BACKGROUND

- The development of therapeutically effective inhibitors of the cyclin-dependent kinase (CDK) family has been challenging due to a poor understanding of target and structural biology leading to the development of drugs that are cytotoxic with limited efficacy.

- Inhibitors of the CDK4/6 complex have been pursued as a therapy for hormone receptor positive breast cancer. While multiple clinical trials have demonstrated promising activity, especially in hormone receptor positive breast cancer, their overall clinical benefit has been limited due to frequent dose interruptions for hematologic toxicities.

- G1T38, a novel, oral, potent and selective CDK4/6 inhibitor, was developed to overcome the limitations of inhibitors currently on the market.

OBJECTIVE

- To develop a compound which is highly efficacious against CDK4/6-dependent tumors while minimizing the undesirable on-target activity of myelosuppression thus obviating the need for a treatment holiday.

RESULTS

- Here, we describe the development of G1T38, a novel, potent and selective CDK4/6 inhibitor, that demonstrates unique pharmacokinetic and pharmacodynamic properties when compared to palbociclib.

- G1T38 has improved concentration-dependent cell cycle arrest in an RB-dependent manner in a variety of tumor types.

- Both CDK4/6-dependent and CDK4/6-independent cell lines were treated with 9 different KdELECT (DiscoveRx) was used as a follow-up to determine the activity of G1T38 in vivo.

- Figure 1A: High selectivity of G1T38. 
- Figure 1B: G1T38 is a potent and selective inhibitor of CDK4/6.
- Figure 2: 24 hour treatment with G1T38 causes a loss of S-phase (indicated by arrow) in CDK4/6-dependent cell lines (CFT231 and MDA MDA MDA MDA MB231), but not in the CDK4/6-independent cell line A2058 (Figure 1B) as measured by propidium iodide staining. (B) G1T38 induces a phase 1 arrest with subsequent cell cycle arrest in an RB-dependent manner in a variety of tumor types. (C) G1T38 concentration dependent cell cycle arrest in an RB-dependent manner in (continued...)

- Figure 3: G1T38 induces cell cycle arrest in both CDK4/6-dependent and CDK4/6-independent cell lines.
- Figure 4: G1T38 inhibits cell proliferation only in CDK4/6 competent cell lines.

- Figure 5: G1T38 causes G1S arrest and increases survival in NHEKxi2 ER+ breast cancer xenografts. 
- Figure 6: G1T38 causes tumor regression and increases survival in Nave2+ breast cancer xenografts.

- In an ER+ human breast tumor xenograft model, MCF7, was implanted in estrogen-supplemented athymic nude mice (START, San Antonio, TX). Mice were given once daily doses of G1T38, palbociclib, or vehicle by oral gavage at 10, 50, or 100 mg/kg for 28 days.

- The treatment holiday may allow for renewed tumor growth and the potential for emergence of drug resistance.

- Figure 7: When adjusted for exposure, G1T38 is more efficacious than palbociclib in human ER+ breast cancer models.

- MCF7 luciferase-bearing mice were treated with daily oral doses of 100 mg/kg G1T38, 10 mg/kg palbociclib, or vehicle for a combination of 28 days. Then mice were euthanized and the luciferase signal was measured. G1T38 was well tolerated, with no evidence of treatment-related toxicities. In contrast, significant weight loss was observed in the palbociclib cohort. G1T38 was well tolerated, with no evidence of treatment-related toxicities.

- Figure 8: G1T38 combination treatment with PI3K inhibitor, GDC0941, is highly efficacious.

SUMMARY

- G1T38 is a novel, potent and selective CDK4/6 inhibitor that induces a precise G1 cell cycle arrest in a variety of tumor types in a RB-dependent manner.

- G1T38 has improved in vivo efficacy and decreased on-target activity of myelosuppression compared to palbociclib.

- G1T38 causes tumor regression in a model of human ER+ breast cancer when given alone or in combination with palbociclib.

- Preclinical studies show that all antagonists are optimal combination therapies with G1T38. Phase I clinical studies in hormone receptor positive breast cancer will begin later this year. 

Contact email address: jcor@tbi.berkeley.edu

G1T38 is a NOVEL, ORAL, POTENT AND SELECTIVE CDK 4/6 INHIBITOR FOR THE TREATMENT OF RB COMPETENT TUMORS

JESSICA A. SORRENTINO, JOHN E. BISI, PATRICK J. ROBERTS, JAY C. STRUM
G1 THERAPEUTICS, INC., RESEARCH TRIANGLE PARK, NC