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Inactivating Mutations in Scaffold Component of PP2A, the Target Enzyme of LIXTE Biotechnology's Clinical Compound LB-100, are Associated with Exceptionally Long Survival of Patients with Ovarian Clear Cell Cancer Treated with Immunotherapy

Outside research reports that immune checkpoint therapy of patients with ovarian clear cell carcinomas with mutations reducing PP2A activity in their cancers (loss-of-function mutations) correlates with marked clinical benefit.

PASADENA, CA, March 22, 2022 (GLOBE NEWSWIRE) -- LIXTE Biotechnology Holdings, Inc. (Nasdaq: LIXT), notes findings by a team of physician-scientists led by principal investigator Dr. Amir Jazaeri, professor of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center, and reported at the annual meeting of Society of Gynecologic Oncology (SGO) in Phoenix, AZ, that a subset of patients with ovarian clear cell carcinoma (OCCC) treated with immune checkpoint inhibitors lived significantly longer (had increased overall survival) than most patients with the same disease treated with the same regimens.

Dr. Emily Hinchcliff (now at Northwestern University Cancer Center), the lead author of the report, noted that based on observations in two exceptional survivors, her team became interested in survival outcomes in patients with inactivating somatic tumor mutations in PPP2R1A, the major scaffold subunit of the protein phosphatase 2A (PP2A) multimeric enzyme. This presentation included preliminary results of 28 recurrent, platinum-resistant OCCC patients enrolled on an ongoing clinical trial testing the efficacy of CTLA4- and PD-L1-targeting immune checkpoint inhibitors (clinicaltrials.gov identifier: NCT03026062). Median overall survival was not reached in seven patients with hotspot inactivation mutations in PPP2R1A versus 6.4 months in the 21 patients without such mutations (p=0.018; HR=0.13 (95% CI: 0.02-0.95). Of note in several patients, response or prolonged disease stabilization leading to longer survival occurred after initial progression. Inactivating mutations in PPP2R1A are known to reduce the enzymatic activity of PP2A.

LIXTE CEO John S. Kovach, MD, commented "the results of Hinchcliff and colleagues strongly support our belief that pharmacologic reduction of PP2A activity by administration of LB-100 will mimic the biological effects of inactivating mutations in the PPP2R1A gene, and therefore may be a general way to enhance immunotherapy for many, if not all, tumor types. Hinchcliff et al. made the striking observation that a few patients with OCCC, a subtype of

ovarian cancer, will likely live an exceptionally long time (years as opposed to months) when treated with immunotherapy after failing on standard treatment. Their genetic analysis of tumors from 28 OCCC patients receiving immunotherapy showed that patients living longer on treatment had mutations known to reduce the activity of PP2A, whereas none of the patients progressing on immunotherapy had these mutations."

Dr. Kovach continued: "Additional evidence supporting our hypothesis that LB-100 may be a general way to enhance the benefit of immunotherapy are other recent outside preclinical studies, showing that LB-100 increases immunotherapy effectiveness against several different tumor types (Ho et al 2018, Cui et al 2020, Yen et al 2021). In particular, the studies by Yen and colleagues show that LB-100 converts immunologically unresponsive ("cold") tumors to immunologically responsive ("hot") tumors. Although immunotherapy is a true breakthrough in cancer treatment and is now approved for use in more than 20 different human cancers, most patients unfortunately do not respond. If pharmacologic inhibition of PP2A significantly enhances immunotherapy of even a few human cancers, it will be a game-changer. Fortunately, this hypothesis is readily testable in the clinic, which LIXTE is planning to do."

About Lixte Biotechnology Holdings, Inc.

LIXTE Biotechnology Holdings, Inc. (Nasdaq: LIXT), is a clinical-stage pharmaceutical company founded to identify new targets for cancer drug development. Major drivers of cancer are defects in the switches that turn the biochemical pathways in cells on or off. Most cancer research over the past 30 years has focused on the "on" switches because the "off" switches, especially the master "off" switch protein phosphatase (PP2A), were believed to cause intolerable toxicity in patients. LIXTE has achieved a breakthrough with its novel, first-in-class lead clinical compound and PP2A inhibitor, LB-100, by demonstrating that LB-100 is readily tolerated in cancer patients at doses associated with anti-cancer activity. Based on extensive published preclinical data (see www.lixte.com), LB-100 has the potential to significantly improve outcomes for patients undergoing various chemotherapies or immunotherapies. LIXTE's new approach has no known competitors and is covered by a comprehensive patent portfolio. Initial proof-of-concept clinical trials are in progress.

Forward-Looking Statements

This announcement contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, and Section 21E of the Securities Exchange Act of 1934. For example, statements regarding the Company's financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about future product demand, supply, manufacturing, costs, marketing and pricing factors are all forward-looking statements. These statements are generally accompanied by words such as "intend," anticipate," "believe," "estimate," "potential(ly)," "continue," "forecast," "predict," "plan," "may," "will," "could," "would," "should," "expect" or the negative of such terms or other comparable terminology. The Company believes that the assumptions and expectations reflected in such forward-looking statements are reasonable, based on information available to it on the date hereof, but the Company cannot provide assurances that these assumptions and expectations will prove to have been correct or that the Company will take any action that the Company may presently be planning. However, these forward-looking statements are inherently subject to known and unknown risks and uncertainties. Actual results or experience may differ materially from those expected or

anticipated in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, regulatory policies, available cash, research results, competition from other similar businesses, and market and general economic factors. This discussion should be read in conjunction with the Company's filings with the United States Securities and Exchange Commission at www.sec.gov/edgar.shtml

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