Interim Open-Label Phase 1 Results of Misetionamide (GP-2250): A Small Molecule Antineoplastic That Inhibits Three Major Transcription Factors

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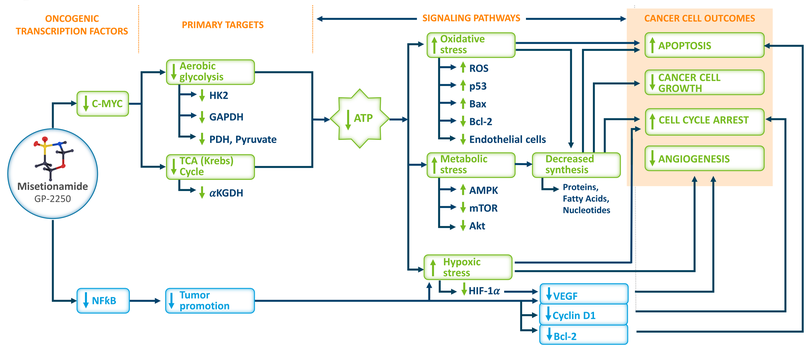
Poster Board: 467

BACKGROUND

- Pancreatic cancer is typically diagnosed at an advanced stage and has a poor prognosis,[1] with an estimated 5-year survival rate of 13%.[2]
- Misetionamide (GP-2250) is a novel, small-molecule, antineoplastic agent demonstrating antitumor activity in preclinical pancreatic cancer models either alone or in combination with gemcitabine.
- Misetionamide inhibits two major oncogenic transcription factors as well as an antiangiogenic transcription factor **(Figure 1)**[3,4]:
  - c-MYC inhibition selectively disrupts the energy metabolism of cancer cells, leading to cancer cell death.
  - NFκB inhibition disrupts cancer cells' ability to proliferate and survive.
  - HIF1α inhibition decreases VEGF production and new blood vessel development in tumors, especially under hypoxic conditions.
- In preclinical studies, misetionamide demonstrated[5–8]:
  - Dose-dependent inhibition of cell proliferation in multiple pancreatic cancer cell lines, including pancreatic neuroendocrine cell lines
  - Inhibition of tumor growth and reduction in tumor volume in patient-derived pancreatic xenograft models
  - Synergistic effect when used in combination with gemcitabine

Figure 1: Mechanism of Action of Misetionamide



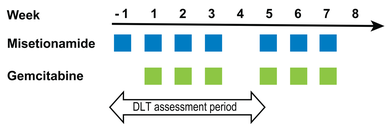
STUDY OBJECTIVES

- This open-label phase 1 trial (NCT03854110) evaluates the safety, tolerability, and preliminary efficacy of escalating doses of misetionamide in combination with gemcitabine as a second-line treatment in adults with advanced pancreatic adenocarcinoma that experienced disease progression with 5-FU–based chemotherapy.

METHODS

Study Population

STUDY SCHEMATIC



- **Misetionamide:** starting dose of 0.25 g escalating up to 21 g once weekly intravenously
- **Gemcitabine:** 1.0 g/m² on day 1, 8, 15 of a 28-day cycle

- Misetionamide dose escalation followed a BOIN design through dose level 5, which transitioned to a 3+3 design at dose level 6.
  - A 1-week run-in of single-agent misetionamide was followed by a full cycle (3 weeks on, 1 week off) of misetionamide plus gemcitabine treatment for each of the 11 dose cohorts. The DLT assessment period was 5 weeks at each dose.
  - Single-patient cohorts with 100% dose escalation between cohorts were enrolled until the first DLT (or cohort 4). Cohorts were then expanded to include 3 patients with 35%–45% dose escalation between cohorts.
  - Patients were treated until disease progression or development of unacceptable toxicity.

Key Inclusion Criteria		
Age ≥18 years old	Histologically or cytologically confirmed advanced unresectable or metastatic pancreatic adenocarcinoma and ≥1 RECIST-defined measurable tumor lesion	Documented disease progression while receiving or within 3 months of completing a 5-FU–containing treatment

RESULTS

Study Population

- To date, 52 patients have been enrolled through 11 dosing cohorts; of these, 49 have discontinued and 3 are ongoing.
  - Reasons for discontinuation included progressive disease (n=35, 71%), adverse event (n=8, 16%), withdrawal by patient (n=3, 6%), death (n=1, 2%), physician decision (n=1, 2%) and other (n=1, 2%).
    - None of the adverse events leading to discontinuation were considered possibly related to misetionamide.
- Patient demographics are shown in **Table 1.**

Table 1. Patient Demographics

	All patients (N=52)
Mean (standard deviation) age, years	62.8 (9.8)
Age category, n (%)	
<65 years	28 (53.8)
≥65 years	24 (46.2)
Sex, n (%)	
Male	33 (63.5)
Female	19 (36.5)
Race, n (%)	
White	47 (90.4)
Asian	2 (3.8)
American Indian/Alaska Native	1 (1.9)
Other	1 (1.9)
Not reported	1 (1.9)

Safety

- All patients experienced at least 1 TEAE, the majority of which were mild to moderate in severity and were not deemed related to misetionamide **(Table 2)**.
- Serious TEAEs were reported in 26 (50%) patients.
  - Of these, one serious case of grade 3 hepatic failure was considered possibly related to misetionamide.
- 5 dose-limiting toxicities were reported in 4 patients.
  - Of these, one report of grade 4 neutropenia and one report of grade 3 platelet count decrease were considered possibly related to misetionamide.
- 8 grade 3 TEAEs in 5 patients were possibly or definitely related to misetionamide.
  - One patient with hepatic failure, one patient with 2 events of platelet count decreased, one patient with neutrophil count decreased, one patient with hypokalemia, and one patient with neutropenia, neutrophil count decreased, and platelet count decreased.

Table 2: Summary of Adverse Events[a]

	All patients, n (%) (N=52)
Any TEAE	52 (100.0)
Any serious TEAE	26 (50.0)
Any TEAE with grade ≥3	38 (73.1)
Any TEAE related to misetionamide	20 (38.5)
Any TEAE with grade ≥3 and related to misetionamide[b]	5 (9.6)
Any serious TEAE related to misetionamide	1 (1.9)
Any TEAE leading to misetionamide dose reduction	0
Any TEAE leading to misetionamide dose interruption[c]	25 (48.1)
Any TEAE leading to study discontinuation	8 (15.4)
Any TEAE leading to death	3 (5.8)

[a] All AEs were categorized using NCI CTCAE version 5.0.
[b] Treatment-related TEAEs include TEAEs that were recorded as Relationship Possible or Definite.
[c] All misetionamide dose interruptions were secondary to required reductions in gemcitabine, as misetionamide was not administered alone.

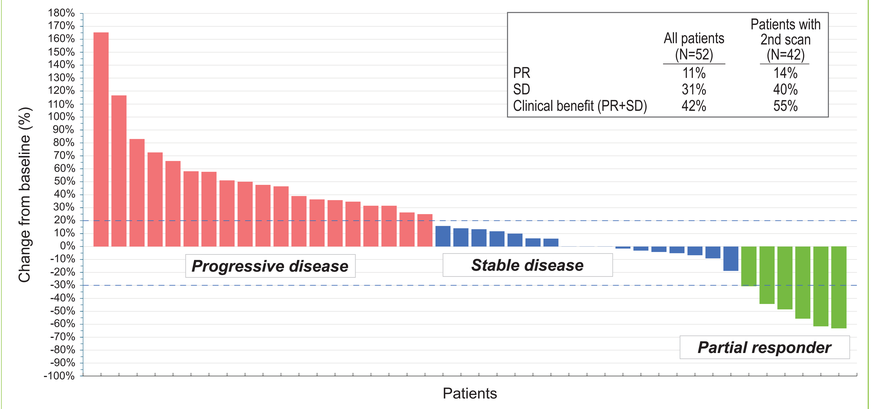
Pharmacokinetics

- While the blood half-life of misetionamide is ~5 hours, preclinical mTOR and AKT pharmacodynamic biomarker data indicate that the biological half-life is longer, at 4–5 days.
- These data are within the concentrations and times required for cytotoxicity in all cancer cell lines tested in vitro and/or in vivo with misetionamide.

Preliminary Efficacy

- Misetionamide and gemcitabine combination therapy resulted in a PR in 11% of patients (which increased to a 14% response rate in patients with a second scan), and SD in 31% of patients. The clinical benefit (SD+PR) was 42% **(Figure 2).**
  - Historically, second-line gemcitabine, following a first-line 5-FU regimen, results in a <11% PR rate.[9]
- Twelve patients (23%) had PFS of ≥16 weeks, or twice as long as historical gemcitabine treatment alone **(Figure 3)**.
- 7 patients (13%) had PFS of 24 weeks, and 4 (8%) had PFS of 32 weeks.
- One patient survived >2 years while receiving treatment.
- **Figure 4** shows a representative patient on misetionamide and gemcitabine combination therapy demonstrating a partial response with a 50%+ reduction from initial tumor size.

Figure 2: Patient's Best Percent Change From Baseline in Sum of Target Lesion Dimensions[a]



[a]Patient responses determined by RECIST criteria.

Figure 3: Encouraging PFS Results in Patients Even at Dose Levels Below Preclinical Testing

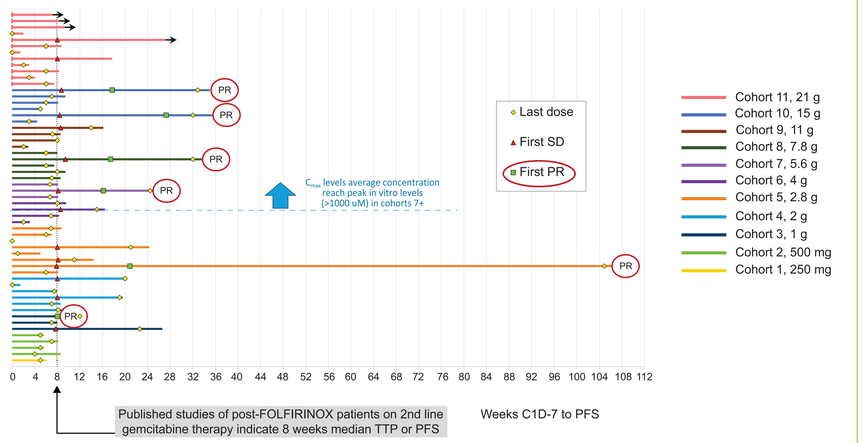
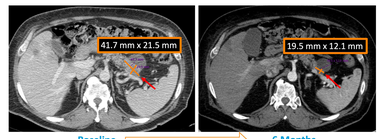


Figure 4: Example of a Partial Responder



CONCLUSIONS

- Misetionamide and gemcitabine combination therapy showed excellent safety and tolerability and encouraging PFS outcomes compared to a historical control of gemcitabine alone.
- These promising results in a historically difficult to treat pancreatic cancer population warrant progress to later-stage studies.

ABBREVIATIONS

αKGDH, alpha-ketoglutarate dehydrogenase; AE, adverse event; AMPK, adenosine 5'-monophosphate-activated protein kinase; Bax, bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; BOIN, Bayesian optimal interval; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; FU, fluorouracil; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HIF, hypoxia-inducible factor; HK2, hexokinase II; mTOR, mammalian target of rapamycin; NCI, National Cancer Institute; p53, tumor protein p53; PDH, pyruvate dehydrogenase; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; ROS, reactive oxygen species; SD, stable disease; TEAE, treatment-emergent adverse event; TTP, time to progression; VEGF, vascular endothelial growth factor.

CONFLICT OF INTEREST DISCLOSURES

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