Clinical Activity of G-202, a Thapsigargin-Based Prostate Specific Membrane Antigen (PSMA)-Activated Prodrug in Patients with Progressive Hepatocellular Carcinoma (HCC)

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Overview

- Pre-clinical and early clinical development G-202
- Design of the current ongoing phase 2 study in advance HCC following sorafenib failures
- Clinical activity and safety of G-202 in advance HCC – combined phase 1b/2 results
INHIBITION OF SERCA PUMP BY THAPSIGARGIN

Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATP (SERCA) pump transfers Ca^{2+} from cytosol to the ER lumen.
Pro-drug concept

G-202 is a small molecule drug conjugate comprising:
- a cytotoxin, 12ADT, (equipotent derivative of thapsigargin)
- a targeting/masking peptide substrate
Prostate Specific Membrane Antigen (PSMA) Function and Expression

- Highly expressed in normal and malignant epithelial prostate cells.
- Positive expression in neo-vasculature of solid tumors

Functions both as a folate hydrolase and a N-acetylated alpha-linked acid dipeptidase (NAALADase)
To target this dual enzymatic activity, we identified PSMA-specific peptide that was coupled to the 12ADT analog to produce a PSMA pro-drug.
Phase I Clinical Trial of G-202

- One-hour iv infusion on Days 1, 2 and 3 of 28-day cycle
- 28 patients were treated at 8 dose levels (1.2 – 88 mg/m²)
- Protocol-defined MTD was not reached
- Infusion-related reactions and creatinine elevations at 88 mg/m² led to declaration of 66.8 mg/m² as MTD
  - A modified regimen to reduce infusion-related reactions of G-202 at 40 mg/m² on Day 1 and 66.8 mg/m² on Days 2 and 3 was selected for tumor specific expansion.

- A further 16 pts were enrolled in the expansion study including 5 with HCC
  - Prolonged disease stabilization in HCC (9-12 months) observed in 2 of 5 patients
  - One pt completed 12 cycles prior to progressing.
  - One pt completed 9 cycles, off study due to unrelated event – resumed on G-202
Single arm Phase II Study of G-202 in advance HCC after Progression on Sorafenib

Primary Efficacy Objective
• To evaluate time to progression (TTP)

Secondary Efficacy Objectives
• To evaluate tumor response rate
• To evaluate progression-free survival (PFS)
• To evaluate overall survival (OS)
• Pharmacodynamic markers
  - Change from baseline to Cycle 2 in tumor blood flow via DCE-MRI
  - Baseline tumor expression of PSMA & optional on treatment biopsy
Study design

Cohort 1
3-6 patients

40 mg/m² on Days 1, 2, 3
66.8 mg/m² on Days 2 and 3

• ECOG Performance Score of 0 or 1
• Histologically confirmed HCC
• Child-Pugh A or B7
• Disease progression on sorafenib
• Adequate liver and kidney function
  • Albumin ≥ 2.8 g/dL
  • AST and ALT ≤ 5 x ULN
  • Total bilirubin < 2 mg/dL
  • Creatinine ≤ 1.5 ULN

Cohort 2
3-6 patients

40 mg/m² on Day 1

Expansion Phase
Up to 23 pts

40 mg/m² on Days 1, 2, 3

Assumptions driving accrual targets:
• Historical median TTP of 2.1 months in 2nd line
  • Hypothesized median TTP of 4.2 months
  • Two-sided testing & significance level of 5%
• Study achieves target power of 80% with 17 evaluable patients
• Accrual target = 23 assuming that 25% of pts will not be evaluable or will be lost to follow-up
Interim clinical efficacy and safety results
## Patient Demographics

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hepatocellular carcinoma, progressed on sorafenib  (23, 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose and Schedule</strong></td>
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</tr>
<tr>
<td>40 mg/m² on Days 1, 2 and 3 of 28-day cycle</td>
<td>(16 pts)</td>
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<tr>
<td>40 mg/m² on Day 1, 66.8 mg/m² on Days 2 and 3 of 28-day cycle</td>
<td>(7 pts)</td>
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<tr>
<td><strong>Performance Status</strong></td>
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<tr>
<td>ECOG 0</td>
<td>(9 pts, 39%)</td>
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<td>ECOG 1</td>
<td>(14 pts, 61%)</td>
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<td><strong>Child-Pugh Score</strong></td>
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<td>A or B7</td>
<td>(23, 100%)</td>
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<tr>
<td><strong>Extra-Hepatic Disease</strong></td>
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<tr>
<td>No</td>
<td>(9 pts, 39%)</td>
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<tr>
<td>Yes</td>
<td>(13 pts, 56%)</td>
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<tr>
<td>NR</td>
<td>(1 pt, 4%)</td>
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<td><strong>Age</strong></td>
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<td>Mean 66 years (range 51 – 80)</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>(17 pts, 74%)</td>
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<tr>
<td>Female</td>
<td>(6 pts, 26%)</td>
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</tbody>
</table>
Safety Observations

G-202 Related AEs ≥ Grade 2 in at least 3 of 23 (13%) Treated Patients*

<table>
<thead>
<tr>
<th>Event</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>ALT increased</td>
<td>4 pts (17%)</td>
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<tr>
<td>bilirubin increased</td>
<td>4 pts (17%)</td>
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<tr>
<td>creatinine increased</td>
<td>5 pts (22%)</td>
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<tr>
<td>fatigue</td>
<td>5 pts (22%)</td>
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<tr>
<td>hyperglycemia</td>
<td>3 pts (13%)</td>
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<tr>
<td>hyperkalemia</td>
<td>4 pts (17%)</td>
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</tbody>
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* Current results; 3 patients continue on study and study is open to enrollment
Safety Observations

G-202 Related SAEs of any Grade*

<table>
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<th>Event</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>creatinine increased/acute renal failure</td>
<td>3 pts (13%)</td>
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<tr>
<td>congestive heart failure</td>
<td>1 pt (4%)</td>
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<tr>
<td>pyrexia</td>
<td>1 pt (4%)</td>
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* Current results; 4 patients continue on study and study is open to enrollment
# TIME ON TREATMENT: Evaluable Patients

## 28-Day Cycles

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<tr>
<th>Phase Ib</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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**Phase II**

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<th>12</th>
<th>(22 months – compassionate use)</th>
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**Patient continues treatment**
G-202 PHASE II RESULTS

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Total</th>
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<tbody>
<tr>
<td>Time To Progression (TTP) Primary Objective</td>
<td>Not Yet Evaluable</td>
</tr>
<tr>
<td>Stable Disease Rate Secondary Objective</td>
<td>69%</td>
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<tr>
<td>Stable Disease ≥4 mos.</td>
<td>44%</td>
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<tr>
<td>Stable Disease ≥6 mos.</td>
<td>25%</td>
</tr>
<tr>
<td>Stable Disease ≥12 mos.</td>
<td>0</td>
</tr>
<tr>
<td>Progression Free Survival Secondary Objective</td>
<td>Not Yet Evaluable</td>
</tr>
<tr>
<td>Overall Survival Secondary Objective</td>
<td>Not yet met</td>
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</tbody>
</table>
DCE-MRI – decrease vascular enhancement
Decrease in contrast agent transfer coefficient ($K_{\text{trans}}$)

Baseline

Post-Cycle 2
Conclusions

• G-202 administered iv for 3 consecutive days of a 28-day cycle is generally well-tolerated.

• G-202 as a single agent promotes disease stabilization (44% pts SD ≥ 4 months) in patients with advanced HCC who have progressed on sorafenib

• Studies to evaluate possible effects of G-202 on tumor vasculature and blood flow metrics are currently ongoing