G1T28, A CYCLIN DEPENDENT KINASE 4/6 INHIBITOR, IN COMBINATION WITH ETOPOSIDE AND CARBOPLATIN FOR EXTENSIVE STAGE SMALL CELL LUNG CANCER (ES-SCLC): PRELIMINARY RESULTS

Caio Max S. Rocha Lima[1], Patrick J. Roberts[2], Victor M. Priego[3], Stephen G. Divers[4], Melanie Thomas[1], Ralph Boccia[3], R. Timothy Webb[4], Katie Stabler[2], Karenann M. Makhuli[2], Rajesh K. Malik[2], Raid Aljumaily[5], Geoffrey I. Shapiro[6]

[1]Gibbs Cancer Center and Research Institute, Spartanburg, SC; [2]G1 Therapeutics, Inc., RTP, NC; [3]The Center for Cancer and Blood Disorders, Bethesda, MD; [4]Genesis Cancer Center, Hot Springs, AR; [5]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK; [6]Dana-Farber Cancer Institute, Boston, MA

BACKGROUND

- Chemotherapy-induced toxicity to the bone marrow and immune system is a significant acute and long-term consequence of chemotherapy
- G1T28 is a highly potent and selective CDK4/6 inhibitor (CDK4/6i) in development to reduce chemotherapy-induced myelosuppression and preserve immune system function in patients with CDK4/6-independent cancers such as SCLC
- Hematopoietic stem and progenitor cells (HSPC) are dependent upon CDK4/6 for proliferation, and preclinical models demonstrated that transient G1T28-induced G1 cell cycle arrest renders them resistant to chemotherapy cytotoxicity, allowing faster hematopoietic recovery, preservation of long-term function, and enhancement of chemotherapy anti-tumor activity
- In a Phase 1a healthy normal volunteer (HNV) study (NCT02243150):
  - G1T28 administered intravenously was well tolerated, with no dose limiting toxicities or serious adverse events
  - G1T28 192 mg/m^2 demonstrated robust G_1-arrest of the HSPC subsets for up to 32 hours, confirming the biological activity of G1T28
  - Single doses of G1T28 had no impact on peripheral blood counts

OBJECTIVES

Assess the dose limiting toxicities (DLTs), safety and tolerability, hematological profile, pharmacokinetics (PK) and anti-tumor activity of G1T28 in combination with etoposide and carboplatin (EP; NCT02499770).

METHODS

Study Design

- Multicenter Phase 1b/2a study
- Part 1 is open-label, dose-finding, followed by open-label expansion in up to 24 patients
- Part 2 is randomized (1:1), double-blind, in 70 patients
- The starting dose of G1T28 was 200 mg/m^2 (derived from study G1T28-1-01 and expected to maintain HSPC G_1-arrest during and for several half-lives beyond EP exposure) administered IV prior to EP on days 1-3 every 21-days
- Carboplatin was dosed at an AUC of 5 and etoposide was dosed at 100 mg/m^2

Selected Inclusion Criteria

1. Age ≥ 18 years
2. Histologically or cytologically confirmed diagnosis of SCLC, including the presence of neuroendocrine features by immunohistochemistry
3. Extensive-stage disease
4. At least 1 target lesion that is unirradiated and measurable by RECIST, version 1.1
5. Organ Function: Hgb ≥ 9.0 g/dL, ANC ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, creatinine ≤ 1.5 mg/dL and GFR of ≥ 60 mL/min, bilirubin ≤ 1.5 × ULN, AST and ALT ≤ 2.5 × ULN or ≤ 5 × ULN in the presence of liver metastases, serum albumin ≥ 3 g/dL
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

Selected Exclusion Criteria

1. Prior chemotherapy for limited or extensive-stage SCLC
2. Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids
3. Concurrent radiotherapy to any site or radiotherapy within 2 weeks prior to enrollment or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response)
4. Cardiac and cerebrovascular disease: uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure (NYHA Grade III or IV); cerebrovascular accident or stroke within 6 months
5. Other uncontrolled serious chronic disease or conditions that in the investigator's opinion could affect compliance or follow-up in the protocol
6. Receipt of any investigational medication within 4 weeks prior to enrollment

Assessments

- Patients assessed for safety continuously
- Tumor response after every even cycle while receiving treatment until disease progression; for patients who did not progress while on treatment, tumor response assessments occur every 60 days ± 7 from the Post-Treatment Visit until disease progression
- Hematology assessments occurred at screening, days 1, 3, 8, 10, and 15 of each cycle and the Post-Treatment Visit
- G1T28, etoposide and carboplatin concentrations were quantified in the plasma by a validated LC-MS/MS (G1T28 and etoposide) or ICP-MS (carboplatin) assay on days 1 and 3 of cycle 1

Definition of Dose-Limiting Toxicities (Applicable to Cycle 1 of Part 1)

- Absolute neutrophil count (ANC) < 0.5 × 10^9/L lasting for ≥ 7 days
- ≥ Grade 3 neutropenic infection/febrile neutropenia
- Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with bleeding
- Unable to start next cycle of chemotherapy due to lack of recovery to an ANC ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L
- ≥ Grade 3 nonhematologic toxicity (nausea, vomiting, and diarrhea failing maximal medical management; fatigue lasting for > 72 hours)

RESULTS

Table 1. Baseline Patient and Disease Characteristics for Enrolled Patients

Patients enrolled	9*
Age, years median (range)	73 (45-80)
Gender	
Male	3
Female	6
Race	
White	8
African-American	1
Ethnicity	
Not Hispanic or Latino	8
Hispanic or Latino	1
ECOG Performance Status	
0	2
1	6
2	1
History of Brain Metastasis	
No	8
Yes	1

* As of data cutoff (01Apr2016), the first 6 enrolled patients were evaluable for safety and response

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

Table 2. Grade 3/4 Treatment-Related Adverse Events*

Event	Grade 3	Grade 4	Mean Duration of Grade 4 (Days)
Anemia	2	0	--
Leukopenia	2	1	3
Lymphopenia	1	1	5
Neutropenia	1	3	5
Thrombocytopenia	0	1	5
Fatigue	1	0	--
Headache	1	0	--

Hematologic Complications	N
Febrile Neutropenia	0
Grade 4 neutropenia for ≥ 7 days	0
Bleeding	0

*Toxicities were graded using NCI CTCAE (Common Terminology Criteria for Adverse Events), Version 4.03. All treatment-related adverse events were attributed to chemotherapy and none were attributed to G1T28.

- Two patients met DLT criteria, but were asymptomatic
  - First patient had ANC of 1.2 × 10^9/L on planned Cycle 2, Day 1; Cycle 2 delayed 1 day
  - Second patient had Grade 4 thrombocytopenia (platelets 24 × 10^9/L and extensive bone disease that may have compromised bone marrow function); Cycle 2 started on time
- There have been no treatment-related serious adverse events (SAEs)

Table 3. Summary of Plasma G1T28, Carboplatin and Etoposide Pharmacokinetic Parameters

	Statistic	C_{max}	$t_{1/2}$	AUC_{last}	CL	V
G1T28 200 mg/m^2		**(ng/mL)**	**(h)**	**(ng.h/mL)**	**(L/h/m^2)**	**(L/m^2)**
Day 1	Mean	1200	8.19	2290	83	694
	min-max	587-2170	6.29-10.6	1530-2860	60.3-121	327-985
Day 3	Mean	1380	9.04	2570	80.2	761
	min-max	355-3360	6.99-11.0	2010-3300	60.7-99.7	299-1310
Carboplatin AUC 5		**(µg/mL)**	**(h)**	**(µg.h/mL)**	**(L/h)**	**(L)**
Free	Mean	22.1	4.89	59.2	9.22	47.2
	min-max	14.3-35.8	1.86-13.9	27.3-90.9	4.18-15.3	30.1-84.1
Total	Mean	20.4	157	270	2.24	443
	min-max	13.6-30.1	74.4-272	133-500	1.04-3.47	227-739
Etoposide 100 mg/m^2		**(µg/mL)**	**(h)**	**(µg.h/mL)**	**(mL/min/m^2)**	**(L/m^2)**
Day 1	Mean	22.6	6.86	144	12.6	6.89
	min-max	19.1-24.6	4.56-10.9	91.9-221	7.54-18.1	6.16-7.60
Day 3	Mean	21.0	6.71	133	13.0	6.57
	min-max	19.1-24.5	4.22-9.6	97.6-163	10.3-17.1	5.61-8.03

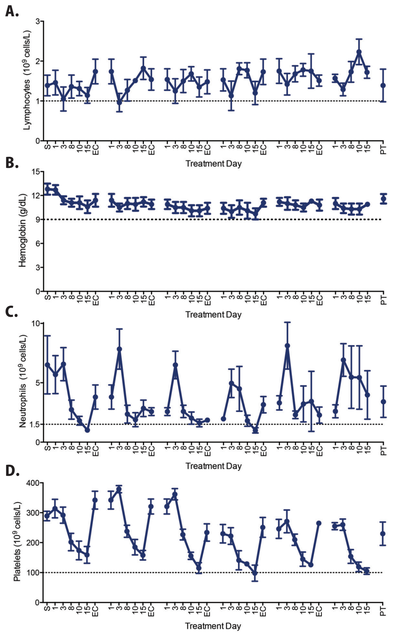
- Based on the HNV study (NCT02243150) results, the G1T28 AUC is slightly lower than expected in the current study
- The lower G1T28 AUC may be an artifact of sampling differences between the studies and the rapid distribution of G1T28 after the end of infusion
- The carboplatin and etoposide PK parameters are within the expected range, indicating that there are no drug-drug interactions

Table 4. Dose Reductions, Dose Delays and Supportive Care

Total cycles administered	34
Cycles delayed for toxicity	3
Patients with ≥ one dose delay	2
Patients with ≥ one dose reduction	1
Patients receiving ≥ one dose of Erythropoietin	2
Patients receiving ≥ one dose of G-CSF Total number of cycles of G-CSF administered*	2 3
Patients receiving IV antibiotics	1
Patients receiving ≥ 1 transfusion	3
Patients receiving ≥ 1 hospitalization	0

*One dose in cycle 5 and two doses in cycle 6.

Figure 1. Hematology Assessments



Mean blood counts with standard error of the mean are shown. Abbreviations: S, screening; EC, end of cycle; PT, post-treatment visit.

Table 5. Tumor Response by RECIST v1.1

Best Overall Response	
Complete Response (CR)	1
Partial Response (PR)	5
Stable Disease (SD)	0
Progressive Disease (PD)	0

Figure 2. Best Change in Tumor Size from Baseline

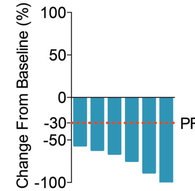
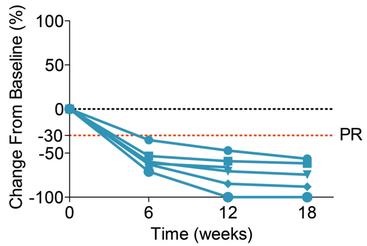


Figure 3. Change in Tumor Size from Baseline Over Time



- 100% confirmed response rate
- The first six enrolled patients have completed treatment
  - Five patients received six cycles and one patient received four cycles
- All six patients are in the survival follow-up phase to determine progression free survival (PFS) and overall survival (OS)
- Two patients in the survival follow-up phase developed asymptomatic brain metastases

CONCLUSIONS

- In this ongoing study, the combination of G1T28 with EP is well tolerated, without any episodes of febrile neutropenia or treatment-related SAEs
- The most common adverse events were hematologic toxicities attributed to chemotherapy
- Grade 3/4 hematologic toxicities, in the setting of frequent hematologic monitoring, recovered quickly resulting in a limited number of dose reductions or delays
- Early anti-tumor activity results are promising with all 6 evaluable patients responding to therapy (CR or PR)
- There was no evidence of a pharmacokinetic drug-drug interaction between G1T28 and carboplatin or etoposide
- This novel approach, allowing the administration of chemotherapy with preservation of hematopoietic and immune system function, could potentially improve treatment outcomes for patients with CDK4/6-independent tumors

ACKNOWLEDGEMENTS

We thank and acknowledge all the patients, their families and study personnel for participating in the study. Wendy Anders, an employee of G1 Therapeutics, Inc., assisted with this poster presentation.