Lyell Immunopharma Announces FDA Clearance of its IND for LYL797, a CAR T-Cell Therapy Incorporating Novel Reprogramming Technologies for Solid Tumors

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- Expects to begin screening patients for the Phase 1 clinical trial by the end of the first quarter; initial data presentation expected in 2023
- ROR1-targeted CAR T-cell therapy designed to overcome T-cell exhaustion and promote durable stemness incorporates Lyell's novel genetic and epigenetic reprogramming technologies, Gen-R™ and Epi-R™
- LYL797 targets ROR1, a highly expressed cell surface antigen present on many aggressive solid tumors

SOUTH SAN FRANCISCO, Calif., Dec. 16, 2021 (GLOBE NEWSWIRE) -- Lyell Immunopharma, Inc. (Lyell), (Nasdaq: LYEL), a T-cell reprogramming company dedicated to the mastery of T cells to cure patients with solid tumors, announced today that the U.S. Food and Drug Administration (FDA) has cleared its Investigational New Drug (IND) application to initiate a Phase 1 clinical trial for LYL797, Lyell's first therapeutic candidate incorporating T-cell reprogramming technologies for the treatment of solid tumors. LYL797 is an investigational chimeric antigen receptor (CAR) T-cell therapy for patients with receptor tyrosine kinase-like orphan receptor 1-positive ($ROR1^+$) solid tumors. LYL797 incorporates two Lyell technologies designed to address major barriers to successful Adoptive Cell Therapy (ACT): Gen-R, a genetic reprogramming technology that endows T cells with the ability to resist exhaustion, and Epi-R, an epigenetic reprogramming technology that creates populations of T cells with the properties of durable stemness. Durable stemness is the quality that enables T cells to self-renew, proliferate and persist, and create daughter cells with anti-tumor functionality. Lyell expects to begin screening patients with relapsed/refractory triple-negative breast cancer (TNBC) who have failed at least two lines of therapy by the end of the first quarter for the Phase 1 dose escalation phase of the trial and plans to expand the trial to include patients with non-small cell lung cancer (NSCLC) when a recommended dose is determined.

"Lyell is applying our understanding of T-cell biology to address what we believe are the primary barriers to consistently effective cell therapies for difficult to treat solid tumors," said Liz Homans, Chief Executive Officer of Lyell. "Submission and clearance of our first IND is an important milestone for Lyell, and we remain on track to generate data for LYL797 in 2022 and plan to share initial data when we have a meaningful number of patients and an indication of clinical effect, which we expect to occur in 2023. We also remain on track to submit three additional INDs for our TIL and partnered TCR programs by the end of 2022."

"This is the first time the FDA has cleared an IND that includes a specific genetic modification to address T-cell exhaustion, a phenomenon that is recognized as being a major barrier to the eradication of tumors by T cells," stated Rick Klausner, MD, Chair of Lyell's Board of Directors. "We look forward to testing this first-generation technology platform in the clinic, thus specifically addressing the question of exhaustion as a barrier to successful cell therapy in solid tumors."

"While CAR T-cell therapies have proven effective in hematologic malignancies, patients with solid tumors have seen limited benefit from these approaches due to a tumor microenvironment that leads to T-cell exhaustion and a loss of durable stemness," said Tina Albertson, MD, PhD, Chief Medical Officer and Head of Development of Lyell. "LYL797 is the first program to clinically evaluate our two T cell reprogramming technologies which are designed to overcome these barriers, with the goal of developing more effective therapies for patients with solid tumor cancers."

Phase 1 Trial Design

The Phase 1 clinical trial is designed to evaluate the safety and anti-tumor activity of LYL797 in patients with $ROR1^+$ TNBC or NSCLC.

The trial is an open label, dose escalation and expansion trial in patients with relapsed/refractory TNBC or NSCLC who have failed at least two lines of therapy. Once a dose is identified during dose escalation in TNBC, up to 15 patients with TNBC and 15 patients with NSCLC are expected to be enrolled at the recommended dose. The primary endpoint of this Phase 1 trial is safety and tolerability of LYL797. Secondary endpoints include clinical activity based on the evaluation of antitumor activity as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and characterization of the pharmacokinetic profile of LYL797. Exploratory biomarkers of T-cell function – exhaustion and stemness – will also be assessed.

About TNBC and NSCLC

Breast cancer is the second most common cancer in American women. Approximately 10-15% of patients with breast cancer have TNBC and triple negative status tends to be more common in women who are younger than age 40, who are African American, or who have a BRCA1 mutation. In the United States, approximately 135,000 women suffered from TNBC in 2017. TNBCs present a high tendency to metastasize, and patients are at a higher risk to relapse compared to other types of breast cancers. TNBCs differ from other types of invasive breast cancer in that they grow and spread faster, have limited treatment options, and a worse prognosis. Once TNBC has spread to other parts of the body, the 5-year survival rate is only 11.5%.

ROR1 is overexpressed in approximately 60% of patients with TNBC and ROR1 expression is correlated with poorer outcomes.

Lung cancer is the second most common cancer and is the leading cause of cancer mortality worldwide. NSCLC accounts for 84% of all lung cancers. ROR1 is overexpressed in approximately 40% of the patients with NSCLC. For people with localized NSCLC, the overall 5-year survival rate is ~60%. For regional NSCLC, the 5-year survival rate is ~35%. Based on current data, when NSCLC metastasizes, the 5-year survival rate is 6%.

About LYL797

LYL797 is a novel, ROR1-targeted CAR T-cell product that incorporates genetic and epigenetic reprogramming technologies, Gen-R and Epi-R, to overcome barriers of CAR T-cell therapies in solid tumors. Gen-R is an *ex vivo* genetic reprogramming technology that engineers CAR T cells to overexpress c-Jun. Dysregulation of activator protein 1 (AP-1) has been implicated in CAR T-cell exhaustion, and studies have demonstrated that overexpression of c-Jun renders CAR T cells less susceptible to exhaustion through the AP-1 pathway, enhancing both anti-tumor efficacy and persistence in preclinical models of hematologic and solid tumors. Epi-R is a proprietary technology that is designed to produce populations of T cells which have the properties of durable stemness – the quality that enables T cells to self-renew, proliferate and persist, and create daughter cells with anti-tumor functionality.

Preclinical *in vitro* and *in vivo* experiments of LYL797 against ROR1^{+} solid tumors have demonstrated that LYL797 maintains stem-like phenotypes and can resist exhaustion while inhibiting tumor growth in models of tumor cells expressing ROR1.

About Lyell Immunopharma, Inc.

Lyell is a T-cell reprogramming company dedicated to the mastery of T cells to cure patients with solid tumors. The Company focuses on addressing what it believes are the primary barriers that limit consistent, reliable, and curative responses to adoptive T-cell therapy: T-cell exhaustion and lack of durable stemness, which includes proliferative capacity, ability to self-renew and ability to differentiate and eliminate solid tumors. Lyell is applying its proprietary *ex vivo* genetic and epigenetic reprogramming technology platforms, Gen-R and Epi-R, to address these barriers in order to develop new medicines with improved, durable, and potentially curative clinical outcomes. Lyell is based in South San Francisco, California and Seattle and Bothell, Washington. To learn more, please visit www.Lyell.com.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements expressed or implied in this press release include, but are not limited to, statements regarding: Lyell's expectation to begin screening patients for the Phase 1 clinical trial and the timing thereof and to present initial data and the timing thereof; LYL797 and its ability to overcome T-cell exhaustion and promote durable stemness; Lyell's plans to screen patients with relapsed/refractory triple-negative breast cancer (TNBC) who have failed at least two lines of therapy by the end of the first quarter for the Phase 1 dose escalation phase of the trial and to expand the trial to include patients with non-small cell lung cancer (NSCLC) when a recommended dose is determined; Lyell's plans to submit three additional INDs for our TIL and partnered TCR programs and the timing thereof; Lyell's vision of curing patients with solid tumors; the therapeutic potential of Lyell's product candidates; and other statements that are not historical fact. These statements are based on Lyell's current plans, objectives, estimates, expectations and intentions, are not guarantees of future performance and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, but are not limited to, risks and uncertainties related to: the effects of the evolving COVID-19 pandemic; Lyell's ability to submit planned INDs on the anticipated timing or at all; initiation of planned clinical trials and enrollment of patients in its future clinical trials; Lyell's ability to manufacture and supply its product candidates for its future clinical trials; the preclinical profiles of Lyell's product candidates not translating in clinical trials; the potential for results from clinical trials to differ from preclinical, early clinical, preliminary or expected results; significant adverse events, toxicities or other undesirable side effects associated with Lyell's product candidates; the significant uncertainty associated with Lyell's product candidates ever receiving any regulatory approvals; Lyell's ability to obtain, maintain, or protect intellectual property rights related to its product candidates; implementation of Lyell's strategic plans for its business and product candidates; the sufficiency of Lyell's capital resources and need for additional capital to achieve its goals; and other risks, including those described under the heading "Risk Factors" in Lyell's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and Lyell's future reports to be filed with the SEC. Forward-looking statements contained in this press release are made as of this date, and Lyell undertakes no duty to update such information except as required under applicable law.

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