Abstract 301

Activity of Mipsagargin (G-202), A Thapsigargin-Based Prostate-Specific Membrane Antigen-Activated Prodrug, In Patients With Progressive Hepatocellular Cancer

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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 observed in 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 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, K_{trans}, 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 K_{trans} 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 K_{trans} 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 cytotoxin
  - ➢ 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/m^2 on day 1-3 prior to RP2D.
- Patients with histologically-confirmed HCC who had progressed on or were intolerant of sorafenib
- ECOG 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 hepatic lesions 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
- Statistical analysis

Demographics

Indication	Hepatocellular carcinoma, progressed on sorafenib (25, 100%)
Dose and Schedule	40 mg/m^2 on Days 1, 2 and 3 of 28-day cycle (19 pts) 40 mg/m^2 on Day 1, 66.8 mg/m^2 on Days 2 and 3 of 28-day cycle (6 pts)
Performance Status	ECOG 0 (9 pts, 36%) ECOG 1 (16 pts, 64%)
Child-Pugh Score	A5 or A6 (17, 64%) B7 or B8 (8, 36%)
Extra-Hepatic Disease	No (6 pts, 24%) Yes (19 pts, 76%)
Age	Mean 65 years (range 52 - 74)
Gender	Male (18 pts, 72%) Female (7 pts, 28%)

Safety Observations

- Adverse events (AE) and serious adverse events (SAE) are summarized below.
  - ➢ A total of 264 AEs judged as related to mipsagargin administration were observed among the 25 patients; 61% of adverse events were Grade 1. Grade ≥ 2 mipsagargin-related adverse events occurring in at least 3 (12%) of patients are listed.
  - ➢ 5 patients experienced an SAE judged as related to mipsagargin. These SAEs are listed.

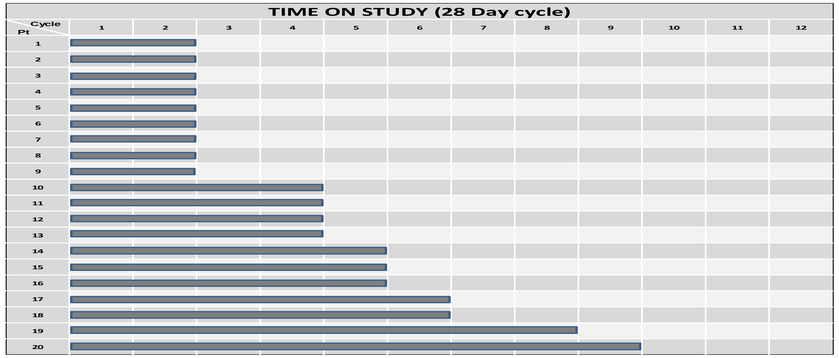
Most Frequently-Occurring Mipsagargin-Related AEs Grade ≥ 2	Number (%) of Patients
Creatinine increased	9 (36%)
Fatigue	7 (28%)
ALT increased	6 (24%)
AST increased	6 (24%)
Bilirubin increased	6 (24%)
LDH increased	5 (20%)
BUN increased	3 (12%)
Hyperkalemia	3 (12%)

All Mipsagargin-Related Serious Adverse Events	Number (%) of Patients	Mipsagargin Dose (Day 1 / Day 2 / Day 3)
Acute renal failure/acute kidney injury	3 (12%)	40/66.8/66.8
Congestive heart failure	1 (4%)	40/40/40
Chest pain	1 (4%)	40/40/40

Clinical Observations

Number of Cycles (n=25 patients)	84 total (average 3.4 per pt; range 1 - 9) 68 cycles at 40/40/40 16 cycles at 40/66.8/66.8
Evaluable for Response	20 patients (80%)
Best Response	CR + PR 0 pts SD 13 pts (65%)
SD ≥ 5 cycles	7 pts (35%)
Time to Progression (TTP)	125 days (4.2 months; 95% CI: 50 - 216 days)
Overall Survival (OS)	197 days (6.6 months; 95% CI: 137 - 211 days)*
Progression-Free Survival (PFS)	110 days (3.7 months; 95% CI: 50 - 204 days)

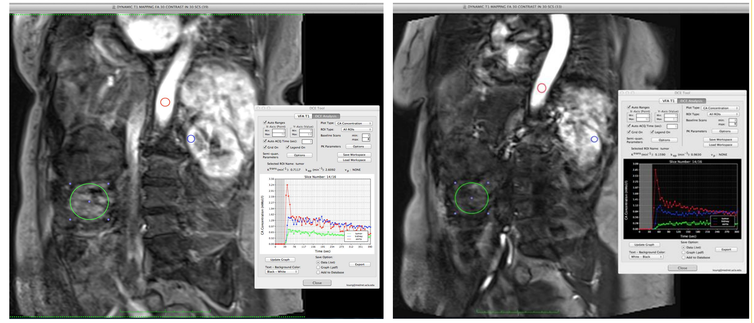
* 8 subjects censored



- While the sample size was small, encouraging observations of benefit were noted:
  - ➢ Several patients experienced transient improvement in performance status while on treatment, including reduced dependence on a wheelchair and reduced pain from metastatic bone lesions
  - ➢ Several patients withdrew from the study due to declining health status or withdrawal of consent in the absence of disease progression and/or with anecdotal evidence of benefit
  - ➢ Some patients were withdrawn due to evidence of a new asymptomatic lesion while target lesions remained stable

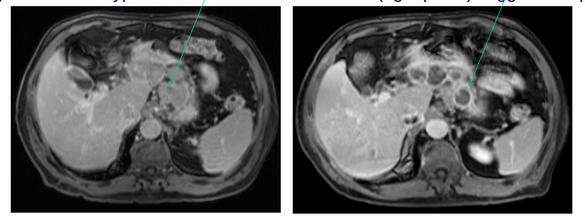
Effects of Mipsagargin on HCC Blood Flow and Tumor Perfusion

- 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 K_{trans} calculation
- Top panels: This patient 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 5-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.



Left: DCE-MRI on 28 Apr 2014; measured K_{trans} = 0.72-0.76 min^{-1}
Right: DCE-MRI on 02 Jun 2014; measured K_{trans} = 0.14-0.16 min^{-1}
Red: aorta; blue: kidney; green: tumor. Range reflects use of larger and smaller regions of interest (ROIs) within the lesion.

- Bottom panels: Patient with gastrohepatic metastatic lymph node involvement (green arrows). Increased hypoenhancement 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 arm[123]
- 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 II study to further characterize the activity of mipsagargin in advanced HCC is warranted.

[1] Finn RS et al. Phase II Open-Label Study of Brivanib as Second-Line Therapy in Patients with Advanced Hepatocellular Carcinoma. CCR 2012; 18: 2090 – 2098
[2] Yau T et al. Phase II Study of Bevacizumab and Erlotonib in the Treatment of Advanced Hepatocellular Patients with Sorafenib-Refractory Disease. Invest New Drugs; 2012; 30(6):2384-2390
[3] Llovet JM et al. Brivanib Versus Placebo in Patients With Advanced Hepatocellular Carcinoma (HCC) Who Failed or Were Intolerant to Sorafenib: Results From the Phase 3 BRISK-PS Study. ILC 2012, Abstract 1398.