Lyell Immunopharma Reports Dose-dependent Clinical Activity from Phase 1 Trial of LYL797, a ROR1-targeted CAR-T Cell Product Candidate Enhanced with its Proprietary Anti-exhaustion Technology

June 26, 2024

- Dose-dependent antitumor clinical activity in ROR1+ relapsed/refractory triple-negative breast cancer; 40% objective response rate and 60% clinical benefit rate at the highest dose cleared to date (150 x 10^6 CAR T cells)
- First demonstration that CAR T cells enhanced with anti-exhaustion technology can both expand and infiltrate into solid tumors
- No significant safety signal related to LYL797 observed in patients without lung involvement; treatable pneumonitis observed in patients with lung metastatic disease; dose escalation continues in separate cohorts
- Expanding development into new tumor types including ROR1+ relapsed/refractory platinum-resistant ovarian cancer, endometrial cancer, multiple myeloma and chronic lymphocytic leukemia
- IND submission completed for LYL119, Lyell's next generation ROR1-targeted CAR T cell product candidate
- Investor Webcast with David R. Spigel, MD, Chief Scientific Officer at the Sarah Cannon Research Institute and a lead investigator in the Phase 1 clinical trial, scheduled for 8:30 am ET today

SOUTH SAN FRANCISCO, Calif., June 26, 2024 (GLOBE NEWSWIRE) -- Lyell Immunopharma, Inc. (Nasdaq: LYEL), a clinical-stage T-cell reprogramming company advancing a diverse pipeline of cell therapies for patients with solid tumors, today announced initial clinical and translational data from its Phase 1 trial of LYL797, its first-generation reprogrammed ROR1 CAR T-cell product candidate enhanced with proprietary anti-exhaustion technology. The initial dataset consists primarily of patients with triple-negative breast cancer (TNBC) and demonstrated dose-dependent antitumor clinical activity and the ability of LYL797 CAR T cells to proliferate, infiltrate tumors and kill cancer cells in patients with relapsed/refractory disease. Patients with TNBC treated with LYL797 had an objective response rate (ORR) of 40% and clinical benefit rate (CBR) of 60% at the 150 x 10^6 CAR T cell dose level, with a CBR of 38% across all dose levels evaluable to date. Common treatment-related adverse events in patients without lung metastases included Grade 1 and 2 cytokine release syndrome (CRS) and headache, and the expected cytopenia from lymphodepletion. There were no reports of immune effector cell-associated neurotoxicity syndrome (ICANS) attributed to LYL797. Pneumonitis occurred in patients with lung metastases and dose escalation is continuing separately and more gradually in those patients. No dose-limiting toxicities have been reported in patients without lung involvement. All patients are now receiving prophylactic steroids prior to LYL797 treatment.

"These are promising initial clinical findings demonstrating that LYL797 ROR-1-targeted CAR T cells had dose-dependent antitumor clinical activity and have the potential to deliver even more meaningful and durable benefit to patients as we continue to dose escalate," said David R. Spigel, MD, Chief Scientific Officer at the Sarah Cannon Research Institute, medical oncologist and a lead investigator in the LYL797 study. "Pneumonitis is a known complication of radiotherapy and several approved cancer therapies, including immune checkpoint blockade and several antibody-drug conjugate therapies. We have implemented a protocol using steroids, the standard of care for treatment of patients with pneumonitis, that I believe will enable us to successfully monitor and manage these events."

The LYL797 study includes a robust translational program from which Lyell reports the first demonstration that CAR T cells enhanced with anti-exhaustion technology expanded, persisted and infiltrated into solid tumors, in some cases with associated evidence of cancer cell killing. TIGIT, a marker of T cell exhaustion, was measured in samples collected on Day 11 post-infusion with only a low proportion of LYL797 CAR T cells demonstrated to be TIGIT-positive. RNAseq data also suggested a significant proportion maintained the targeted stem-like and effector memory cell phenotype.

"We are encouraged to see clinical responses and a clear dose-dependent indication of antitumor clinical activity from treatment with LYL797 in patients with advanced triple-negative breast cancer," said Lynn Seely, MD, President and Chief Executive Officer of Lyell. "Our translational data provide, to our knowledge, the first demonstration of persistent CAR T cell infiltration into solid tumors associated with evidence of cancer cell killing. This early validation of our anti-exhaustion technology gives us the conviction to expand our trial to include patients with ROR1+ ovarian or endometrial cancers, while continuing to enroll patients

with triple-negative breast or non-small lung cancers, and also to initiate a new clinical trial for patients with multiple myeloma and chronic lymphocytic leukemia. This compelling early clinical data from LYL797 gives us a high degree of confidence to advance LYL119, our next generation ROR1-targeted product candidate with even more powerful anti-exhaustion technology. We have submitted an IND for LYL119 and expect to enter the clinic this year."

Initial LYL797 Phase 1 Clinical Trial Results

This initial dataset of 20 treated patients includes 16 patients with TNBC and four patients with non-small cell lung cancer. All patients enrolled had relapsed/refractory metastatic disease and the mean lines of prior therapies for metastatic disease was six. Four dose levels, including two interim dose levels, have been explored to date: 50 x 10^6 cells, 100 x 10^6 cells, 150 x 10^6 cells and 300 x 10^6 cells. The efficacy evaluable subset includes 16 patients, and the safety evaluable subset includes 18 patients. The manufacturing success rate was 100%.

Of the five patients with TNBC treated with LYL797 at the 150 x 10^6 cell dose level, the highest dose level cleared to date, two patients had confirmed partial responses to Day 90, resulting in an ORR of 40%. The CBR, defined as a best response of stable disease, partial response or complete response, was dose-dependent with 60% at the 150 x 10^6 cell dose level and 38% across all four dose levels evaluated.

The most frequently reported related adverse events of any grade are CRS (61%), pneumonitis (22%) and headache (17%), as well as the expected cytopenia from lymphodepletion in all patients. The CRS was generally mild (Grade 1 or 2 only), characterized by fever, and treated with tocilizumab and steroids. There were no reports of immune effector cell-associated neurotoxicity syndrome (ICANS) attributed to LYL797. The most frequently reported Grade $\geq$ 3 related adverse events were pneumonitis (17%) and hypoxia (11%), as well as the expected cytopenia from lymphodepletion in 78% of patients. One patient had Grade 5 respiratory failure on Day 41. The adverse event of Grade $\geq$ 3 pneumonitis occurred only in patients with TNBC and lung metastases, resulting in the separation of dose escalation into two cohorts based upon lung involvement (lung primary, lung metastatic disease or pleural effusion). No dose-limiting toxicities occurred in patients without lung involvement. All patients are now receiving prophylactic therapy with dexamethasone to mitigate pneumonitis. Patients without lung involvement are currently under evaluation at the 300 x 10^6 cell dose level and patients with lung involvement are currently under evaluation at 75 x 10^6 cell dose level.

Translational data are described on a subset of patients and include CAR T cell expansion in peripheral blood, phenotypic analysis of T cell exhaustion and stem-like markers and on-study tumor biopsies to assess for CAR T cell tumor infiltration. LYL797 CAR T-cell expansion was observed in peripheral blood samples at Day 60 in all patients assessed to date (n = 11) with peak expansion occurring between Days 8 and 11. Peak expansion was on average three-fold higher in patients receiving 150 x 10^6 cells compared to those receiving 50 x 10^6 cells. The exhaustion marker, TIGIT, was found only in a low proportion of LYL797 CAR T cells at Day 11 (n = 4) providing support for the role of c-Jun overexpression as an anti-exhaustion technology. A significant proportion of cells with stem-like and effector memory phenotypes were demonstrated at Days 11 and 22 following RNAseq transcriptomic analysis supporting the role of Epi-R to preserve a stem-like phenotype. Nine evaluable on-treatment tumor biopsies collected between Days 21 and 30 after LYL797 infusion were assessed. LYL797 CAR T cells were present in all solid-tumor biopsies, indicating that LYL797 CAR T cells enhanced with Lyell's anti-exhaustion technology were able to infiltrate and persist in the solid tumor microenvironment. In addition, the tumor biopsies have features consistent with T cell-mediated tumor lysis, including T cell-rich inflammation with scattered tumor cells.

Conference Call and Webcast Details

Lyell's management, together with David R. Spigel, MD, Chief Scientific Officer at the Sarah Cannon Research Institute and a lead investigator in the Phase 1 clinical trial, will host an investor conference call and Webcast beginning at 8:30 am ET today, to discuss the initial data from the LYL797 Phase 1 clinical trial.

- The Webcast can be accessed here.
- To join the live conference call, please register here to receive a dial-in number and unique PIN to access the call.

It is recommended callers join ten minutes prior to the start of the event (although you may register and join at any time during the Webcast). A replay of the event and presentation materials will be archived on the Investor page of the Lyell Website following the end of the event.

LYL797 Phase 1 Clinical Trial Design (NCT05274451)

The Phase 1 clinical trial is designed as an open-label, dose-escalation and expansion trial in patients with relapsed/refractory TNBC who have failed at least two lines of therapy and NSCLC who have failed at least one line of therapy. The trial has been amended to also include patients with platinum-resistant ovarian cancer or endometrial cancer. All patients enrolled have tumor specimens positive for ROR1 protein expression by immunohistochemistry.

More information on the Phase 1 trial can be found on clinicaltrials.gov here.

About LYL797

LYL797 is a receptor tyrosine kinase-like orphan receptor 1 (ROR1) -targeted CAR T-cell product candidate enhanced with Lyell's

anti-exhaustion genetic reprogramming technology (c-Jun) and epigenetic reprogramming technology (Epi-R). LYL797 overexpresses c-Jun to correct for an imbalance in the AP-1 family of transcription factors present in exhausted T cells. In preclinical studies, overexpression of c-Jun enables T cells to resist exhaustion, infiltrate solid tumors and maintain their functionality. LYL797 is manufactured utilizing Epi-R, Lyell's proprietary ex vivo manufacturing protocol that is designed to generate populations of stem-like T cells with reduced exhaustion and improved proliferation and antitumor activity.

ROR1 is a fetal protein expressed during embryogenesis and is believed to be important in cell migration, polarity and survival. Significant subsets of patients with common cancers express ROR1 and it is generally associated with a poor prognosis.

About Lyell Immunopharma, Inc.

Lyell is a clinical-stage T-cell reprogramming company advancing a diverse pipeline of cell therapies for patients with solid tumors. Lyell is currently enrolling a Phase 1 clinical trial evaluating a first-generation ROR1-targeted CAR T-cell therapy enhanced with anti-exhaustion technology in patients with relapsed/refractory triple-negative breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer and endometrial cancer. A second Phase 1 clinical trial is ongoing to evaluate reprogrammed tumor infiltrating lymphocytes (TIL) in patients with advanced melanoma, NSCLC and colorectal cancer. An investigational new drug application has been submitted to the FDA for LYL119, a next-generation ROR1-targeted CAR T-cell product candidate with even more powerful anti-exhaustion technologies.

The technologies powering Lyell's product candidates are designed to address barriers that limit consistent and long-lasting responses to cell therapy for solid tumors: T-cell exhaustion and lack of durable stemness, which includes the ability to persist and self-renew to drive durable tumor cytotoxicity. Lyell is applying its proprietary ex vivo genetic and epigenetic reprogramming technologies to address these barriers to develop new medicines with improved durable clinical outcomes. Lyell is based in South San Francisco, California with facilities in 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: the continued clinical progress of the LYL797 trials; the effectiveness of prophylactic steroids or other treatments to mitigate adverse events; the potential to deliver more meaningful and durable benefit to patients with dose escalation; Lyell's plans to enroll patients with platinum-resistant ovarian cancer and endometrial cancer in the LYL797 trial; Lyell's plans to submit an IND for LYL797 to initiate a new Phase 1 study evaluating LYL797 in patients with multiple myeloma or chronic lymphocytic leukemia and the timing thereof; Lyell's development plans for LYL119 and the effectiveness of any technologies incorporated into LYL119; the ability of Lyell's reprogramming technologies to infiltrate and persist in the solid tumor microenvironment; 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: macroeconomic conditions, including the effects of geopolitical instability and actual or perceived changes in interest rates and economic inflation; Lyell's ability to submit planned INDs, obtain approval of submitted INDs, or initiate or progress clinical trials on the anticipated timelines, if at all; the potential for results from clinical trials to differ from nonclinical, early clinical, preliminary or expected results; Lyell's limited experience as a company in enrolling and conducting clinical trials, and lack of experience in completing clinical trials; Lyell's ability to manufacture and supply its product candidates for its clinical trials; the nonclinical profiles of Lyell's product candidates or technology not translating in clinical trials; 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 Annual Report on Form 10-K for the year ended December 31, 2023, filed with the Securities and Exchange Commission (SEC) on February 28, 2024, and the Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, filed with the SEC on May 6, 2024. 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**.**

Contact:
Ellen Rose
Senior Vice President, Communications and Investor Relations
erose@lyell.com