Ac-rhPSMA-10.1, while using 1,000-fold lower radioactivity than ^{177}Lu-rhPSMA-10.1, with similar *in vitro* characteristics and *in vivo* therapeutic efficacy observed for both compounds. ^{225}Ac-rhPSMA-10.1 represents a novel alpha-targeted therapy that we intend to advance into the clinic. IND-enabling studies have been completed and we plan to initiate a Phase 1 clinical study of ^{225}Ac-rhPSMA-10.1 in the first half of 2024."

About the study

The findings presented at EANM'23 evaluated ^{225}Ac-rhPSMA-10.1 and ^{177}Lu-rhPSMA-10.1 in preclinical models for the treatment of prostate cancer. Binding affinity and cellular internalization assays were conducted in LNCaP cells, using ^{177}Lu-PSMA-I&T as a reference compound. The lipophilicity of ^{225}Ac-rhPSMA-10.1 and ^{177}Lu-rhPSMA-10.1 was determined by the shake-flask method, measuring the distribution coefficient in n-octanol and PBS at pH 7.4 (log $D_{7.4}$). Therapeutic response to single-administration of ^{225}Ac-rhPSMA-10.1 (30 kBq) or ^{177}Lu-rhPSMA-10.1 (30 MBq) was evaluated in the 22Rv1 preclinical model (n=8 per group). Efficacy was assessed based on relative tumour growth (change in tumour volume from treatment administration day/baseline) and survival of treated groups versus untreated controls ≤49 days post-treatment initiation. Body weights were monitored throughout for toxicity assessment.

Results

Both ^{nat}La-rhPSMA-10.1 and ^{nat}Lu-rhPSMA-10.1 (^{nat}La and ^{nat}Lu being cold surrogates of ^{225}Ac and ^{177}Lu) showed excellent PSMA binding affinity (IC_{50} = 3.6±0.6 nM and 1.6±0.1 nM, respectively). High cellular internalization and similar lipophilicity were observed for both ^{225}Ac-rhPSMA-10.1 and ^{177}Lu-rhPSMA-10.1 (% internalization = 99±14 and 108±5; log$D_{7.4}$ = -3.4±0.2 and -3.8±0.1; respectively). ^{225}Ac-rhPSMA-10.1 treatment significantly reduced tumour growth *in vivo* versus controls (from day 14 to 31, $p<0.05$), and prolonged survival (median survival: 27, 43.5, and 42 days for untreated, ^{225}Ac-rhPSMA-10.1, and ^{177}Lu-rhPSMA-10.1 groups, respectively). There were no significant differences in tumour growth suppression or survival between the ^{225}Ac-rhPSMA-10.1 and ^{177}Lu-rhPSMA-10.1 groups, and both treatments were well-tolerated.

The results were discussed in an oral presentation, "Preclinical Evaluation of ^{225}Ac-rhPSMA-10.1, a Novel Radiohybrid PSMA Compound for Targeted Alpha Therapy of Prostate Cancer," by Caroline Foxton, Ph.D., Blue Earth Group, Oxford, UK, at the Annual Congress of the European Association of Nuclear Medicine on September 10, 2023. Full session details and the abstract are available in the EANM 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 diagnostic isotopes such as ^{18}F or ^{68}Ga for PET imaging, or with therapeutic isotopes such as ^{177}Lu or ^{225}Ac for radioligand therapy – enabling the potential for 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, Blue Earth Therapeutics' 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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