PRESS RELEASE

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Blue Earth Therapeutics Announces Promising Results from Preclinical Evaluation of Synergistic Drug Combinations with Radiopharmaceutical ^{177}Lu-rhPSMA-10.1 for Treatment of Prostate Cancer

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

– Combination of MEK inhibitor cobimetinib with ^{177}Lu-rhPSMA-10.1 radioligand therapy showed enhanced therapeutic effect versus single agents in preclinical models –

– Research presented at AACR Annual Meeting 2024 complements Company's ongoing Phase 1/2 clinical trial of ^{177}Lu-rhPSMA-10.1 in men with metastatic castrate resistant prostate cancer –

MONROE TOWNSHIP, N.J. and OXFORD, UK, April 8, 2024 – 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 identify synergistic combinations of known anticancer drugs with ^{177}Lu-rhPSMA-10.1 radioligand therapy, and from a preclinical efficacy analysis of the lead novel drug combination for the treatment of prostate cancer. Results from a systematic *in vitro* screen identified MEK inhibitor cobimetinib as a lead candidate with potential for synergistic combination with ^{177}Lu-rhPSMA-10.1, and the preclinical efficacy analysis showed enhanced therapeutic effect of this drug combination when compared to the untreated control and to the single agents alone. The data were presented in a poster presentation at the American Association for Cancer Research (AACR) Annual Meeting 2024 in San Diego, Calif. ^{177}Lu-rhPSMA-10.1, an investigational radiohybrid (rh) Prostate-Specific Membrane Antigen-targeted therapeutic radiopharmaceutical, is the lead candidate in Blue Earth Therapeutics' oncology development program of next generation therapeutic radiopharmaceuticals.

"Radioligand therapy targeting PSMA has been shown to be an effective therapy in men with prostate cancer, and we are pleased to share these promising preclinical results from our study of ^{177}Lu-rhPSMA-10.1 drug combinations with the scientific community at the prestigious AACR Annual Meeting 2024," said David E. Gauden, D.Phil., Chief Executive Officer of Blue Earth Therapeutics. "Combination approaches are of increasing interest among the medical community, as we know tumors are heterogeneous and some prostate cancer cells do not express PSMA. Importantly, these combinations need to avoid overlapping toxicity. Results from this preclinical study presented at AACR demonstrated a synergistic therapeutic effect between ^{177}Lu-rhPSMA-10.1 and an MEK inhibitor. This may be due to inhibition of the MEK-MAPK pathway during DNA damage response, resulting in radiosensitization of cancer cells to ^{177}Lu-rhPSMA-10.1. Our ongoing Phase 1/2 clinical trial (NCT05413850) is evaluating ^{177}Lu-rhPSMA-10.1 radioligand therapy as a monotherapy in treating men with metastatic castrate resistant prostate cancer, and we may look to evaluate this combination in the clinic in the future."

About the study

More than 150 FDA-approved anticancer drugs were screened in a clonogenic survival assay of 22Rv1 cells using the test drug alone, at a range of concentrations <20 μM to determine the $IC_{50.}$ The results were then compared to incubations of the drug plus 15 MBq/mL ^{177}Lu-rhPSMA-10.1 (2 hour incubation) after 10 days. Five lead candidates were then selected for a focused screen where the impact of ^{177}Lu-rhPSMA-10.1 (0–25 MBq/mL) on the drug IC_{50} was determined. A synergy score was determined using the zero interaction potency (ZIP) reference model and the multi-dimensional synergy of combinations (MuSyc) platform. Therapeutic efficacy of the lead combination, ^{177}Lu-rhPSMA-10.1 (single 30 MBq iv dose) plus cobimetinib (0.25 mg orally per day for 21 days), was then evaluated in 22Rv1 prostate tumor xenograft models and compared to the single agents alone (n = 8 per group, plus untreated controls). Tumor volume was measured 2 times per week for 69 days. Two-way ANOVA and Tukey's multiple comparisons test (data analyzed until n = 3 remained per group) and Kaplan-Meier Log-rank survival analyses were performed.

Results

The *in vitro* screen identified the MEK inhibitor cobimetinib as a lead candidate for synergistic combination with ^{177}Lu-rhPSMA-10.1 across a wide concentration range, with a ZIP synergy score of 13.25% (95% CI ± 2.17) and promising results on MuSyc analysis. The ^{177}Lu-rhPSMA-10.1 plus cobimetinib MEK inhibitor combination significantly suppressed tumor growth *in vivo* versus untreated controls (from day 13–30; $p<0.01$) and ^{177}Lu-rhPSMA-10.1 alone (from day 17–30; $p<0.001$). The median survival in the combination group (49 days) was significantly longer versus the untreated group (23 days; $p=0.001$) and the group treated with ^{177}Lu-rhPSMA-10.1 alone (36 days; $p=0.002$).

The results were discussed in a poster presentation, "Evaluation of a synergistic drug combination with ^{177}Lu-rhPSMA-10.1 for prostate cancer: Results of an *in vitro* screen and *in vivo* proof of concept study," by Caroline Foxton, Ph.D., Blue Earth Group, Oxford, UK, at the AACR Annual Meeting 2024 on April 7, 2024. The abstract is available in the 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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