# Trilaciclib Increases Pool of Memory T Cells in the Tumor Microenvironment Responsible for Long Term Immune Surveillance and Efficacy

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- Phase 2 Mechanism of Action Trial Results Demonstrate the Immunomodulatory Effects of Trilaciclib in the Tumor Microenvironment -

- Trilaciclib Enhances Expression of Genes Associated with Memory T Cells -

- Trilaciclib Increases Multiple Surrogate Immune Markers for Memory CD8+ T Cell Differentiation, Infiltration, and Function -

RESEARCH TRIANGLE PARK, N.C., June 04, 2023 (GLOBE NEWSWIRE) -- G1 Therapeutics, Inc. (Nasdaq: GTHX), a commercial-stage oncology company, today presented results from 24 patients enrolled in its Phase 2, single arm mechanism of action study of trilaciclib administered as a single agent to patients with early-stage triple-negative breast cancer (TNBC) prior to receiving trilaciclib and neoadjuvant therapy. These results highlight the potential for trilaciclib to enhance long term immune surveillance by increasing T cell function and generation of certain memory T cells and demonstrate gene expression profiles that may be associated with improved clinical outcome. These data support earlier findings from this Phase 2 trial demonstrating an increase in the ratio of CD8+ T cells to regulatory T cells (Tregs); a high ratio of CD8+ T cell to Tregs is predictive of overall survival (OS) and is associated with pathologic complete response (pCR). As expected, high rates of pCR were observed in patients with PD-L1(+) tumors and in patients with inflamed tumor immune microenvironments.

Data generated across multiple preclinical and clinical studies to date show that trilaciclib has the greatest effect on longer term endpoints including OS rather than earlier efficacy measures such as objective response rate (ORR), pCR, and progression free survival (PFS), consistent with other immunotherapies like checkpoint inhibitors. These results suggest that this is likely due to trilaciclib's immune-mediated mechanism of action that protects the immune system from damage caused by cytotoxic therapy and enhances long-term immune surveillance by increasing the generation of certain memory T cells. This dual benefit may provide important longer-term benefits for patients by improving their ability to generate robust immune responses, particularly when treated with future subsequent therapies.

"Trilaciclib is a highly active molecule that enhances T cell activation, favorably alters the tumor microenvironment, and improves long term immune surveillance; these new immune analyses help identify potential correlates of treatment response and extend our understanding of the mechanism," said Raj Malik, M.D., Chief Medical Officer at G1 Therapeutics. "Trilaciclib drives increases in certain memory T cells which are important for longer term outcomes like overall survival, consistent with our understanding of the mechanism of action of trilaciclib."

These results are being presented today at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting. The poster, titled, "*Neoadjuvant Single-Dose Trilaciclib Prior To Combination Chemotherapy in Patients with Early Triple-Negative Breast Cancer: Safety, Efficacy, And Immune Correlate Data from a Phase 2 Study,*" can be found here.

**Patient Demographics**

As of the data cut date of April 3, 2023, all patients (N = 24) had received a median (range) of 16 (3–16) cycles of treatment; 21 (87.5%) patients received pembrolizumab, and 21 (87.5%) patients received carboplatin, per investigator discretion. All patients completed the study; five underwent definitive surgery prior to completing planned study treatment. At diagnosis, 79% of patients had stage II tumors and 88% had ductal carcinoma; 38% of patients had PD-L1+ tumors, consistent with early TNBC.

Tumor immune microenvironment status was determined at baseline. All participants with immune-desert tumor microenvironments at baseline had PD-L1(-) tumors; an additional nine participants with immune-excluded tumor microenvironments had PD-L1(-) tumors. All participants with immune-inflamed tumor microenvironments at baseline had PD-L1(+) tumors; an additional five participants with immune-excluded tumor microenvironments had PD-L1(+) tumors. Data published by G1 and others show that trilaciclib can promote trafficking of immune cells out of the stroma and into the tumor microenvironment via chemokine release, thus leading to an inflamed tumor immune microenvironment status.

**Baseline Correlates of Clinical Outcome: Pathologic Complete Response (pCR)**

Tumor infiltrating lymphocytes (TIL) infiltration is associated with better outcomes with trilaciclib. In this mechanism of action trial, the pCR rate is higher (77.8%) in patients with PD-L1(+) tumors relative to that of the overall enrolled patient population. The pCR rate in the overall enrolled population (41.7%) is comparable to that of standard neoadjuvant therapy in this population of patients. As anticipated, the pCR rate was higher in patients with an immune-inflamed tumor microenvironment (75.0%) than those with immune-excluded (35.7%) or immune desert (33.3%) tumor microenvironments.

The tumor status of four enrolled patients converted from PD-L1(-) at baseline to PD-L1(+) after trilaciclib monotherapy (day 7); 50% of these patients achieved pCR during the study.

**Immunomodulatory Effects of Trilaciclib**

Trilaciclib was shown to enhance the number and function of CD8+ T cells in the tumor microenvironment. Seven days after monotherapy with trilaciclib, the number of CD8+ T cells and GZMB+ cells, which is a surrogate marker for T cell function, were enhanced with statistical significance in patients achieving a pCR. There was also an increase in stromal TILs within the tumor microenvironment after a single dose of trilaciclib.

RNA-sequence analysis revealed 59 genes that were differentially expressed seven days after single-dose trilaciclib in patients who achieved pCR, compared to those who did not. Furthermore, assessment of signaling pathways associated with pCR revealed significant enrichment in pathways associated with immune modulation including T cell receptor signaling and cytokine-cytokine receptor interaction that were not observed at baseline. Key genes associated with memory T cells - SELL (CD62L), IL-7R, and TCF7 - increased from baseline to Day 7, and a subset analysis based on pCR status revealed significant increases in these genes when individually assessed and as a gene signature among patients who achieved pCR.

These results help confirm the role of trilaciclib in increasing the pool of functional memory T cells that could contribute to long-term immune surveillance and efficacy, as measured by longer term endpoints like OS.

**Safety Results (n=24)**

Trilaciclib continues to show a strong tolerability profile. Trilaciclib in combination with anthracycline (doxorubicin)/ cyclophosphamide/paclitaxel (AC/T) ± pembrolizumab ± carboplatin in the neoadjuvant setting for early-stage TNBC has a similar safety and tolerability profile as standard neoadjuvant regimens. The most common treatment-related adverse events (TRAEs; any grade) related to any study drug were fatigue, nausea, alopecia, and neutropenia/neutrophil count decreased. There were no adverse events leading to discontinuation of trilaciclib.

**Trilaciclib Phase 2 Mechanism of Action Trial Design**

Tumor tissue was obtained at baseline prior to study drug administration. Patients then received a single dose of monotherapy (240 mg/m2) trilaciclib, followed by a tumor biopsy approximately one week later to assess the ability of a single dose of trilaciclib monotherapy to favorably alter the tumor microenvironment. Paired tumor biopsies were available for 22 patients. Patients then entered the treatment phase in which trilaciclib is administered on day 1 of each cycle of anthracycline/cyclophosphamide for four cycles followed by trilaciclib administered on day 1 of each weekly cycle of taxane chemotherapy for 12 cycles. Pembrolizumab and/or carboplatin was added at the discretion of the investigator. Three to five weeks after the treatment phase, patients had definitive surgery and a final tumor tissue sample was collected if the patient has residual disease. pCR was assessed at definitive surgery by a local pathologist, per the current American Joint Committee on Cancer staging system .

The primary objective was to evaluate the immune-based mechanism of action of a single dose of trilaciclib as measured by the change in the ratio of CD8+ T cells to Tregs in the tumor microenvironment. Secondary endpoints include assessment of pCR rate at the time of definitive surgery, and safety of the combination of trilaciclib with neoadjuvant regimen. Exploratory endpoints include assessment of the immune response, and identification of molecular and cellular biomarkers in tumor or blood samples that may be associated with clinical response/resistance, pharmacodynamic activity, and/or the mechanism of action of trilaciclib.

**About G1 Therapeutics**
G1 Therapeutics, Inc. is a commercial-stage biopharmaceutical company focused on the development and commercialization of next generation therapies that improve the lives of those affected by cancer, including the Company's first commercial product, COSELA® (trilaciclib). G1 has a deep clinical pipeline and is executing a development plan evaluating trilaciclib in a variety of solid tumors, including breast, lung, and bladder cancers. G1 Therapeutics is based in Research Triangle Park, N.C. For additional information, please visit www.g1therapeutics.com and follow us on Twitter @G1Therapeutics.



**Forward-Looking Statements**

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "may," "will," "expect," "plan," "anticipate," "estimate," "intend" and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. Forward-looking statements in this press release include, but are not limited to, the potential for trilaciclib to enhance long term immune surveillance by enhancing T cell function and the generation of certain memory T cells, the association between gene expression profiles demonstrated by the Phase 2 Mechanism of Action Trial results and the improved clinical outcome, the expectations for further Phase 2 Mechanism of Action Trial results to support the current observation of an increase in the ratio of CD8+ T cells to regulatory T cells (Tregs), that trilaciclib's greatest effect is on longer term endpoints including OS rather than earlier efficacy measures such as pCR, ORR and PFS, and that the reason why trilaciclib's greatest effect on longer term endpoints is because of its immune-mediated mechanism of action are based on the company's expectations and assumptions as of the date of this press release. Each of these forward-looking statements involves risks and uncertainties. Factors that may cause the company's actual results to differ from those expressed or implied in the forward-looking statements in this press release are discussed in the company's filings with the U.S. Securities and Exchange Commission, including the "Risk Factors" sections contained therein and include, but are not limited to, the company's dependence on the commercial success of COSELA (trilaciclib); the development and commercialization of new drug products is highly competitive; the company's ability to complete clinical trials for, obtain approvals for and commercialize any of its product candidates; the company's initial success in ongoing clinical trials may not be indicative of results obtained when these trials are completed or in later stage trials; the inherent uncertainties associated with developing new products or technologies and operating as a commercial-stage company; and market conditions. Except as required by law, the company assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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