A Phase 1b Trial of IPI-926 (Saridegib), a Hedgehog (Hh) Pathway Inhibitor, Plus Gemcitabine in Patients with Metastatic Pancreatic Cancer

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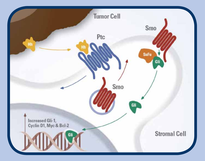
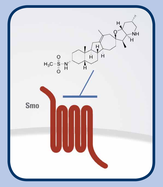
Background



- In Hh ligand-dependent tumors, such as pancreatic cancer, Hh ligand produced by tumor cells activates the Hh pathway in stromal cells in the tumor microenvironment by binding to Patched (Ptc). This mode of tumor-stroma paracrine signaling provides support for tumor growth and survival through mechanisms originating in the stromal cells.
- In pancreatic cancer models, inhibition of Hh signaling by saridegib within the tumor microenvironment depletes the desmoplastic stroma, increases the vascularity of the tumor, and renders the tumor more accessible to chemotherapy.
- Pancreatic cancer is a devastating diagnosis with median progression-free survival of ~ 3 months and median overall survival of ~ 6 months. The overall response rate to gemcitabine is 5 – 10%, underscoring the urgent need for new therapies for this disease. (Moore, et al. JCO 2007;25:1960-6. Seitz et al. Oncology 2004;18:43-7)
- Saridegib is a potent, orally delivered small molecule that is currently being investigated as an inhibitor of Smo in multiple Phase 2 trials in a variety of ligand-dependent cancers.



Study Design

Phase 1b Objectives

- Determine the safety, maximum tolerated dose (MTD), and recommended Phase 2 dose for saridegib + gemcitabine
  - Evaluate pharmacokinetics of saridegib, gemcitabine, and relevant metabolites

Study Design

- Phase 1b portion of a Phase 1b/2 study in which saridegib was dose-escalated with gemcitabine
- Cohorts of 3 or 6 patients were enrolled and administered saridegib orally, daily up to its single agent MTD (160 mg) plus gemcitabine (1000 mg/m²) given intravenously 3 weeks on, 1 week off
- Dose-limiting toxicities (DLTs) were determined during the first 28-day cycle

Patient Population

- Adults with pathologically confirmed diagnosis of metastatic pancreatic adenocarcinoma and at least 1 radiologically evaluable metastatic lesion (RECIST 1.1)
- ECOG Performance Score (0 or 1)
- No prior treatment with chemotherapy for pancreatic cancer and no known central nervous system metastases

Demographics & Disposition

Saridegib Dose Group	Patients Treated (N)
110 mg	3
130 mg	6
160 mg	7

- Demographics (N = 16)
  - 14 males, 2 females; mean age 69 years (range 58 - 86)
  - 15 White; 1 Black/African-American
- 1 patient currently on study (Cycle 17)
- Reasons for Discontinuation (N = 15)
  - Disease progression: 8 patients
  - Withdrawal of consent: 1 patient
  - Adverse events: 3 patients
  - Physician decision: 3 patients

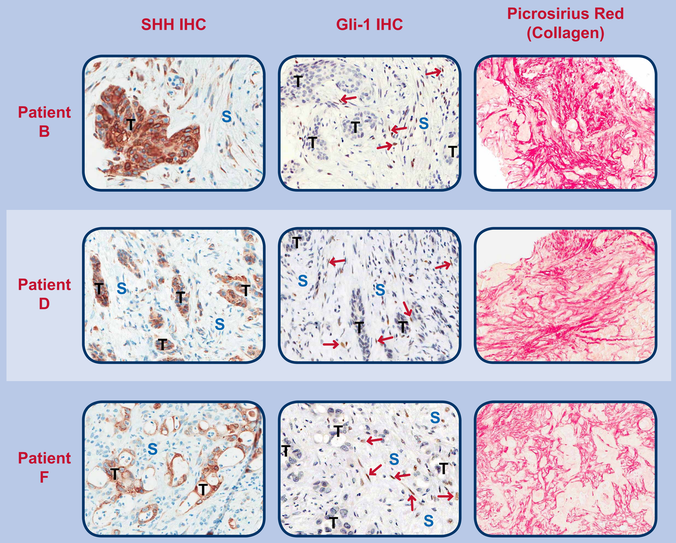
Safety

	110 mg (N = 3)	130 mg (N = 6)	160 mg (N = 7)	Total (N = 16)
Neutropenia, n (%)				
Grade 3	0 (0)	3 (50)	1 (14)	4 (25)
Grade 4	0 (0)	0 (0)	1 (14)	1 (6)
Thrombocytopenia, n (%)				
Grade 3	1 (33)	1 (17)	1 (14)	3 (19)
Grade 4	0 (0)	1 (17)	0 (0)	1 (6)
Anemia, n (%)				
Grade 3	1 (33)	0 (0)	1 (14)	2 (13)
Elevated Transaminases, n (%)				
Grade 3	0 (0)	1 (17)	1 (14)	2 (13)
Hyponatremia, n (%)				
Grade 3	0 (0)	0 (0)	2 (29)	2 (13)

Treatment-emergent adverse events (TEAEs) in ≥ 2 patients, regardless of relationship to either study drug

- The majority of TEAEs were Grade 1 or 2
- No deaths related to saridegib or gemcitabine
- One DLT (130 mg): Grade 3 asymptomatic AST increase that resolved after saridegib dose reduction
- Study Drug Reductions:
  - Gemcitabine: 11 (69%) patients (majority due to thrombocytopenia)
  - Saridegib: 2 (13%) patients due to elevated transaminases
- TEAEs observed were consistent with the known toxicity profiles of each drug
- Recommended Phase 2 regimen is saridegib (160 mg) given orally, daily plus gemcitabine (1000 mg/m²) given intravenously 3 weeks on, 1 week off

Evidence of Hh Signaling & Fibrosis in Metastases



Tumor (T), Stroma (S), Representative Gli-1 stromal staining (arrow)

Patient Sample Summary

Patient	Scoring:* Stromal Cilia by IF	Scoring:† Tumor SHH by IHC	Scoring:‡ Stromal Gli-1 by IHC	Scoring:† Fibrosis by Picrosirius Red
A	3	2	3	3
B	3	3	3	2
C	3	3	1	3
D	1	2	2	2
E	1	0	1	1
F	2	3	3	2
G	0	3	0	0

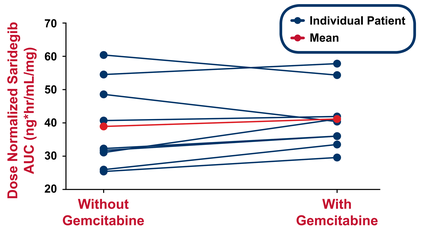
* Scoring: negative (0), scattered positive (1), more frequent positive (2), numerous positive (3)

† Scoring: negative (0), diffusely weakly positive (1), diffusely moderately positive (2), diffusely strongly positive (3)

‡ Scoring: negative (0), 1-5% nuclear positive (1), 5-20% nuclear positive (2), >20% nuclear positive (3)

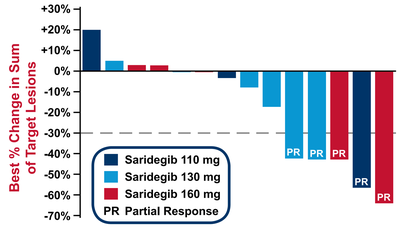
IF = immunofluorescence; IHC = immunohistochemistry; SHH = sonic hedgehog; Fibrosis determined by collagen staining with Picrosirius Red

Pharmacokinetics



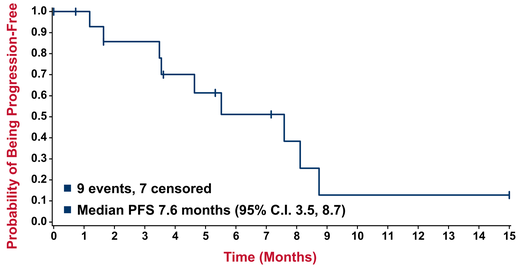
- Steady-state saridegib systemic exposure (AUC) is similar with and without concomitant administration of gemcitabine.

Best Shrinkage of Target Lesions on Study

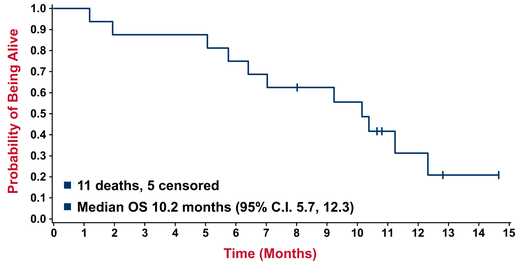


- 2 patients came off-study before their first on-study scan

Progression-Free Survival



Overall Survival



Conclusions

- Saridegib administered in combination with gemcitabine was well-tolerated at the recommended Phase 2 dose, without evidence of a drug-drug interaction.
  - The recommended Phase 2 regimen is saridegib (160 mg) given orally, daily plus gemcitabine (1000 mg/m²) given intravenously 3 weeks on, 1 week off.
- The activity observed in this Phase 1b study supports further development of saridegib in pancreatic cancer.
  - Evidence of Hh ligand-dependent signaling from tumor cells to stromal cells was identified.
  - Associated stromal fibrosis in metastatic lesions was identified, supporting the rationale for the study of saridegib in patients with metastatic lesions.
- The Phase 2 portion of this study, a randomized, placebo-controlled, double-blind study of gemcitabine with and without saridegib, is fully enrolled.

Poster presented at the American Society of Clinical Oncology (ASCO) 2012 Gastrointestinal Cancers Symposium, January 19-21, 2012, San Francisco, CA