Aileron Therapeutics Is Pleased to Outline Strategy to Strengthen Phase 1b Clinical Trial of ALRN-6924 in Patients with p53-Mutated Breast Cancer

August 1, 2022

- Enhancements to protocol, informed by recent ALRN-6924 data, are designed to improve the opportunity to demonstrate protection against chemotherapy-induced severe neutropenia, alopecia (hair loss) and potentially other toxicities in patients with p53-mutated breast cancer
- Key protocol enhancements include:
  - Selection of 1.2 mg/kg dose of ALRN-6924 with the goal to extend duration of cell cycle arrest and, thus, chemoprotection
  - New primary endpoint that is more closely aligned with regulatory precedents for approved supportive care products
- Planned readouts include: data from initial patients in 4Q 2022; interim analysis on 12 patients in 2Q 2023; and topline results from 20 patients in 3Q 2023
- Cash runway has been extended; now expected to fund operations through end of 1Q 2024, including Phase 1b trial topline results and preparations for a pivotal trial, pending breast cancer trial data

BOSTON, Aug. 01, 2022 (GLOBE NEWSWIRE) -- Aileron Therapeutics (Nasdaq: ALRN), a chemoprotection oncology company that aspires to make chemotherapy safer and thereby more effective to save more patients' lives, today outlined its strategy to strengthen the company's Phase 1b chemoprotection trial of ALRN-6924 in patients with p53-mutated breast cancer.

The Phase 1b, open-label, single-arm[i], multicenter trial is designed to evaluate the safety, tolerability and chemoprotective effect of ALRN-6924 in up to 24 patients with p53-mutated breast cancer undergoing either neoadjuvant or adjuvant treatment with docetaxel, doxorubicin and cyclophosphamide, also known as TAC. The primary endpoints are duration and incidence of severe neutropenia (Grade 4) in cycle 1. Secondary endpoints include the chemoprotective effect of ALRN-6924 on chemotherapy-induced alopecia, as well as other hematologic and non-hematologic toxicities. TAC will be administered every 3 weeks for 4 to 6 cycles based on investigators' discretion. ALRN-6924 will be administered at 1.2 mg/kg on 3 consecutive days in each treatment cycle, Days 0, 1 and 2, while chemotherapy will be administered on Day 1.

"Our team has worked methodically and expeditiously to modify the Phase 1b breast cancer trial in order to enhance our opportunity to demonstrate a robust chemoprotective effect of ALRN-6924 in patients with p53-mutated breast cancer. The evidence-based modifications we are implementing reflect key, collective learnings from our healthy volunteer study, as well as our non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) clinical trials. We are also expanding the eligibility criteria and plan to activate additional sites in additional countries, which we believe will help ensure we are able to recruit the targeted number of patients in a timely and cost-efficient manner," said Manuel Aivado, M.D., Ph.D., President and Chief Executive Officer at Aileron.

Dr. Aivado continued, "We have been closely evaluating operations and have successfully identified cost efficiencies that we've already begun to implement. With our decision to cease enrollment in our NSCLC trial last month, and the cash preservation measures we have identified, we believe that our cash resources will now fund our continued operations through the end of the first quarter of 2024. We expect that this will allow us to get to topline readouts for the breast cancer trial next year and if warranted by the trial results, to initiate preparation for a potential pivotal trial."

Nashat Gabrail, M.D., founder of the Gabrail Cancer Center in Canton, Ohio, President of Innovative Community Oncology Practices (ICOP), and the U.S. lead investigator in the ALRN-6924 breast cancer trial commented, "We are excited to continue our participation in this important clinical trial of ALRN-6924 in patients with p53-mutated breast cancer, and we fully support the protocol enhancements. Protecting cancer patients from chemotherapy-induced toxicities remains a critical unmet need. For bone marrow toxicities, such as neutropenia, existing treatments are often not effective and are associated with significant drawbacks. For other side effects, such as alopecia, there currently are no pharmacological options. We look forward to the continued clinical investigation of this potentially transformative therapy to prevent multiple chemotherapy-induced side effects and help patients fight cancer more effectively."

The Gabrail Cancer Center is part of the Sargon Research network, comprising community oncology practices throughout the U.S., whose goal is to drive critical oncology research in the community oncology setting. Five of the Sargon Research network sites, in addition to the Gabrail Cancer

Center, will participate in the Aileron breast cancer trial.

Key Enhancements to ALRN-6924 Breast Cancer Trial Design and Study Conduct

- **Increase the ALRN-6924 dose from the previous 0.3 mg/kg and 0.6 mg/kg dose levels to 1.2 mg/kg with the goal of extending duration of cell cycle arrest.** In recently generated data from Aileron's Phase 1 pharmacology study of ALRN-6924 in healthy human volunteers, higher ALRN-6924 dose levels yielded longer-lasting pharmacodynamic (PD) effects. Specifically, the PD data demonstrated that serum levels of MIC-1 were correlated with bone marrow p21, which is a marker for cell cycle arrest. Based on these findings, Aileron believes that prolonged elevation of serum levels of MIC-1 at higher ALRN-6924 dose levels may result in more durable cell cycle arrest.

  Andres Brainsky, M.D., Vice President of Clinical Development at Aileron, commented, "While the ALRN-6924 0.3 mg/kg dose demonstrated protection against topotecan-induced hematologic toxicities in patients enrolled in our SCLC trial, based on the data we now have in hand, we believe a higher dose level should provide more durable cell cycle arrest and, therefore, more durable chemoprotection against certain chemotherapies, including TAC. Moreover, the ALRN-6924 1.2 mg/kg dose was well tolerated and demonstrated a robust chemoprotective effect on hematologic toxicities when co-administered with topotecan to SCLC patients daily for 5 consecutive days[ii], giving us confidence in the tolerability of this dose level for the breast cancer trial."

- **Change from an exploratory primary composite endpoint across cycles to an established primary endpoint in cycle 1.** In a recent interim analysis of Aileron's NSCLC trial, ALRN-6924-treated patients completed more cycles of chemotherapy than placebo-treated patients. 45% (5/11) of patients on ALRN-6924 completed 6 planned cycles of chemotherapy versus only 11% (1/9) of patients on placebo. With each cycle of chemotherapy, patients are at risk of experiencing toxicities. The higher number of cycles in the ALRN-6924 arm introduced an imbalance between the ALRN-6924 and placebo arms that resulted in a bias against ALRN-6924 on the composite primary endpoint in the NSCLC trial, which evaluated toxicities in up to 6 cycles. Limiting the primary endpoint to an evaluation of severe neutropenia exclusively in cycle 1 eliminates a confounding factor that may result from assessing toxicities across multiple treatment cycles.

- **Utilize a chemotherapy regimen that enables the evaluation of protection against severe hematologic toxicities in cycle 1.** Previous data has shown that, despite prophylactic administration of G-CSF products (filgrastim or pegfilgrastim), up to 75% of breast cancer patients receiving TAC still experience severe neutropenia (Grade 4) in cycle 1.[iii] Patients in the ALRN-6924 breast cancer trial will not be administered prophylactic G-CSF products in cycle 1, which we expect would increase the likelihood that these patients would experience severe neutropenia in cycle 1 if they were not receiving ALRN-6924.

  In addition to a high rate of severe neutropenia, TAC chemotherapy, specifically docetaxel, is also associated with a high rate of alopecia – approximately 90% of patients treated with this chemotherapy experience hair loss. (The exact rate of chemotherapy-induced alopecia specific to cycle 1 is unknown.) Thus, the breast cancer trial will also enable the evaluation, across treatment cycles, of ALRN-6924's ability to prevent chemotherapy-induced alopecia.

- **Align the trial design with clinical and regulatory precedents.** The use of TAC and a primary endpoint of duration of severe neutropenia in cycle 1 have been used in pivotal trials supporting the approval of multiple supportive care drugs indicated to prevent neutropenia; all of these trials were conducted in breast cancer. Each of these drugs was approved for all cancers outside of myeloid malignancies on the basis of these pivotal trials in breast cancer.[iv]

- **Expand eligibility to patients with p53-mutated breast cancer receiving adjuvant or neoadjuvant chemotherapy.** The expanded eligibility criteria is intended to enable a larger number of patients with p53-mutated breast cancer to be considered for inclusion in the trial. Several of the clinical and regulatory precedents also included both neoadjuvant and adjuvant treatment settings.[v]

- **Expand number of sites.** Aileron plans to expand the number of sites in the trial, including opening sites in additional countries. Targeted sites will include those that have enrolled breast cancer patients in previously conducted studies evaluating TAC.

About Aileron Therapeutics

Aileron is a clinical stage chemoprotection oncology company that aspires to make chemotherapy safer and thereby more effective to save more patients' lives. ALRN-6924, our first-in-class MDM2/MDMX dual inhibitor, is designed to activate p53, which in turn upregulates p21, a known inhibitor of the cell replication cycle. ALRN-6924 is the only reported chemoprotective agent in clinical development to employ a biomarker strategy, in which we exclusively focus on treating patients with p53-mutated cancers. Our targeted strategy is designed to selectively protect multiple healthy cell types throughout the body from chemotherapy without protecting cancer cells. As a result, healthy cells are spared from chemotherapeutic destruction while chemotherapy continues to kill cancer cells. By reducing or eliminating multiple chemotherapy-induced side effects, ALRN-6924 may improve patients'

quality of life and help them better tolerate chemotherapy. Enhanced tolerability may result in fewer dose reductions or delays of chemotherapy and the potential for improved efficacy.

Our vision is to bring chemoprotection to all patients with p53-mutated cancers, which represent approximately 50% of cancer patients, regardless of type of cancer or chemotherapy. Visit us at aileronrx.com to learn more.

Forward-Looking Statements
Statements in this press release about Aileron's future expectations, plans and prospects, as well as any other statements regarding matters that are not historical facts, may constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements about the potential of ALRN-6924 as a chemoprotective agent, the Company's strategy, the Company's clinical development plans, including the design of the Phase 1b trial referred to in this release, and the Company's cash runway. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including whether Aileron's cash resources will be sufficient to fund its continuing operations for the periods anticipated or with respect to the matters anticipated; whether the cash preservation measures referenced in this release will result in the savings anticipated; whether the modifications to the Phase 1b trial referred to in this release will have the effects anticipated; whether preclinical or clinical results will be indicative of results obtained in future clinical trials, including trials in different indications or with different chemotherapies; whether ALRN-6924 will advance through the clinical trial process on a timely basis, or at all; whether the results of such trials will be accepted by and warrant submission for approval from the United States Food and Drug Administration or equivalent foreign regulatory agencies; whether ALRN-6924 will receive approval from regulatory agencies on a timely basis or at all or in which territories or indications ALRN-6924 may receive approval; whether, if ALRN-6924 obtains approval, it will be successfully distributed and marketed; what impact the coronavirus pandemic may have on the timing of our clinical development, clinical supply and our operations; and other factors discussed in the "Risk Factors" section of Aileron's annual report on Form 10-K for the year ended December 31, 2021, filed on March 28, 2022, and risks described in other filings that Aileron may make with the Securities and Exchange Commission. Any forward-looking statements contained in this press release speak only as of the date hereof, and Aileron specifically disclaims any obligation to update any forward-looking statement, whether because of new information, future events or otherwise.

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[i] The original ALRN-6924 breast cancer trial design included a control cohort, given lack of relevant historical controls. In the updated trial design, the control cohort has been removed since Aileron can now leverage as historical controls established third-party clinical data from previous trials that utilized the same primary endpoint and chemotherapy regimen.

[ii] Andric et al., ESMO 2021

[iii] U.S. Food & Drug Administration (FDA) Statistical Review of FULPHILA®

[iv] ZARXIO®, FULPHILA® and ZIEXTENZO®

[v] NEULASTA®, FULPHILA® and ZIEXTENZO®