FIRST-IN-HUMAN PHASE 1a SAFETY, PK, AND PD STUDY OF THE CDK4/6 INHIBITOR G1T28 (G1T28-1-01)

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BACKGROUND

- Chemotherapy-induced myelosuppression continues to represent the major dose-limiting toxicity of cytotoxic chemotherapy
  - manifested as neutropenia, lymphopenia, anemia, and/or thrombocytopenia
  - source of many important side effects of cancer treatment such as infection, sepsis, bleeding, and fatigue leading to the need for hospitalizations, growth factor support and transfusions (red blood cells or platelets)
  - clinical concerns raised by myelosuppression commonly lead to chemotherapy dose reductions and limit therapeutic dose-intensity
- G1T28 (formerly G1T28-1) is a highly potent, selective, and reversible CDK4/6 inhibitor being developed for intravenous (IV) administration to cancer patients to reduce chemotherapy-induced myelosuppression
- G1T28 acts by transiently producing a G1 cell cycle arrest of hematopoietic stem and progenitor cells (HSPCs) in the bone marrow
  - G1-arrested HSPC are more resistant to the DNA damaging effects of chemotherapy, thereby preserving bone marrow and immune system function
- In preclinical animal models, administration of G1T28 prior to myelosuppressive chemotherapy resulted in:
  1. improved recovery of all blood cell counts, including neutrophils, lymphocytes, red blood cells, and platelets
  2. preservation of long-term bone marrow function
  3. ability to tolerate more cumulative chemotherapy
- To ensure selective bone marrow and immune system protection without antagonizing the intended tumor efficacy of the chemotherapy, G1T28 will be developed in patients with CDK4/6-indpendent tumors, with early clinical development focused on patients with Rb-null tumors such as SCLC

OBJECTIVES

Primary

- Assess the safety and tolerability of G1T28 administered IV

Secondary

- Assess the pharmacokinetic (PK) profile of G1T28
- Assess potential pharmacodynamic (PD) markers of G1T28
- Define G1T28 dose(s) for further study

METHODS

- This first-in-human study included a double-blind, randomized, placebo-controlled, single ascending dose (SAD) part in 6 dose cohorts and an open-label cohort to confirm the biologically effective dose (BED) of G1T28 (clinicaltrials.gov identifier: NCT02243150)
- G1T28 or placebo were administered as an IV infusion over 30 minutes in D5W
- The main criteria for inclusion included healthy male and/or female subjects between 18-60 years of age, with a weight of ≥50 kg and a body mass index of 18-32 kg/m^2
- 107 subjects were screened and 45 were enrolled in the study
- 33 subjects were randomly assigned (3:1 G1T28:placebo) to receive a single dose of G1T28 (6, 12, 24, 48, 96, or 192 mg/m^2) or placebo in 6 successive dose cohorts in the SAD part
- 12 subjects (Cohort 7) were enrolled to confirm the BED (192 mg/m^2) of G1T28, based on the totality of the available safety, PK, and PD data
- PD activity of G1T28 was evaluated in three assays: 1) evaluation of CBCs, 2) *ex-vivo* phytohemagglutinin (PHA)-stimulated lymphocyte proliferation assay, 3) evaluation of bone marrow HSPC proliferation (BED cohort of 12 subjects; Abstract #2529)
- All subjects were included in the safety population, completed the study per protocol, and none were withdrawn or dropped out of the study

RESULTS

STUDY POPULATION AND DOSING

TABLE 1. SUMMARY OF DEMOGRAPHIC CHARACTERISTICS

Parameter	Category or Statistic	Placebo (N=9)	6 mg/m^2 (N=3)	12 mg/m^2 (N=3)	24 mg/m^2 (N=3)	48 mg/m^2 (N=3)	96 mg/m^2 (N=6)	192 mg/m^2 (N=6)	BED (192 mg/m^2) (N=12)	Both (192 mg/m^2) (N=18)	Total (N=45)
Gender n (%)	Male	8 (89)	3 (100)	3 (100)	3 (100)	1 (33)	4 (67)	3 (50)	5 (42%)	8 (44%)	30 (67%)
	Female	1 (11)	--	--	--	2 (67)	2 (33)	3 (50)	7 (58%)	10 (56%)	15 (33%)
Race n (%)	White	7 (78)	2 (67)	2 (67)	3 (100)	3 (100)	6 (100)	5 (83)	11 (92%)	16 (89%)	39 (87%)
	Black	1 (11)	--	--	--	--	--	--	--	--	1 (2%)
	Multiple	1 (11)	1 (33)	1 (33)	--	--	--	1 (17)	1 (8%)	2 (11%)	5 (11%)
Age (years)	mean (SD)	31 (10)	23 (3)	25 (5)	37 (20)	32 (21)	41 (16)	51 (12)	39 (14)	43 (14)	37 (15)
	min-max	21-50	20-26	22-30	23-60	20-57	21-59	26-58	21-59	21-59	20-60

Height, weight, body mass index, and body surface area were comparable across all groups.
All subjects, except for one (24 mg/m^2 cohort), were of non hispanic or latino ethnicity.

TABLE 2. SUMMARY OF G1T28 ADMINISTRATION

Study part	Cohort	G1T28 Planned dose	Duration	Actual dose per subject (min-max)	Number of subjects exposed
SAD	1	6 mg/m^2	single dose	12 - 13.2 mg	3
	2	12 mg/m^2	single dose	21.9 - 23.3 mg	3
	2	24 mg/m^2	single dose	44.4 - 51.1 mg	3
	4	48 mg/m^2	single dose	81.9 - 101.1 mg	3
	5	96 mg/m^2	single dose	174.3 - 206.3 mg	6
	6	192 mg/m^2	single dose	302.8 - 403.4 mg	6
	Placebo (all cohorts)	Not applicable	single dose	Not applicable	9
BED	7	192 mg/m^2	single dose	306 - 460 mg	12

BED = biologically effective dose; max = maximum; min = minimum; SAD = single ascending dose

SAFETY

TABLE 3. SUMMARY OF RELATED TEAES REPORTED IN ≥ 10% OF SUBJECTS

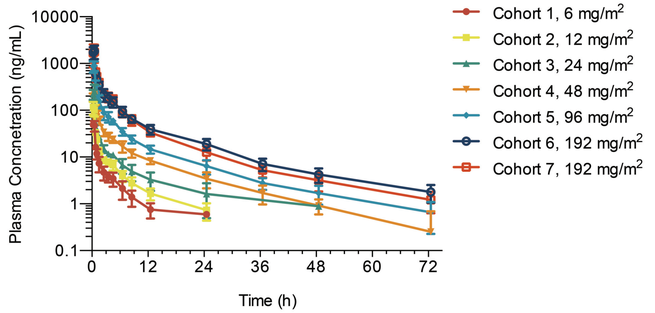
System Organ Class / Preferred Term	96 mg/m^2 (N=6)		192 mg/m^2 (N=6)		BED (192 mg/m^2) (N=12)		Both (192 mg/m^2) (N=18)		Total (N=45)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total Number of TEAEs	7		12		31		43		51	
Total Subjects with at least 1 TEAE	5	(83)	5	(83)	10	(83)	15	(83)	21	(47)
Nervous system disorders										
Total Subjects with at least 1 TEAE	2	(33)	4	(67)	9	(75)	13	(72)	15	(33)
headache	2	(33)	4	(67)	9	(75)	13	(72)	15	(33)
Gastrointestinal disorders										
Total Subjects with at least 1 TEAE	1	(17)	4	(67)	6	(50)	10	(56)	11	(24)
nausea	1	(17)	3	(50)	6	(50)	9	(50)	10	(22)
Musculoskeletal & connective tissue disorders										
Total Subjects with at least 1 TEAE	4	(67)	2	(33)	3	(25)	5	(28)	9	(20)
pain in extremity	4	(67)	1	(17)	3	(25)	4	(22)	8	(18)

Data from placebo and doses 6-48 mg/m^2 are not shown; TEAEs were coded according to MedDRA Version 17.1.
BED = biologically effective dose; N = number of subjects exposed; n = number of subjects that experienced the adverse event;
TEAE = treatment emergent adverse event

- 83 TEAEs reported in 32 out of 45 (71%) subjects; 59 TEAEs were reported in the combined 192 mg/m^2 dose group; and 1 TEAE reported in the placebo group
- Most TEAEs were mild in intensity, with only 13 subjects experiencing a total of 19 TEAEs of moderate intensity
- There were no deaths, other SAEs, or TEAEs that resulted in withdrawal from the study. All TEAEs were transient and had recovered/resolved by the end of the study

PHARMACOKINETICS

FIGURE 1. G1T28 DEMONSTRATES DOSE DEPENDENT PHARMACOKINETICS



Blood samples were collected for measurement of G1T28 concentrations in plasma at the following time points: prior to G1T28 dosing, during infusion (0.25 hours), immediately prior to end of infusion (EOI; 0.5 hours), and at the following times after EOI (0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours). G1T28 plasma concentration-time plots (log-linear) are shown, with data represented as mean ± standard deviation.

TABLE 4. SUMMARY OF PLASMA G1T28 PHARMACOKINETIC PARAMETERS

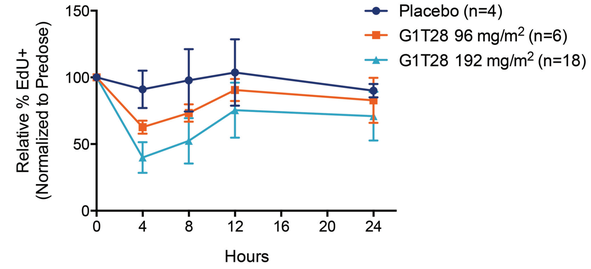
Dose Cohort	Statistic	C_{max} (ng/mL)	t_{max}* (h)	AUC_{0-t} (ng.h/mL)	AUC_{inf} (ng.h/mL)	$t_{1/2}$ (h)
6 mg/m^2 (N=3)	Mean	50.4	0.25	61.9	66.6	5.32
	min-max	42.7 - 60.5	0.25 - 0.47	52.8 - 79.6	57.1 - 86.6	3.90 - 8.17
12 mg/m^2 (N=3)	Mean	119	0.47	135	143	7.62
	min-max	87.4 - 143	0.25 - 0.47	112 - 170	119 - 182	6.96 - 8.21
24 mg/m^2 (N=3)	Mean	255	0.47	266	279	9.28
	min-max	177 - 334	0.25 - 0.47	211 - 374	220 - 392	7.35 - 13.8
48 mg/m^2 (N=3)	Mean	224	0.47	503	518	12.9
	min-max	217 - 228	0.25 - 0.48	463 - 525	472 - 544	9.96 - 18.5
96 mg/m^2 (N=6)	Mean	910	0.37	1323	1341	14.7
	min-max	654 - 1320	0.25 - 0.48	1094 - 1582	1108 - 1614	10.2 - 18.7
192 mg/m^2 (N=6)	Mean	1969	0.47	3068	3106	14.5
	min-max	1460 - 2930	0.25 - 0.47	2475 - 3829	2495 - 3869	13.0 - 16.5
BED Cohort 192 mg/m^2 (N=12)	Mean	1705	0.47	2964	2991	14.5
	min-max	885 - 3280	0.25 - 0.48	2360 - 3750	2379 - 3762	11.9 - 17.3

BED = biologically effective dose; max = maximum; min = minimum; N = number of subjects
Geometric mean and minimum-maximum are presented.
* For t_{max} the median and minimum-maximum are presented.

- C_{max} increased in a dose proportional manner following a single 30 minute IV infusion of G1T28 over the dose range of 6 to 192 mg/m^2
- Total systemic (AUC) exposure increased more than dose-proportionally over the dose range of 6 to 192 mg/m^2 G1T28.
- Clearance of G1T28 was relatively unchanged over the dose range of 6 to 192 mg/m^2
- Urinary excretion appears to be a minor route of elimination for unchanged G1T28 (data not shown)

PHARMACODYNAMICS

FIGURE 2. G1T28 DEMONSTRATES A DOSE DEPENDENT INHIBITION OF PROLIFERATION OF CD45$^+$CD3$^+$ LYMPHOCYTES



Peripheral blood samples were drawn from subjects in Cohorts 5-7 at predose, 4, 8, 12, and 24 hours postdose. After a five-fold dilution in media, whole blood was stimulated with phytohaemagglutinin (PHA) for 48 hours *ex vivo*. One hour before harvest (47 hours into PHA stimulation) cells were treated with ethynyl 2' deoxyuridine (EdU). At harvest, cells were stained for CD3 and CD45, and assayed for EdU incorporation. Through flow cytometric analysis, CD3$^+$CD45$^+$EdU$^+$ cells were measured to determine the G1T28 effect on proliferation. Data shown are mean ± standard deviation.

- A single IV infusion of G1T28 at 96 and 192 mg/m^2 resulted in a dose dependent inhibition of the proliferation of CD45$^+$/CD3$^+$ lymphocytes (maximum mean inhibition 4 hours after end of infusion of 37.2% and 60%, respectively)
- Administration of G1T28 at the BED of 192 mg/m^2 produced robust inhibition of HSPCs within the bone marrow, which persisted for 32 hours (data not shown here; see Abstract #2529)
- Administration of G1T28 up to 192 mg/m^2 had no effect on CBCs (data not shown here; see Abstract #2529)

SUMMARY

- G1T28, a potent and selective CDK4/6 inhibitor, was well tolerated when administered as an single IV infusion over 30 minutes
- G1T28 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/m^2 had no effect on CBCs
- Based on the observed PK, PD, and safety profile, G1T28 200 mg/m^2 IV (rounded up from the BED of 192 mg/m^2) was selected as the starting dose for further development in patients with CDK4/6-independent cancers
- 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
  - 1st line with G1T28 administration prior to etoposide/carboplatin
  - 2nd/3rd line with G1T28 administration prior to topotecan

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