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✯A First-in-Human, Phase I Clinical Study of G-202, a Thapsigargin-Based Prostate-Specific Membrane Antigen (PSMA)-Activated Prodrug, in Patients with Advanced Solid Tumors

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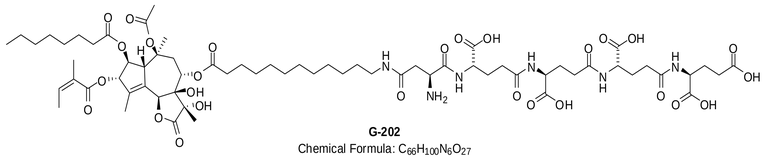
Abstract

Background Thapsigargin induces apoptosis through disruption of calcium homeostasis. G-202 is a thapsigargin-based prodrug whose cytotoxic activity is blocked by a masking peptide that is cleaved by PSMA, a membrane-bound protease expressed in prostate cancer cells and the endothelium of tumor vasculature but not in most other tissues or normal tissue vasculature. An open-label, single-arm, dose-escalation Phase I study was performed in patients with advanced solid tumors to evaluate the safety and pharmacokinetics of G-202 and establish a Phase II dosing regimen.
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. A Phase II dosing regimen was established and evaluated in an expansion cohort. PK parameters were measured in Cycle 1.
Results In the dose escalation, 28 patients (pts) were treated at 8 dose levels (1.2 to 88 mg/m^2). A protocol-defined MTD was not reached, but infusion-related reactions and creatinine elevation at 88 mg/m^2 led to declaration of 66.8 mg/m^2 as MTD. A modified regimen to reduce infusion-related reactions of G-202 at 40 mg/m^2 on Day 1 and 66.8 mg/m^2 on Days 2 and 3 was evaluated in an expansion cohort of 16 pts with a total of 48 cycles administered (avg 3/pt, range 1-12). Among the 44 pts treated on the study, there were 132 drug-related AEs, 60% of which were Grade 1. Related AEs of any grade reported in at least 4 (10%) patients were fatigue (16 pts), rash (16 pts), increased creatinine/acute kidney injury/acute renal failure (12 pts), nausea (12 pts), fever (8 pts), infusion-related reaction (8 pts), anorexia (7 pts), chills (7 pts), pruritus (7 pts), AST elevation (5 pts), heartburn (5 pts), vomiting (5 pts), and thrombocytopenia (4 pts). Prophylactic intravenous hydration on the day of infusion appeared to ameliorate creatinine elevations. G-202 has a mean half-life of 21 hours and steady state distribution volume of 4995 mL/m^2, suggesting confinement to plasma. Because PSMA is highly expressed in hepatocellular carcinoma (HCC), the expansion cohort was enriched with HCC pts. Five HCC pts were enrolled and received a total of 29 cycles (avg 6/pt, range 2-12). One pt completed 12 cycles before exhibiting disease progression and one pt completed 9 cycles before being withdrawn due to an unrelated treatment delay.
Conclusions The MTD of G-202 administered intravenously for 3 consecutive days of a 28-day cycle is 66.8 mg/m^2. A dosing regimen of 40 mg/m^2 on Day 1 and 66.8 mg/m^2 on Days 2 and 3 appears to be well-tolerated and may have activity in HCC. G-202 is being evaluated in a Phase 2 study in patients with HCC who have progressed on sorafenib.

Introduction and Study Design

The prodrug G-202 consists of a cytotoxic analog of thapsigargin coupled to a masking peptide which inhibits its biologic activity until proteolytic cleavage. 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. PSMA sequentially hydrolyzes G-202 to release the active cytotoxin 12ADT-Asp. Because PSMA is expressed on the surface of prostate cancer cells and on the surface of vascular endothelial cells within most solid tumors, but not in normal tissues and not on vascular endothelial cells outside of most solid tumors, release of 12ADT-Asp is expected to be primarily confined to tumor tissue and tumor vasculature.



G-202
Chemical Formula: $C_{66}H_{100}N_6O_{27}$

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-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

Summary of Patient Enrollment and Study Status

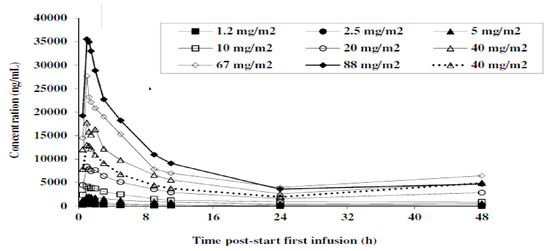
- 44 patients were treated, including 28 in the dose escalation portion of the study in which 8 dose levels ranging from 1.2 to 88 mg/m^2 were evaluated.
- Based on non-DLT observations of Grade 2 infusion-related reaction (IRR) despite pre-medication (2 patients) and Grade 2 creatinine elevation (1 patient) at the 88 mg/m^2 dose level, the MTD was established as 66.8 mg/m^2.
- To reduce IRR, a modified dosing regimen of G-202 dose on Day 1 of 40 mg/m^2 and 66.8 mg/m^2 on Days 2 and 3 of a 28-day cycle, was designated as the recommended Phase II regimen and was evaluated in an expansion cohort of 16 patients.
- Based on laboratory data suggesting that PSMA is highly expressed in prostate cancer as well as tumors with increased vascularity such as hepatocellular carcinoma, we enriched patients with these specific tumor types in the expansion cohort.

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

G-202 Pharmacokinetics

G-202 was measured in blood collected prior to C1D1 dosing, after beginning C1D1 infusion (30, 60, 75, 90, 120 min), 2, 4, 8, 10-12 hours after completion of C1D1 infusion, prior to C1D2 and prior to C1D3. Data suggest a bi-exponential model with time-invariant kinetics.



PK Parameters	
Half-Life	
$t_{1/2}\alpha$	2.05 hours (range 0.118 – 5.88 hours)
$t_{1/2}\beta$	21.0 hours (range 4.28 – 69.3 hours)
Systemic Clearance (CL)	199 mL/h/m^2
Volume of Distribution at Steady State (Vss)	4995 mL/m^2
Distribution	G-202 largely confined to plasma without extensive tissue distribution

Length of Time On Study

The majority (n=35, 80%) of patients received at least two cycles of treatment. Eight (8) patients received at least 3 cycles of treatment. Nine (9) patients completed only 1 cycle, with withdrawal frequently due to deteriorating medical condition as anticipated in this patient population. Among the 16 patients enrolled in the expansion cohort were 7 heavily-pretreated patients with castrate-resistant prostate cancer and 5 patients with HCC who had progressed on sorafenib. Among the prostate cancer patients, the best response was observed in 1 patient who completed 4 cycles of treatment. Among the 5 patients with HCC, 3 (60%) had time to progression of 16 weeks or more, a significant improvement over the typical time to progression after sorafenib failure of ~2.1 months.

Time on Study	All Patients Enrolled (n=44) Number (%)	Patients with Prostate Cancer at Phase II Dose (n=7) Number (%)	Patients with HCC at Phase II Dose (n=5) Number (%)
8 weeks	27 (61%)	3 (43%)¶	2
16 weeks	5 (11%)	1 (14%)	1*
>16 weeks	2 (5%)		
36 weeks	1		1*§
48 weeks	1		1*

¶ Three patients completed 1 cycle
* Improvement over historic time to progression after sorafenib failure
§ Patient discontinued study after 9 cycles due to an unrelated treatment delay; patient had SD at time of discontinuation

Adverse Events

	Across All Dose Levels	Phase II Dosing Regimen	Patients with HCC at Phase II Dosing Regimen
Number of Patients Treated	**44**	**16**	**5**
Number of Cycles Administered	105 (average 2/patient)	48 (average 3/patient)	29 (average 6/patient)
Adverse Events	**453**	**209**	**77**
Related to G-202	221	101	29
Serious Adverse Events	**34**	**7**	**2**
Related to G-202	19	3	0
Deaths Due to Adverse Events	0	0	0

Most Frequently-Occurring Adverse Events	Number of Patients (%)
Rash/Pruritus	18 (41%)
Fatigue	16 (36%)
Nausea	12 (27%)
Renal Changes (creatinine elevation, acute kidney injury, acute renal failure)	12 (27%)
Infusion-Related Reaction	8 (18%)
Pyrexia	8 (18%)
Chills	7 (16%)
Anorexia	6 (14%)
Dyspepsia	5 (11%)
AST Elevation	5 (11%)
Vomiting	5 (11%)

Renal changes consisted of creatinine elevation (n=7), acute kidney injury (n=3) or acute renal failure (n=2). Reports of acute kidney injury and renal failure were typically based on laboratory observation of creatinine elevation without other symptoms of renal failure, such as hyperkalemia, acidosis or need for dialysis. Creatinine elevations were typically observed on Day 8 and resolved prior to the next planned cycle; prophylactic hydration on the day of infusion appeared to reduce the likelihood of renal observations.

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	
Hypertension			1	
Acute Renal Failure			2 (1*)	
Acute Kidney Injury		2	1*	
Nausea			1	
Vomiting			1	
Infusion-Related Reaction		2	2*	
Morbilliform Rash			1	
Thrombocytopenia			1	1

Patients Discontinuing Due to Adverse Events	G-202 Dose mg/m^2	Adverse Event (CTC Grade)
025	66.8	acute kidney injury (Gr 2) morbilliform rash (Gr 3)
040	Phase II Regimen 40/66.8/66.8	acute kidney injury (Gr 3)

Conclusions

- ✯ The 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 fatigue, morbilliform rash, nausea and renal changes (primarily transient creatinine elevation).
- ✯ The modified regimen of G-202 at 40 mg/m^2 on Day 1 and 66.8 mg/m^2 on Days 2 and 3 to reduce day 1 infusion related reactions appears well-tolerated and was selected as the Phase II dosing regimen.
- ✯ Among the 44 patients treated across 9 dose levels and regimens, 27% exhibited stable disease, albeit of short duration as expected in this heavily-pretreated patient population.
- ✯ Among the 5 patients with HCC at the Phase II dosing regimen, two patients had prolonged stable disease of more than 9 cycles. A Phase II study of G-202 in patients with advanced HCC following progression on sorafenib is underway.