**EVALUATION OF TARGETED BONE MARROW ARREST BY G1T28, A CDK4/6 INHIBITOR IN HUMAN FOLLOWING G1T28 ADMINISTRATION**

**ABSTRACT#2529**

**BACKGROUND**

G1T28 is a CDK4/6 inhibitor in clinical development to reduce chemotherapy-induced myelosuppression in hematologic malignancies with the potential for increased patient compliance and reduced drug dosing interactions. Clinical data from a phase 1a study demonstrated 2-compartment linear PK, with rapid distribution and nearly linear scaling of clearance with dose. Two Phase 1b/2a studies in SCLC will be initiated in Q3 2015 to evaluate the potential of G1T28 to protect the bone marrow/immune system, preserve cell function, and enhance cancer treatment outcomes.\

**OBJECTIVES**

- To precisely understand the magnitude and duration of G1T28-induced G1 cell cycle arrest in human bone marrow hematopoietic stem/progenitor cells (HSC/MPP) at a given dose level of G1T28 to ensure:
  - That chemotherapy-induced myelosuppression continues to represent the major dose-limiting toxicity of cytotoxic chemotherapy
  - That the effect of G1T28 does not last too long such that prolonged G1 cell cycle arrest prevents recovery of circulating hematopoietic cells
  - That G1T28-induced G1 cell cycle arrest is not associated with premature senescence of mature hematopoietic cells

**METHODS**

- **Preclinical and clinical data were used to develop dosing recommendations for the human Phase 1a study that included pharmacokinetic/pharmacodynamic (PK/PD) modeling and an allometrically-scaled pharmacokinetic (PK) comparison study**

**EVALUATION OF BONE MARROW PROLIFERATION IN HUMAN FOLLOWING G1T28 ADMINISTRATION**

- In the first-in-human Phase 1a study, PK, and PD study of the CDK4/6 inhibitor G1T28, 12 subjects (Cohort 7) were enrolled to confirm the predicted biologically effective dose (BED) of G1T28 (G1T28-1-01; NCT02243150; Abstract #2527)

**RESULTS**

- **A single bone marrow aspirate was obtained from all subjects following a single dose of G1T28 in humans**

**TABLE 3. PERCENT OF BONE MARROW LINEAGE POPULATIONS IN G1 OR S2/M PHASE OF THE CELLCYCLE FOLLOWING A SINGLE DOSE OF G1T28 IN DATES**

**TABLE 4. PERCENT OF BONE MARROW LINEAGE POPULATIONS IN G1 OR S2/M PHASE OF THE CELLCYCLE FOLLOWING A SINGLE DOSE OF G1T28 IN DATES**

**SUMMARY**

- Following a single 80 mg dose of G1T28, a clear decrease was observed in the percentage of bone marrow progenitor subsets in the G1 cell cycle phase at 24 hours post dose
- No changes were observed in the peripheral blood counts, indicating that the bone marrow environment is transient, reversible, and consistent with the effects seen in animals and Phase 1a model simulations

**Contact us at g1therapeutics.corporatecares@g1.com**

**ACKNOWLEDGMENTS**

BG, bone marrow; EDU, 5-ethynyl-2'-deoxyuridine; IP, intraperitoneal; MPP, multipotent progenitors; PMNs, peripheral blood mononuclear cells; SD, standard deviation; T28, time to complete arrest; BMT, bone marrow transplantation; SCLC, small cell lung cancer; PK/PD, pharmacokinetic/pharmacodynamic; HSC, hematopoietic stem cell; MPP, multipotent progenitor; EDU, 5-ethynyl-2’-deoxyuridine; CML, chronic myeloid leukemia; IP, intraperitoneal; MPP, multipotent progenitor; PBMC, peripheral blood mononuclear cell.