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Actinium Pharmaceuticals Announces Clinical Trial Program in Solid Tumors Combining Actimab-A with PD-1 Checkpoint Inhibitors KEYTRUDA® and OPDIVO®

- Trials are designed to demonstrate whether the addition of Actimab-A to either KEYTRUDA® or OPDIVO® can result in improved patient outcomes

- MDSCs – Myeloid Derived Suppressor Cells in the tumor microenvironment are believed to reduce effectiveness of PD-1 inhibitors like KEYTRUDA® and OPDIVO®

- Trials supported by preclinical data showing Actimab-A can selectively target and deplete MDSCs which express CD33

- Clinical proof of concept data expected in 2025 could potentially open up a multi-billion-dollar market opportunity for Actimab-A as a combination therapy with PD-1 inhibitors in multiple solid tumors

NEW YORK, March 18, 2025 /PRNewswire/ -- **Actinium Pharmaceuticals, Inc.** (NYSE AMERICAN: ATNM) (Actinium or the Company), a pioneer in the development of targeted radiotherapies, today announced a clinical program comprising of trials studying Actimab-A in combination with either KEYTRUDA® (pembrolizumab) or OPDIVO® (nivolumab) which are blockbuster immunotherapies known as PD-1 inhibitors which are approved in multiple solid tumor indications. KEYTRUDA® developed and commercialized by Merck & Co. and OPDIVO® developed and commercialized by Bristol Myers Squibb, collectively generated $38.8 billion in sales in 2024 across several solid tumor cancer indications. However, the efficacy of these drugs has shown to be limited by a certain type of cell known as MDSCs or Myeloid Derived Suppressor Cells which accumulate in the tumor microenvironment. MDSCs express the CD33 antigen which is targeted by Actimab-A. The rationale for studying Actimab-A in combination with either KEYTRUDA® or OPDIVO® is based on the premise that depleting MDSCs with Actimab-A will improve the efficacy of these drugs.

MDSCs are immune-suppressive cells that help tumors evade immune detection and promote disease progression. They are overexpressed in the tumor microenvironment in several different solid tumors and associated with poor outcomes. They work by multiple mechanisms but most relevant to PD-1 inhibitors which work by keeping T-cells active is that MDSCs prevent T-cells from recognizing and attacking cancer cells. There is considerable preclinical scientific evidence in the literature that depleting MDSCs could be a viable strategy in improving the outcomes of PD-1 directed immunotherapy, however, there have been no viable clinical approaches that have been tried successfully to our knowledge. MDSCs are known to express the CD33 antigen which is the target of Actimab-A. Actinium has also generated published and unpublished preclinical data showing that Actimab-A can selectively deplete MDSCs in solid tumors. Actinium believes that in the clinic Actimab-A can deplete CD33 expressing MDSCs and hence improve the outcomes with PD-1 inhibitors such as KEYTRUDA® and OPDIVO®.

Actimab-A is Actinium's lead radiotherapeutic that delivers Actinium-225, a potent alpha-emitter radioisotope payload that can produce lethal double strand DNA breaks to kill targeted cells. Actimab-A has been studied in over 150 patients in several clinical trials in Acute Myeloid Leukemia or AML. Based on its safety and tolerability, Actimab-A is under clinical development via an NCI CRADA in the front-line AML setting with an expected registrational study in combination with CLAG-M in relapsed/refractory AML expected to initiate in 2025.

The Actimab-A solid tumor program is comprised of several controlled, head-to-head clinical trials that will evaluate the combination of Actimab-A with KEYTRUDA® versus KEYTRUDA® alone, and Actimab-A with OPDIVO® versus OPDIVO® alone. The initial tumors that are being targeted are HNSCC or Head and Neck Squamous Cell Carcinoma and NSCLC or Non-Small Cell Lung Cancer with a separate trial for each indication. The patient population for these trials will be adults with PD-L1 expression and locally advanced metastatic HNSCC or NSCLC randomized to either Actimab-A alone or Actimab-A with a specific checkpoint inhibitor. The objective of each trial would be to evaluate the safety and tolerability as well as following endpoints including ORR – Overall Response Rate, PFS – Progression Free Survival and OS – Overall Survival. Further, the following biomarker data would be collected including the pattern of depletion of CD33+ MDSCs and T-Cell activity in peripheral blood. Actinium expects to present initial proof of concept clinical data from the first of these trials in the second half of 2025 as well as provide an update on the outlook for the rest of the trials in the Actimab-A solid tumor program.

Dr. Avinash Desai, Actinium's Chief Medical Officer, said, "The Actimab-A solid tumor program is highly novel and has the potential to address the high unmet need of patients receiving PD-1 checkpoint inhibitors whose cancer stops responding or progresses. Our preclinical data is highly encouraging and we believe this novel approach combining Actimab-A with PD-1 inhibitors has immense potential. We are greatly enthusiastic about these head-to-head trials, and eager to present our initial proof-of-concept results by the end of 2025."

Sandesh Seth, Actinium's Chairman and CEO, said, "We have great enthusiasm for Actimab-A in combination with PD-1 checkpoint inhibitors given the large potential addressable patient population. MDSCs are over expressed in multiple solid tumors giving Actimab-A pan tumor potential in indications that are treated with checkpoint inhibitors. Per

our initial estimates this represents a treatment population in excess of 500,000 patients. Together with our efforts in myeloid malignancies, this is another important program for Actimab-A. This year, clinical data from Actimab-A as a potential backbone therapy in radiation sensitive myeloid malignancies, and in solid tumors in combination with PD-1 checkpoint inhibitors, can establish its potential to become a leading blockbuster targeted radiotherapy."

About Actinium Pharmaceuticals, Inc.

Actinium is a pioneer in the development of targeted radiotherapies intended to meaningfully improve patient outcomes. Actinium is advancing its lead product candidate Actimab-A, a CD33 targeting therapeutic, as potential backbone therapy in acute myeloid leukemia (AML) and other myeloid malignancies leveraging the mutation agnostic alpha-emitter radioisotope payload Actinium-225 (Ac-225). Actimab-A has demonstrated potential activity in relapsed and refractory acute myeloid leukemia (r/r AML) patients in combination with the chemotherapy CLAG-M including high rates of Complete Remissions (CR) and measurable residual disease (MRD) negativity leading to improved survival outcomes and is being advanced to a pivotal Phase 2/3 trial. In addition, Actinium is engaged with the National Cancer Institute (NCI) under the Cooperative Research and Development Agreement (CRADA) for development of Actimab-A in AML and other myeloid malignancies. The first clinical trial under the CRADA will evaluate the triplet combination comprised of Actimab-A, Venetoclax (Abbvie/Roche) an oral Bcl-2 inhibitor and ASTX-727 (Taiho Oncology, an Otsuka holdings company) a novel oral hypomethylating agent (HMA) in frontline acute myeloid leukemia (AML) patients. Additionally, Actinium is developing Actimab-A as a potential pan tumor therapy in combination with PD-1 checkpoint inhibitors including KEYTRUDA® and OPDIVO® by depleting myeloid derived suppressor cells (MDSCs), which represents a potential multi-billion-dollar addressable market. Iomab-ACT, Actinium's next generation conditioning candidate, is being developed with the goal of improving patient access and outcomes for potentially curative cell and gene therapies. Iomab-B is an induction and conditioning agent prior to bone marrow transplant in patients with r/r AML, which Actinium is seeking a potential strategic partner for in the U.S. In addition, the company's R&D efforts are primarily focused on advancing several preclinical programs for solid tumor indications. Actinium holds 230 patents and patent applications including several patents related to the manufacture of the isotope Ac-225 in a cyclotron.

For more information, please visit: https://www.actiniumpharma.com/

Forward-Looking Statements

This press release may contain projections or other "forward-looking statements" within the meaning of the "safe-harbor" provisions of the private securities litigation reform act of 1995 regarding future events or the future financial performance of the Company which the Company undertakes no obligation to update. These statements are based on management's current expectations and are subject to risks and uncertainties that may cause actual results to differ materially from the anticipated or estimated future results, including the risks and uncertainties associated with preliminary study results varying from final results, estimates of potential markets for drugs under development, clinical trials, actions by the FDA and other governmental agencies, regulatory clearances, responses to regulatory matters, the market demand for and acceptance of Actinium's products and

services, performance of clinical research organizations and other risks detailed from time to time in Actinium's filings with the Securities and Exchange Commission (the "SEC"), including without limitation its most recent annual report on form 10-K, subsequent quarterly reports on Forms 10-Q and Forms 8-K, each as amended and supplemented from time to time.

Investors:
investorrelations@actiniumpharma.com

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