G1 Therapeutics Announces Positive Phase 1a Data for CDK4/6 Inhibitor G1T28

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- *G1T28 produced robust, transient, G1 cell cycle arrest of bone marrow cells*
- *Compound was well tolerated with predictable pharmacokinetic / pharmacodynamic activity*
- *Data support advancement into two Phase 1b/2a studies in patients with small-cell lung cancer*

RESEARCH TRIANGLE PARK, NC, May 27, 2015 – G1 Therapeutics, Inc., a clinical-stage oncology company, announced today that its lead compound G1T28, a highly potent and selective CDK4/6 inhibitor, demonstrated robust, transient cell-cycle arrest of hematopoietic stem and progenitor cells (HSPCs) in a first-in-human Phase 1a study. The compound was well tolerated with predictable pharmacokinetic (PK) / pharmacodynamic (PD) activity. These data will be presented on Saturday, May 30 in two posters at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting at McCormick Place in Chicago.

G1T28 is being developed for intravenous (IV) administration to patients with CDK4/6-independent cancers to protect the bone marrow and immune system from damage by chemotherapy. G1T28 acts by transiently producing a G1 cell cycle arrest of HSPCs in the bone marrow.

"These Phase 1a data demonstrate the potential of G1T28 to protect the bone marrow and immune system, preserve cell function, and improve cancer treatment outcomes," said Raj Malik, MD, Chief Medical Officer of G1 Therapeutics. "G1T28 may enhance anti-tumor activity both by enabling maintenance of planned chemotherapy dose density and schedule, and by preserving immune system function. Results of this study support the advancement of G1T28 into two Phase 1b/2a studies in patients with small-cell lung cancer."

Details on the data to be presented are as follows:

Title: First-in-human Phase 1a safety, PK, and PD study of the CDK4/6 inhibitor G1T28.
Session: Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics
Date and time: Saturday, May 30, 8 – 11:30 a.m.
Location: S Hall A
Abstract: #2527
Presenting author: Raj Malik, G1 Therapeutics, Inc**.**

This study assessed the safety and tolerability of G1T28, and also characterized PK and PD. Part 1 was a double-blind, placebo-controlled, single escalating dose study in healthy volunteers where subjects were randomized (3:1) to receive G1T28 or placebo as a single 30-minute IV infusion. In Part 2, twelve subjects received G1T28 alone to confirm the biologically effective dose (BED) of 192 mg/m2. PD assessments included evaluation of *ex vivo* stimulation of lymphocytes and bone marrow cell cycle analysis.

G1T28 was well tolerated when administered as a single IV infusion over 30 minutes. The compound demonstrated predictable PK, with low inter-subject variability. Robust PD effect was demonstrated with a dose-dependent decrease in PHA-stimulated lymphocyte proliferation *ex vivo.* Single administration of doses up to 192 mg/m2 had no effect on complete blood cell counts.

Title: Evaluation of targeted bone marrow arrest by G1T28, a CDK4/6 inhibitor in clinical development to reduce chemotherapy-induced myelosuppression.
Session: Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics
Date and time: Saturday, May 30, 8 – 11:30 a.m.
Location: S Hall A
Abstract: #2529
Presenting author: Patrick J. Roberts, G1 Therapeutics, Inc.

To rationally design tolerable and active chemotherapy combination regimens with reduced multilineage myelosuppression, the magnitude and duration of G1T28-induced HSPC G1 arrest in human bone marrow was characterized. Data from three species (mouse, rat, dog) were used to evaluate dose response relationships for HSPC G1 cell cycle arrest and to construct a cross-species allometrically scaled PK / PD model. Model simulations and human PK / PD data from a Phase 1a trial were used to predict the BED in humans, which was assessed by obtaining bone marrow aspirates from twelve subjects and evaluating G1 arrest of HSPCs by flow cytometry.

Following a single IV infusion of 192 mg/m2 G1T28, a clear increase was observed in the percentage of bone marrow progenitor subsets in the G1 cell cycle phase up to 32 hours post dose. No changes were noted in the peripheral blood cell counts, indicating that the bone marrow arrest is transient and reversible, and is consistent with the effects seen in animals and predicted by the PK / PD model.

Based on the observed PK, PD and safety profile, G1T28 200 mg/m2 IV (rounded up from the BED of 192 mg/m2) was selected as the starting dose for two Phase 1b/2a trials in patients with small-cell lung cancer.

About G1 Therapeutics, Inc.
G1 Therapeutics, Inc. is a privately held clinical-stage pharmaceutical company based in Research Triangle Park, NC that focuses on the discovery and development of novel, small-molecule therapies to address significant unmet needs in oncology. The company is leveraging its proprietary kinase drug discovery platform to advance a pipeline of best-in-class compounds and first-in-class drug candidates that address two markets: CDK4/6 antineoplastics and protection of the bone marrow and immune system from damage by chemotherapy (chemoprotection). Visit www.g1therapeutics.com for more information.

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