

Pancreatic Cancer

abstr 0910

Phase II Study of Imatinib Mesylate and Gemcitabine for First-line Treatment of Metastatic Pancreatic Cancer

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Background: Gemcitabine (GEM) is the standard of care for pancreatic cancer. Unfortunately, median progression-free survival (PFS) is 2.2 months and overall survival (OS) is 5.65 months. Imatinib mesylate (IM) inhibits the Bcr-Abl tyrosine kinase and receptors for platelet-derived growth factor (PDGF) and c-kit. Preclinical data suggest that the pancreatic tumor microenvironment is PDGFR-rich; by inhibiting PDGFR, IM may decrease tumor interstitial fluid pressure and improve efficacy of chemotherapy. To evaluate the efficacy and toxicity of intermittently dosed IM in combination with low-dose GEM as first-line therapy in metastatic or recurrent pancreatic cancer, a phase II trial was developed based on results of a phase 1 study.

Methods: Patients with chemotherapy-naïve locally advanced or metastatic pancreatic cancer with at least one measurable lesion were eligible. Other eligibility criteria included no previous GEM or IM therapy, ECOG performance status ≤ 2 , adequate organ and bone marrow function, and signed informed consent. GEM is given at 1,200 mg/m²/120 minutes as an intravenous infusion on days 3 and 10. IM, 400 mg, is to be taken orally with a meal on days 1-5 and 8-12. No drugs are given on days 6, 7, or 13 through 21. Response is assessed according to RECIST after every 3 cycles (9 weeks) of therapy. All patients were evaluated by baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan and tumor markers (CEA/CA19-9). Planned sample size was 42 patients to have 80% power to detect a median PFS of 4 months at a 5% significance level vs. historical PFS of 2.2 months for single-agent GEM. The primary end point is PFS; secondary end points include response rate, toxicity, and OS.

International Society of Gastrointestinal Oncology
2009 Gastrointestinal Oncology Conference
October 1–3, 2009
ABSTRACTS

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Results: A total of 44 patients from seven centers were enrolled between October 2005 and July 2009. One patient withdrew consent prior to starting treatment, and one was determined after initiating treatment to have an ampullary cancer and is evaluable for toxicity but not response; therefore, two additional patients were enrolled. Interim safety analysis was conducted when 14 patients had received treatment and had been followed for 6 weeks. The median patient age is 62 years; ECOG performance status is 0 (n=12), 1 (n=28), 2 (n=2), and one not recorded; 5 patients had locally advanced disease, 37 had metastatic disease. At the time of this analysis, 41 patients are evaluable for response. There have been no objective partial or complete responses; 17 pts had stable disease, 16 had progressive disease while on treatment, and 9 came off treatment before response assessment. Eight patients still alive at the time of this analysis were censored. Five patients remained on treatment. Median OS is 5.9 months (95% CI 4.7, 8.5); median PFS is 3.9 months (95% CI 1.9, 5.1). The major grade 3/4 hematologic toxicities were neutropenia (58%), thrombocytopenia (17%), anemia (4%). The major grade 3/4 nonhematologic toxicities were dehydration (11%) and thrombus/embolism (15%). No treatment-related deaths occurred during the study.

Conclusions: In an ongoing trial, IM in combination with GEM is tolerated in patients with metastatic/recurrent pancreatic cancer and shows promise in increasing PFS over historical data for GEM alone.