Abstract

Background Mipsagargin (G-202) is a thapsigargin-based prodrug whose cytotoxic activity is blocked by a masking peptide that is cleaved by prostate-specific membrane antigen (PSMA), a membrane-bound protease expressed in prostate cancer cells and the endothelium of tumor vasculature but not in most other tissues or normal vasculature of normal tissue. In a Phase I study of mipsagargin, prolonged disease stabilization was achieved at the subset of patients with hepatocellular carcinoma (HCC) and prompted development of a Phase II study to further evaluate activity of mipsagargin in patients with HCC who progressed on sorafenib.

Methods Mipsagargin is administered by intravenous infusion on Days 1, 2, 3 and 3 of a 28-day cycle with prophylactic hydration and standard pretreatment medications. HCC is typically highly-vascularized and DCE-MRI is performed in consenting patients at baseline and on approximately Day 6 of Cycle 2 to evaluate possible effects of mipsagargin on blood flow metrics in hepatic lesions. DCE-MRI is a non-invasive method of investigating vascular structure and function and is sensitive to alterations in vascular permeability and blood flow. DCE-MRI measurements were made on a 1.5 Tesla MRI and the volume transfer coefficient, Ktrans, was calculated using the arterial input function derived from the signal in the abdominal aorta.

Results Among the 22 patients treated to date, mipsagargin-related SAEs in this patient population have been creatinine increase/acute renal failure/acute kidney injury (3 pts) and congestive heart failure (1 pt). While objective responses (CR, PR) have not been observed in these patients with advanced disease, the rate of disease stabilization has been remarkable, with >70% of patients exhibiting SD. In patients undergoing DCE-MRI, an average 56% decrease in Ktrans has been observed after administration of mipsagargin.

Conclusions Mipsagargin is generally well-tolerated and promotes disease stabilization in patients with advanced HCC who have progressed on sorafenib. Evidence of disease stabilization is observed, with a significant decrease in Ktrans suggesting mipsagargin reduces blood flow in hepatic lesions.

Introduction

• Mipsagargin (G-202) is a prodrug targeted to the cell-surface enzyme PSMA
  - Consists of a potent cytotoxic derivative of thapsigargin coupled to a PSMA substrate peptide
  - Removal of the peptide by PSMA liberates the active cytotoxicity
  - Represents first-in-class molecule for treatment of HCC

• PSMA is highly and selectively expressed in tumor associated neovasculature of HCC and other tumor types
  - A Phase I study of mipsagargin revealed prolonged disease stabilization in HCC patients, prompting the Phase II study.

Study Design

• Single arm, multi-center Phase II study with safety lead-in at a dose of 40 mg/m² on day 1-3 prior to RP20.
  - Patients with histologically-confirmed HCC who had progressed on or were intolerant of sorafenib were eligible
  - ECOC PS 0 or 1
  - Child-Pugh A and B7.
  - Patients received prophylactic intravenous hydration with saline and standard premedications on days of infusion
  - Response was assessed after two cycles of treatment using mRECIST for HCC in patients with enhancing lesions and/or RECIST in patients with documented HCC but without hepatic lesions.
  - DCE-MRI assessment of tumor blood flow was performed before and after treatment in consenting patients

• The primary objective was evaluation of time to progression
• Secondary endpoints were evaluation of response rate, progression-free survival and overall survival

Demographics

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Hepatocellular carcinoma, progressed on sorafenib (25, 100%)</th>
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<tbody>
<tr>
<td>Number of Cycles</td>
<td>(45 patients)</td>
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<tr>
<td>Evaluable for Response</td>
<td>20 patients (80%)</td>
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<tr>
<td>Best Response</td>
<td>CR + PR, 0 pts</td>
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<td>SD ≤ 5 cycles</td>
<td>7 pts (35%)</td>
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<tr>
<td>Time to Progression (TTP)</td>
<td>154 days (4.2 months; 95% CI: 55 - 216 days)</td>
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<td>Overall Survival (OS)</td>
<td>197 days (6.3 months; 95% CI: 137 - 211 days)</td>
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<tr>
<td>Progression-Free Survival (PFS)</td>
<td>110 days (3.7 months; 95% CI: 50 - 204 days)</td>
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Effects of Mipsagargin on HCC Blood Flow and Tumor Perfusion

- In consenting patients, DCE-MRI was performed at baseline and within 3 days of completing treatment in Cycle 2 to evaluate blood flow metrics.
- DCE-MRI scans were transferred to an external central imaging facility for analysis; measurements were made using arterial input function derived from signal in the abdominal aorta, using a standard Tofts model for Ktrans calculation.
- Top panels: Patient who had multifocal disease that included a previously-treated large lesion in the inferior right hepatic lobe. Directly inferior and lateral to the large treated lesion, a 6-cm rounded lesion with arterial phase hyper-enhancement and prompt washout on the baseline DCE-MRI exam was selected for analysis. The posterior portion of this lesion was incompletely included, but the anterior portion was well visualized and appropriate for evaluation of blood flow parameters.
- Bottom panels: Patient with gastrointestinal metastatic lymph node involvement (green arrows). Increased hyperenhancement after treatment (right panel) suggests response.

Conclusions

- Mipsagargin is a first-in-class PSMA-targeted prodrug
- Mipsagargin is a relatively well-tolerated drug in advanced HCC patients including those with CP-B status
- The TTP of 4.2 months is approximately twice that observed in prior studies with a placebo or an ineffective comparator arm1-3
- DCE-MRI assessment suggests mipsagargin decreased blood flow in HCC lesions and metastatic lymph nodes consistent with known expression of PSMA in tumor vasculature.
- A Phase III study to further characterize the activity of mipsagargin in advanced HCC is warranted.