ZIOPHARM Oncology, Inc.

ZIOPHARM Oncology Presents Compelling Data Showing Palifosfamide Activity in Breast Cancer Models at AACR Meeting

Company to Explore Proof-of-Concept Clinical Study in Breast Cancer in the Second Half of 2012

CHICAGO, April 3, 2012 (GLOBE NEWSWIRE) -- ZIOPHARM Oncology, Inc. (Nasdaq:ZIOP), a biopharmaceutical company with small molecule and synthetic biology approaches to new cancer therapies, announced today the presentation of two preclinical studies demonstrating compelling results for palifosfamide in breast cancer. The results were presented at the 2012 American Association for Cancer Research (AACR) Annual Meeting, being held March 31 — April 4 in Chicago, IL. Palifosfamide is currently being evaluated in a randomized, double-blinded, placebo-controlled Phase 3 trial (PICASSO 3) for the treatment of metastatic soft tissue sarcoma in the front-line setting.

Norton-Simon Modeling for the Optimization of Dose and Schedule of Palifosfamide in Breast Cancer (Abstract 3908)

The first presentation describes the use of Norton-Simon mathematical engineering modeling to analyze the impact of palifosfamide on breast cancer growth. In contrast to other agents of its class, palifosfamide's rapid onset of action and safety profile permit optimization of efficacy right through resistance. Palifosfamide is also active against $ALDH^{hi}$, cyclophosphamide-resistant, osteosarcoma xenografts, suggesting that it has the potential of overcoming resistance to cyclophosphamide and treating $ALDH^{hi}$ breast cancer. ALDH overexpression ($ALDH^{hi}$) is associated with cancer stem cell-like potential in several tumor types and is thought to confer resistance to various anticancer agents.

In breast cancer models, the administration of palifosfamide over a 5-day dosing cycle, as optimized through Norton-Simon modeling, preserved almost full efficacy but delayed the time of emergence of drug resistance by 43% (from 7 days to 10 days) compared to a single dose on day 1. Analysis of the effects of palifosfamide alone, docetaxel alone, and the simultaneous combination indicates that the shapes and magnitudes of the single-agent curves add to perfectly predict that of the combination, with minimal loss of single-agent activity. A daily x 5 schedule (9 days off) at highest tolerated dose level is therefore the proposed dose for clinical study in breast cancer, both as a single agent and in combination with other anticancer medications.

"As has been seen with other solid tumor types, palifosfamide demonstrates compelling activity in breast cancer models. This includes an ability to overcome a key resistance pathway of the disease," said Larry Norton, M.D., Deputy Physician-in-Chief for Breast Cancer Programs at Memorial Sloan-Kettering Cancer Center and Medical Director of the Evelyn H. Lauder Breast Center, said. "Engineering dose and schedule demonstrates our ability to modulate resistance, which is mediated in part through palifosfamide's independence of ALDH pathways. These results suggest that palifosfamide may prove an important component of treating ALDH-overexpressing metastatic breast cancer, and merits study in the clinical setting."

"In a difficult to treat disease, these data are encouraging and, importantly, may quickly translate into clinical study," said Tiffany A. Traina, M.D., lead author of the study and a clinical investigator at the Breast Cancer Medicine Service, Memorial Sloan-Kettering. "I look forward to studying the potential clinical benefit of palifosfamide in this area of high unmet need in breast cancer."

Combination of Intratumoral Regulated IL-12 Gene Delivery and Systemic Chemotherapy with Palifosfamide (IPM-Tris) Enhances Anti-Tumor Effects in Breast Cancer (4T1) Model (Abstract 4396)

The second presentation includes preclinical data examining the anti-tumor effect of combining palifosfamide with the regulated, *in vivo* expression of the immunomodulatory cytokine Interleukin-12 (IL-12) in a breast cancer model. In this study, the effect of Ad-RTS-mIL12 + AL (an intratumorally administered adenoviral vector (Ad) expressing murine IL-12 (mIL-12) under the control of the RheoSwitch Therapeutic System® (RTS®) technology, a novel inducible promoter system regulated by an oral small molecule activator ligand, INXN-1001 [AL]), in combination with palifosfamide was evaluated in a subcutaneous breast cancer xenograft model. Combined treatment with Ad-RTS-mIL12 + AL and low dose palifosfamide significantly inhibited tumor growth inhibition (~71-90%, $p < 0.001$) and increased median survival rate by 8-14 days when compared to either agent alone, without overt toxicity as assessed by change in body weight.

Commenting on the combination use of low dose palifosfamide and the immunomodulatory cytokine interleukin-12 (IL-12) delivered by DNA synthetic biology therapy, Hagop Youssoufian, M.Sc., M.D., President of Research and Development and

Chief Medical Officer, said: "A major obstacle for the development of effective immunotherapy is the ability of tumors to escape detection and/or destruction by the immune system. Data from breast cancer models are supportive of our hypothesis that cytotoxic agents at low doses may prime the immune system to enhance immunotherapy. Importantly, efficacy is achieved with safety by using low doses of palifosfamide as well as IL-12 expressed in a controlled manner, *in vivo*, using a regulated gene system."

Based on results from these studies, ZIOPHARM plans to explore the use of palifosfamide, as a single agent and in combination with other anticancer agents, in a proof-of-concept clinical study anticipated to begin in the second half of 2012.

About ZIOPHARM Oncology, Inc.:

ZIOPHARM Oncology is a biopharmaceutical company engaged in the development and commercialization of small molecule and synthetic biology approaches to new cancer therapies. The Company's clinical programs include:

Palifosfamide (Zymafos® or ZIO-201) is a novel DNA cross-linker that in preclinical study has been shown to bypass resistance mediated by aldehyde dehydrogenase (ALDH), in addition to conferring a favorable toxicity profile compared to other in-class agents. Palifosfamide, administered intravenously, is currently in a randomized, double-blinded, placebo-controlled Phase 3 trial for the treatment of metastatic soft tissue sarcoma in the front-line setting. A Phase 1 trial is also nearing completion with palifosfamide in combination with etoposide and carboplatin to determine appropriate safety for initiating a potentially pivotal, adaptive Phase 3 trial in front-line, extensive SCLC expected to initiate in the second half of 2012. Additionally, an investigational new drug application has been accepted for the oral form of palifosfamide.

DNA-based therapeutics (synthetic biology), in partnership with Intrexon Corporation, include two clinical-stage product candidates, both of which are DNA IL-12 using the RheoSwitch Therapeutic System® technology to be turned *on/off* by an oral activator ligand and are currently in Phase 1. Additionally, multiple INDs are expected in the next 12-24 months resulting from preclinical and discovery work underway to advance multiple antibody, immunotoxin, and protein decoy candidates, systemic delivery and a next generation RheoSwitch Therapeutic System®.

Indibulin (Zybulin™ or ZIO-301) is a novel, oral tubulin binding agent that is expected to have several potential benefits including oral dosing, application in multi-drug resistant tumors, no neuropathy and a quite tolerable toxicity profile. It is currently being studied in Phase 1/2 in metastatic breast cancer.

Darinaparsin (Zinapar® or ZIO-101) is a novel mitochondrial- and hedgehog-targeted agent (organic arsenic) currently in a solid tumor Phase 1 study with oral administration and has been developed intravenously for the treatment of relapsed peripheral T-cell lymphoma.

ZIOPHARM's operations are located in Boston, MA, Germantown, MD and New York City. Further information about ZIOPHARM may be found at www.ziopharm.com.

Forward-Looking Safe Harbor Statement:

This press release contains certain forward-looking information about ZIOPHARM Oncology that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. Words such as "expect(s)," "feel(s)," "believe(s)," "will," "may," "anticipate(s)" and similar expressions are intended to identify forward-looking statements. These statements include, but are not limited to, statements regarding our ability to successfully develop and commercialize our therapeutic products; our ability to expand our long-term business opportunities; financial projections and estimates and their underlying assumptions; and future performance. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include, but are not limited to: whether Palifosfamide, Darinaparsin, Indibulin, or any of our other therapeutic products will advance further in the clinical trials process and whether and when, if at all, they will receive final approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies and for which indications; whether Palifosfamide, Darinaparsin, Indibulin, and our other therapeutic products will be successfully marketed if approved; whether our DNA-based biotherapeutics discovery and development efforts will be successful; our ability to achieve the results contemplated by our collaboration agreements; the strength and enforceability of our intellectual property rights; competition from pharmaceutical and biotechnology companies; the development of and our ability to take advantage of the market for DNA-based biotherapeutics; our ability to raise additional capital to fund our operations on terms acceptable to us; general economic conditions; and the other risk factors contained in our periodic and interim SEC reports filed from time to time with the Securities and Exchange Commission, including but not limited to our Annual Report on Form 10-K for the fiscal year ended December 31, 2011. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or

circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

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