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A First-in-Human, Phase I Clinical Study of the Safety, Tolerability and Pharmacokinetics (PK) of G-202, a Thapsigargin-Based PSMA-Activated Prodrug, in Patients with Advanced Solid Tumors

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Abstract

Background G-202 is a prodrug developed to strategically affect activation of a cytotoxic pro-apoptotic analog of thapsigargin in human tumors. In G-202, cytotoxic activity is blocked by a masking peptide that is selectively cleaved by Prostate-Specific Membrane Antigen (PSMA), a protease expressed in prostate cancer cells and most tumor endothelial cells but not in normal vasculature or normal tissue epithelium. G-202 has potent anti-tumor activity in human cancer xenografts and a favorable safety profile in toxicology models. An open-label, single-arm, dose-escalation Phase I study was performed to determine the maximum tolerated dose (MTD) of G-202 in patients with advanced solid tumors.

Methods 3+3 dose escalation of G-202 starting at 1.2 mg/m^2 administered by intravenous infusion on Days 1, 2 and 3 of a 28-day cycle. Dose escalated in 100% increments until occurrence of at least two G-202 related equivalent Grade 2 adverse events (AEs) in the same cohort, at which time 33% dose increments were implemented. DLT was defined as non-hematologic toxicity ≥Grade 3 or hematologic toxicity ≥Grade 4 lasting ≥5 days in ≤2/3 or 2/6 pts; MTD was the dose level preceeding the DLT dose. PK parameters were measured before and at intervals after the first infusion and at the end of Cycle 1.

Results In the dose escalation portion of the trial, 28 patients were treated at 8 dose levels, ranging from 1.2 to 88 mg/m^2. The most frequently-observed AEs were fatigue (39% of pts); nausea (36%); rash (29%); and vomiting, infusion-related reactions, pyrexia and cough (each 21%). While not DLTs, observations of Grade 2 infusion-related reaction despite pre-medication with anti-histamine and corticosteroids (2 patient, observed on Day 1 but absent or diminished on Days 2 and 3), and Grade 2 creatinine elevation (1 patient) at the 88 mg/m^2 dose level led investigators to establish 66.8 mg/m^2 as the MTD. Preliminary PK data show a geometric mean half-life associated with each of 2 exponential phases ($t_{1/2\alpha}$ and $t_{1/2\beta}$) of 1.70 hours and 18.1 hours, respectively. The geometric mean systemic clearance was 181 mL/h/m^2. The apparent volume of distribution at steady state was 4059 mL/m^2, suggesting that G-202 is confined to plasma and does not undergo extensive tissue distribution. Although not a primary objective of the study, evidence of clinical activity was observed in some patients.

Conclusions The MTD of G-202 administered intravenously for 3 days of a 28-day cycle is 66.8 mg/m^2. A modified dosing regimen of 40 mg/m^2 on Day 1 to suppress infusion-related reactions and 66.8 mg/m^2 on Days 2 and 3 of each cycle is being evaluated in an expansion cohort and will be evaluated in Phase 2 studies in castrate-resistant prostate cancer and as second-line therapy in hepatocellular carcinoma.

Introduction and Study Design

The prodrug G-202 consisting of a cytotoxic analog of thapsigargin coupled to a masking peptide which inhibits its biologic activity until proteolytic cleavage at the tumor site. Thapsigargin binds to and blocks activity of the Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase pump, leading to increases in cytosolic calcium and induction of apoptosis. The masking peptide is a substrate for Prostate-Specific Membrane Antigen (PSMA), a glutamate carboxypeptidase. G-202 is produced by coupling 12-aminododecanoyl thapsigargin (12ADT) to the masking peptide Asp-Glu-Glu-Glu-Glu (Figure 1). PSMA sequentially hydrolyzes the Glu residues to release the active cytotoxin 12ADT-Asp. Because PSMA is expressed on the surface of prostate cancer cells and on the surface of endothelial cells within most solid tumors, but not in normal tissues and not on endothelial cells outside of most solid tumors, release of 12ADT-Asp is expected to be primarily confined to tumor tissue.

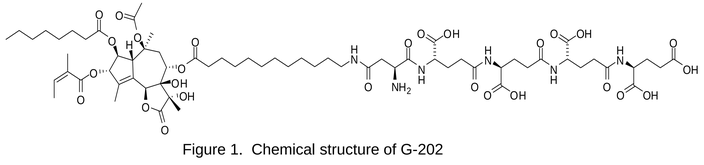


Figure 1. Chemical structure of G-202

Design Sequential dose escalation phase to establish MTD; expansion phase to evaluate safety and PK of recommended Phase II dose; treatment until disease progression or unacceptable toxicity

Schedule Intravenous infusion over 60 minutes on Days 1, 2 and 3 of a 28-day cycle

Dose Levels Eight dose levels, ranging from 1.2 – 88 mg/m^2

Dose-Limiting Toxicity Defined as toxicity during the first cycle not attributed to underlying disease or intercurrent illness. This included Grade 4 neutropenia lasting for 5 days; Grade 3 febrile neutropenia; Grade 4 thrombocytopenia (Grade 3 with bleeding); Grade 3 nausea, vomiting or diarrhea despite optimal management; Grade 4 hematologic or Grade 3 non-hematologic toxicity persisting more than 5 days

Safety Parameters Adverse events per NCI/CTCAE v4.0 **Clinical Activity** Based on RECIST 1.1

Pharmacokinetic Analysis G-202 measured in blood collected prior to C1D1 dosing, after beginning C1D1 infusion (30, 60, 75, 90, 120 min; 2, 4, 8, 10-12 after completion of C1D1 infusion, prior to C1D2, prior to C1D3, prior to C2D1

Summary of Results and Study Status

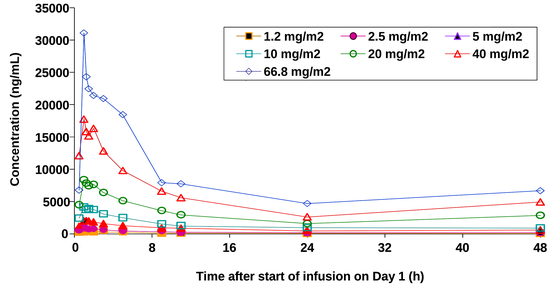
A total of 44 patients were enrolled on the Phase I study; 28 were enrolled into the dose escalation portion of the study. Based on non-DLT observations of Grade 2 infusion-related reaction despite pre-medication (2 patients) and Grade 2 creatinine elevation (1 patient) at the 88 mg/m^2 dose level, the MTD was established as 66.8 mg/m^2. To reduce the likelihood of infusion-related reactions, a modified dosing regimen was developed in which the G-202 dose on Day 1 is 40 mg/m^2 and 66.8 mg/m^2 on Days 2 and 3 of each 28-day cycle. This regimen is being evaluated in an expansion cohort, into which 16 patients have been enrolled. The expansion cohort is closed to new patient accrual with 5 active patients. Data shown are based on interim analysis of preliminary data.

Patient Demographics and Baseline characteristics

	G-202 Dose Level (mg/m^2)								
	1.2	2.5	5	10	20	40	66.8	88	40/66.8/66.8
Sex									
Male	3	2	2	3	1	4	4	3	13
Female	0	1	1	0	2	0	2	0	3
Race									
White/Caucasian	3	3	3	2	3	4	5	2	10
Hispanic/Latino	0	0	0	0	0	0	1	1	6
Eastern European	0	0	0	1	0	0	0	0	0
Median Age (range)	61 (51-71)	64 (57-69)	59 (48-76)	70 (64-70)	62 (54-62)	71 (49-81)	60 (52-79)	58 (58-71)	68 (50-83)
ECOG PS									
0	1	0	0	1	0	1	2	0	3
1	2	3	3	2	3	3	4	3	13
Primary Tumor Type									
Bladder	0	1	0	0	0	1	0	0	0
Cholangiocarcinoma	0	1	0	0	0	0	0	0	0
Colorectal	1	0	3	1	3	0	4	0	2
Endometrial	0	0	0	0	0	0	0	0	1
Esophageal	1	0	0	0	0	0	0	0	0
Head and Neck	0	0	0	0	0	1	0	0	0
Hepatocellular	0	0	0	0	0	0	0	1	5
Lung (NSCLC)	0	0	0	1	0	0	0	0	1
Pancreas	0	0	0	0	0	1	1	1	0
Prostate	1	0	0	0	0	0	0	1	7
Renal	0	0	0	0	0	1	0	0	0
Unknown Primary	0	0	0	1	0	0	1	0	0
Urothelial	0	1	0	0	0	0	0	0	0

Pharmacokinetics

Pharmacokinetic data from the 25 patients enrolled into the first 7 cohorts of the dose escalation portion of the study suggest a bi-exponential model with time-invariant kinetics.



PK Parameters	
Half-Life	
$t_{1/2}\,\alpha$	1.70 hours (range 0.07 – 4.22 hours)
$t_{1/2}\,\beta$	18.1 hours (range 4.56 – 69.3 hours)
Systemic Clearance (CL)	181 mL/h/m^2
Volume of Distribution at Steady State (Vss)	4059 mL/m^2
Distribution	G-202 largely confined to plasma

Adverse Events

Number of Patients Treated	**44**
Number of Cycles Administered	85
Adverse Events	**385**
Related to G-202	204 (53%)
Serious Adverse Events	**33**
Related to G-202	19 (61%)

Most Frequently-Occurring Adverse Events	Number of Patients (%)
Rash	14 (32%)
Fatigue	13 (29%)
Blood Creatinine Elevated	10 (23%)
Nausea	8 (18%)
Infusion-Related Reaction	7 (16%)
Decreased Appetite	6 (14%)
Pyrexia	5 (11%)
Vomiting	5 (11%)

G-202 Related Serious Adverse Events	Number of Patients Experiencing the SAE			
	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hyponatremia			1*	
Hyperkalemia	1		1	
Acute Renal Failure			1	
Nausea			1	
Vomiting			1	
Infusion-Related Reaction		2	2	
Hypotension			1	
Hypertension		1		
Thrombocytopenia			1	1
Morbilliform Rash			1	
Acute Kidney Injury		1	1	
Blood Creatinine Increased		1		

* 1 patient with two occurrences

Length of Time On Study

The majority (n=34, 77%) of patients received at least two cycles of treatment. Six patients received at least 3 cycles of treatment. 10 patients completed only 1 cycle, with withdrawal frequently due to deteriorating medical condition as anticipated in this advanced patient population. Five patients remain on study.

Time on Study	Number of Patients (%)
8 weeks	28 (64%) *
16 weeks	4 (9%) **
>16 weeks	1 (3%) ***

* 3 patients remain on-study (2 with hepatocellular carcinoma; 1 with prostate cancer)
** 1 patient remains on-study (prostate cancer)
*** 1 patient remains on-study (hepatocellular carcinoma)

Conclusions

- MTD of G-202 administered by intravenous infusion on Days 1, 2 and 3 of a 28-day cycle in patients with advanced cancer is 66.8 mg/m^2
- Most frequently-observed drug-related adverse events were morbilliform rash (32%), fatigue (29%), creatinine elevation (23%) and infusion-related reaction (16%).
- Most frequently-observed SAEs were infusion-related reaction (observed in 9% of patients) and renal observations (observed in 9% of patients).
- Creatinine elevations were transient and typically observed on Day 8.
- A lower dose of G-202 (40 mg/m^2) on Day 1 of each cycle and implementation of premedication guidelines appears to reduce or eliminate the incidence of infusion-related reactions.
- Maintenance of adequate hydration by prophylactic infusion of fluid (250 – 500mL) on each day of infusion appears to reduce or eliminate the incidence of renal observations.
- With incorporation of the modified dosing regimen, guidelines for premedication and prophylactic hydration, G-202 appears to be well-tolerated in patients with advanced solid tumors and should be evaluated in Phase II studies.