Title: A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer.

Authors: Kindler HL, Richards DA, Garbo LE, et al.


Purpose: Pancreatic cancer is the fourth leading cause of cancer death in the United States. First-line therapy for metastatic disease consists of single-agent gemcitabine (Gemzar) or gemcitabine combinations. Slight improvement in overall survival (OS) has been noted with the addition of erlotinib (Tarceva) to gemcitabine with longer improvements in OS noted in patients with good performance status treated with the multidrug combination FOLFIRINOX (Adrucil, leucovorin, Camptosar, Eloxatin). Still, more effective therapy with novel agents is needed. The insulin-like growth factor-1 receptor (IGF1R) and its ligands, IGF-1 and IGF-2, are overexpressed in both normal and malignant pancreatic cells. Pharmacological blockade of IGF1R inhibits the growth and viability of pancreatic cancer cells, and tumor cells with KRAS mutations remain sensitive to IGF1R inhibition. Ganitumab is a fully humanized monoclonal antibody inhibitor of IGF1R that prevents the binding of IGF-1 and IGF-2 to IGF1R. In human pancreatic xenografts, ganitumab exhibited single-agent activity that was enhanced with the addition of gemcitabine. In a phase 1B study, the combination was associated with disease control (complete response + partial response + stable disease) in 80 percent of patients with advanced solid tumors. Pancreatic tumors also express higher levels of apoptosis ligand 2/tumor necrosis factor receptor–related apoptosis-inducing ligand (TRAIL), death receptor (DR) 4 and DR5 than does normal pancreatic tissue. Conatumumab is an investigational, fully humanized monoclonal antibody agonist of DR5 that induces apoptosis. Like ganitumab, it showed single-agent activity versus a pancreatic cancer xenograft model that was enhanced by the addition of gemcitabine.

Methods: Patients ≥ 18 years of age with a histologically or cytologically documented metastatic adenocarcinoma of the pancreas who had no previous therapy (chemo or radiation) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible to participate. Other eligibility criteria included adequate end-organ function and if the patient was diabetic, the condition had to be adequately controlled. Patients were randomized 1:1:1 to receive gemcitabine in combination with ganitumab, conatumumab or placebo. Gemcitabine was administered at a dose of 1,000 mg/m² intravenously on days one, eight and 15 of a 28-day cycle. Ganitumab, 12 mg/kg intravenously; conatumumab, 10 mg/kg intravenously; or placebo was administered by one-hour infusions that, if tolerated, could be...
subsequently reduced to 30 minutes. Both monoclonal antibodies were administered on an every-two-weeks basis, days one and 15. The primary end point of the study was six-month survival rate. Secondary end points included objective response rate (ORR) and safety.

**Results:** A total of 125 patients were randomized to receive ganitumab (n = 42), conatumumab (n = 41) and placebo (n = 42), and 40, 41 and 40 patients received the investigational products, respectively. The median number of cycles in the ganitumab group was four, the conatumumab group was four and the placebo group was two. The six-month survival rate was 57 percent (95 percent confidence interval [CI], 41-70 percent) in the ganitumab arm and 50 percent (95 percent CI, 33-64 percent) in the placebo arm. The 12-month survival rates were 39 percent (95 percent CI, 25-54 percent) and 23 percent (95 percent CI, 12-38 percent), respectively. The ORRs in the ganitumab, conatumumab and placebo arms were 10 percent, 3 percent and 3 percent, with all responses being partial responses. The most common grade ≥ 3 adverse events in the ganitumab, conatumumab and placebo arms, respectively, included neutropenia (18/22/13 percent), thrombocytopenia (15/17/8 percent), fatigue (13/12/5 percent), increased alanine aminotransferase (15/5/8 percent) and hyperglycemia (18/2/3 percent).

**Conclusion:** Ganitumab combined with gemcitabine had tolerable toxicity and showed a trend toward an improved six-month survival and overall survival. Additional investigation of this combination is warranted. Conatumumab and gemcitabine showed some evidence of activity as assessed by the six-month survival rate.

**Managed Care Implications:** New drug combinations are needed to treat patients with metastatic pancreatic cancer. Monoclonal antibodies such as ganitumab may offer patients a survival advantage when combined with gemcitabine.

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**Title:** A multicentre randomized phase II trial of gemcitabine alone vs. gemcitabine and S-1 combination therapy in advanced pancreatic cancer: GEMSAP study.

**Authors:** Nakai Y, Isayama H, Sasaki T, et al.


**Purpose:** Prognosis for patients with advanced pancreatic cancer remains poor. Single-agent gemcitabine (Gemzar) is superior to bolus 5-fluorouracil (5-FU; Adrucil) with response rates of 5 percent and a median overall survival (OS) of 5.7 months. This has led to combination therapy with only erlotinib (Tarceva) in combination with gemcitabine showing a statistically significant but clinically small improvement in OS. S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of 5-FU, and two biochemical modulators that has been shown to have activity as a single agent in patients with advanced pancreatic cancer comparable to that of gemcitabine. The combination of gemcitabine and S-1 is reportedly well tolerated and active in this patient population. This phase 2 study will compare gemcitabine alone vs. gemcitabine and S-1 in patients with advanced pancreatic cancer.

**Methods:** Eligibility for this multicenter, open-label, randomized trial included patients with unresectable locally advanced or metastatic pancreatic adenocarcinoma who had received no prior treatment (including surgery and/or radiation), had an ECOG performance status of 0-2, were at least 20 years of age, had a life expectancy of > 12 weeks and had adequate end-organ function. Patients were randomized 1:1 to receive either gemcitabine 1,000 mg/m² intravenously on days one, eight and 15 of a four-week cycle or gemcitabine 1,000 mg/m².
intravenously on days one and 15 and S-1 orally twice daily for two weeks followed by a two-week rest between each four-week cycle. Three doses of S-1 were established according to body surface area (BSA): BSA ≤ 1.25, 80 mg per day; BSA > 1.25 but ≤ 1.5, 100 mg per day; BSA ≥ 1.5, 120 mg per day. All therapy was administered until disease progression, unacceptable toxicity or withdrawal of consent. The primary end point of the study was progression-free survival (PFS) with secondary end points including OS, overall response rate (ORR) and safety.

Results: A total of 106 patients were randomized, 53 to each treatment arm. The baseline characteristics, age, performance status, extent of disease and CA 19.9 levels were well balanced. The ORR was 18.8 percent (95 percent CI, 10.6-31.4 percent) in the gemcitabine and S-1 arm compared to 9.4 percent (95 percent CI, 4.9-20.3 percent) in the gemcitabine arm (p = 0.265) with only one patient in the combination arm achieving a complete response. The median duration of response was 10.0 months in the gemcitabine plus S-1 group and 10.6 months in the gemcitabine arm. The disease control rate was 79.2 percent in the combination arm vs. 56.6 percent in those patients treated with gemcitabine alone (p = 0.021). The median PFS for the combined therapy was 5.4 months (95 percent CI, 3.7-9.4 months) vs. 3.6 months (95 percent CI, 2.0-5.1 months) in the monotherapy arm. PFS was significantly improved in the gemcitabine plus S-1 group with a hazard ratio of 0.64 (95 percent CI, 0.42-0.97 months; p = 0.036). The median OS was 13.5 months (95 percent CI, 7.8-16.3 months) in the combination arm vs. 8.8 months (95 percent CI, 7.0-10.6 months) in the monotherapy arm. The improvement in OS did not meet statistical significance with a p value of 0.104. The one-year survival rate was 52.8 percent in the gemcitabine and S-1 arm vs. 30.2 percent in the gemcitabine arm (p = 0.031). The incidence of grade 3 and 4 neutropenia was similar in both treatment arms, while nonhematologic adverse events, such as stomatitis, diarrhea and rash, were more commonly seen in those patients treated with gemcitabine and S-1.

Conclusion: Gemcitabine and S-1 combination therapy demonstrated a longer PFS in patients with advanced pancreatic cancer. An improved OS duration of 4.7 months was also noted with the combination but was not statistically significant.

Managed Care Implications: Combination therapy is superior to single-agent therapy in patients with advanced pancreatic cancer.

Identification of the most active combination(s) is still ongoing, but oral S-1 may play a role in future studies.

Title: Clinical and immunologic evaluation of dendritic cell-based immunotherapy in combination with gemcitabine and/or S-1 in patients with advanced pancreatic cancer.

Authors: Kimura Y, Tsukada J, Tomoda T, et al.


Purpose: Pancreatic cancer is the fifth leading cause of cancer deaths worldwide, with a five-year survival rate of only 5 percent. Since early-detection methods are under development and the disease is usually diagnosed in its advanced stage, surgical resection can only be performed on a small number of patients. Gemcitabine (Gemzar) has been established as the most active single chemotherapy agent, with moderate increases in survival seen in comparison to 5-fluorouracil (5-FU; Adrucil). Recent studies report
that S-1, an oral form of 5-FU, can improve the prognosis of patients with gemcitabine refractory disease as well as chemo-naive patients with pancreatic cancer. Since most patients treated with gemcitabine do not survive longer than six months and effective treatment options are limited, new treatment modalities are needed. Immunotherapy is potentially another option for patients with advanced pancreatic cancer. Dendritic cells (DCs) are antigen-presenting cells with the capacity to elicit a primary immune response. DCs can be pulsed with peptides derived from the known tumor-associated antigens, such as MUC1, to induce antigen-specific cytotoxic T lymphocytes that can kill tumors. Recent reports suggest that gemcitabine may enhance responses to specific vaccines or immunotherapy by inducing T-cell activation, resulting in proliferation of γ interferon production and proliferation of CD14+ monocytes. DCs were enhanced in patients treated with gemcitabine. Previous reports also suggest that 5-FU induces cytokines and natural killer cell activity in vivo and in vitro. Thus, the most effective treatment strategy may require a combined approach of immunotherapy and chemotherapy.

**Methods:** This retrospective study included 49 patients with advanced pancreatic cancer refractory to standard therapy who were treated with DC-based immunotherapy in combination with standard chemotherapeutic agents gemcitabine and/or S-1. Patients were treated with gemcitabine 800-1,000 mg/m² intravenously on days one, eight and 15, followed by a one-week rest period (three on, one off). S-1, 60-80 mg/m² orally, was administered for four weeks followed by a two-week rest period (four on, two off). Autologous DCs (1 x 10⁷) were administered intradermally every 14 days. Tolerable doses of 1 to 5 KE of OK-432, a streptococcal immunological adjuvant, were administered together with the DC vaccine. Lymphokine-activated killer (LAK) cells were simultaneously injected intravenously in 34 patients at 14-day intervals. Clinical responses were stratified according to RECIST criteria.

**Results:** Of the 49 patients receiving DC-based immunotherapy in combination with chemotherapy, there was a complete response rate (CR) of 4.1 percent, a partial response rate (PR) of 10.2 percent and a stable disease rate (SD) of 12.2 percent. Overall survival ranged from 57 to 975 days with a median survival of 360 days. Median survival time of stage IVB patients with metastatic disease was 250 days. Of the 34 patients who received LAK cells in addition to DCs, their CR rate was 5.9 percent, PR rate was 26.5 percent and SD rate was 14.7 percent. In the 15 patients not receiving LAK cells, their CR was 0 percent, PR was 13.3 percent and SD was 6.7 percent. The median survival time (MST) for patients receiving LAK cells was 396 days in comparison to 229 days in those patients not receiving LAK cells (p = 0.075). These data suggest that LAK cell therapy increases the anticancer effect of DC vaccination. Patients treated with DCs and gemcitabine alone experienced a MST of 360 days in comparison to 168 days in those patients treated with DCs and S-1. In the DCs, gemcitabine and S-1 treated patients, the MST was 508 days, which was not statistically significant when compared to the other two treatment groups. No patient experienced a grade 3 or 4 adverse event during the treatment period. The most common toxicities reported were leukocytopenia, anemia and nausea.

**Conclusion:** Dendritic cell vaccination–based immunotherapy combined with chemotherapy was shown to be safe and possibly effective in patients with advanced pancreatic cancer refractory to standard therapy.

**Managed Care Implications:** Vaccine therapy may play an important role in combination with chemotherapy in patients with advanced pancreatic cancer by enhancing the immune response. Additional studies in both chemo-refractory and chemo-naive patients with metastatic disease are ongoing.

**Title:** Gemcitabine plus erlotinib followed by capecitabine versus
capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomized phase 3 trial of the "Arbeitsgemeinschaft Interistische Onkologie" (AIO-PK0104).


Purpose: As of 2008, 165,100 new cases of pancreatic cancer were diagnosed worldwide with nearly the same number of deaths, 161,800, reported. Gemcitabine (Gemzar) has been regarded as the standard of care for over a decade, providing clinical benefit and a moderate improvement in survival for patients with advanced disease. Several randomized phase 3 trials have failed to show survival benefit for gemcitabine-based combination therapy; however, meta-analyses suggest a possible survival benefit for use of platinum analogues or fluoropyrimidines in combination with gemcitabine in selected patients with metastatic disease and good performance status. Based upon results from a randomized trial, the combination of gemcitabine and erlotinib (Tarceva), a novel anti-EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor, received U.S. regulatory approval for treatment of advanced pancreatic cancer. The observed survival advantage in this unselected patient population was statistically significant but clinically rather modest, 5.9 vs. 6.2 months (p = 0.038). Early clinical data support the investigation of erlotinib in combination with the oral fluoropyrimidine capecitabine (Xeloda). Another phase 2 study in gemcitabine-pretreated patients with advanced pancreatic cancer found the combination of capecitabine and erlotinib to be safe and feasible. However, no internationally accepted standard approach for salvage chemotherapy after failure of first-line gemcitabine has been established.

Methods: Adults between the ages of 18 and 75 with a histologically or cytologically confirmed diagnosis of treatment-naive (stage III or IV) pancreatic cancer with adequate end-organ function were eligible. Patients were also required to have a Karnofsky performance status of at least 60 percent. Patients were randomized 1:1 to receive gemcitabine, 1,000 mg/m² intravenously over 30 minutes weekly for seven weeks followed by a one-week rest, then every three or four weeks in combination with erlotinib 150 mg orally daily. In case of treatment failure, second-line therapy consisted of single-agent capecitabine 1,000 mg/m² orally twice a day for 14 days followed by a seven-day rest period. This was considered the reference arm. The experimental arm consisted of capecitabine and erlotinib followed by gemcitabine in those patients who progressed. The dosing was identical to the reference arm for all three drugs. Treatment in either arm continued until disease progression, unacceptable toxicity or withdrawal of patient consent. The primary end point of the study was time to treatment failure (TTF2) after second-line therapy. Secondary end points included overall survival and safety.

Results: A total of 281 patients were randomized with 274 eligible for the trial (Gem + E/Cap n = 143 and Cap + E/Gem n = 131). The groups were well balanced with regard to age, stage of disease and performance status. The median number of cycles administered was five in each group (range 0-26). Median TTF2 was estimated at 4.2
months in each arm (HR 1.00; 95 percent CI, 0.78-1.28 months; p = 1.0). The objective response rate (ORR) during first-line therapy was 16 percent for gemcitabine and erlotinib versus 5 percent for capecitabine and erlotinib with a corresponding disease control rate (complete response + partial response + stable disease) of 51 percent and 38 percent, respectively. The use of second-line chemotherapy showed a further objective disease control rate of 22 percent in those patients treated with capecitabine and 36 percent for those treated with gemcitabine. Time to treatment failure after first-line therapy (TTF1) was significantly prolonged in the gemcitabine/erlotinib arm (3.2 vs. 2.2 months), but this advantage did not translate into a difference in TTF2. The one-year overall survival rate was 22 percent in the gemcitabine/erlotinib arm followed by capecitabine and 23 percent in the capecitabine/erlotinib arm followed by gemcitabine. The median overall survival was 6.2 months with gemcitabine/erlotinib followed by gemcitabine and 6.9 months with capecitabine/erlotinib followed by gemcitabine (HR 1.02; p = 0.90). Hematologic toxicity was more common in the gemcitabine-containing arm whereas stomatitis and hand-foot syndrome occurred more often in the capecitabine/erlotinib arm. Skin rash was associated with both TTF2 (grade 0/1/2-4: 2.9/4.3/6.7 months, p < 0.0001) and survival (3.4/7.0/9.6 months, p < 0.0001). A KRAS wild type status (52/173 patients or 30 percent) was associated with an improved overall survival (HR 1.68; p = 0.005).

Conclusion: Both treatment strategies are feasible and demonstrate comparable efficacy. KRAS may serve as a biomarker in patients with advanced pancreatic cancer treated with erlotinib.

Managed Care Implications: New drug combinations show promise in patients with advanced pancreatic cancer. KRAS testing is important in determining appropriate therapy.

Title: Prospective randomized evaluation of traditional Chinese medicine combined with chemotherapy: a randomized phase II study of wild toad extract plus gemcitabine in patients with advanced pancreatic adenocarcinoma.

Authors: Meng Z, Garrett CR, Shen Y, et al.


Purpose: Traditional Chinese medicine is currently practiced worldwide and is frequently used to treat cancer, either alone or in combination with Western medicines. Huachansu is sterilized hot water extract of dried toad skin and is used for the treatment of liver, lung, pancreatic and colorectal cancers in China. Its two active chemical components are indole alkaloids and steroidal cardiac glycosides. Three of the major cardiac glycosides (bufalin, resibufogenin and cinobufagin) are responsible for the anticancer activity of huachansu. These effects include vasoconstriction, anti-inflammation, increased vascular resistance and inhibition of cancer proliferation. In vitro studies have shown inhibition of human heptocellular, gastric and colon cancer cell line proliferation. Additionally, huachansu has been shown to inhibit proliferation and induce apoptosis in gastric carcinoma cell lines. This activity was mediated through S-phase arrest and inhibition of bcl-2 expression as well as marked inhibition of the biosynthesis of DNA and RNA. Previous phase I dose-escalation trials have shown antitumor activity based on radiographic response. Tolerance was excellent and toxicity was not observed in the study. Due
to its wide use in China, its clearly defined mechanism of action, and preclinical and early clinical studies indicating efficacy and no previous study combining huachansu with conventional chemotherapy, this present study was undertaken.

**Methods:** Patients 18 years of age or older with a histological or cytological diagnosis of unresectable (locally advanced and/or metastatic) pancreatic carcinoma with measurable disease, a Karnofsky performance status of > 60 percent and a life expectancy of at least three months were eligible for enrollment. This randomized, phase 2, single-institution, single-blind study compared gemcitabine 1,000 mg/m² intravenously over 30 minutes on days one, eight and 15, with either huachansu 20 ml/m² intravenously over two hours daily for five days a week for three weeks followed by one week off or the same dose of gemcitabine and an intravenous saline (placebo) infusion with the same schedule as the huachansu. Cycles were repeated every 28 days. Assessment of response via roentgenogram, computed tomography or magnetic resonance imaging was performed approximately every eight weeks. Blood counts were assessed on a weekly basis. The primary objective was to compare the four-month progression-free survival (PFS) rates of the two treatment arms. Secondary end points included time to progression (TTP), overall response rate (ORR) and toxicity.

**Results:** A total of 80 patients were enrolled in the study, of which 76 received at least one cycle of therapy and were evaluable. Thirty-nine patients received combination therapy (Arm A) and 37 patients received gemcitabine and placebo (Arm B). A median of two cycles of therapy was administered in both arms of the study. The four-month PFS was 99 days in those patients receiving gemcitabine and huachansu and 98 days in those patients receiving gemcitabine and placebo (p = 0.679). Median overall survival was 160 days for Arm A and 156 days for Arm B (p = 0.339). The ORR was 9 percent and 3 percent in arms A and B (p = 0.332), respectively. There was also no statistically significant difference in TTP, 98 days for Arm A versus 115 days for Arm B (p = 0.825). The incidence of grade 3 and 4 toxicity in both groups was low and consisted of neutropenia, thrombocytopenia, nausea and vomiting.

**Conclusion:** Huachansu when combined with gemcitabine did not improve the outcome of patients with locally advanced and/or metastatic pancreatic cancer.

**Managed Care Implications:** The addition of traditional Chinese medicine to Western medicine will continue, particularly in the area of oncology. While this study was negative, other combinations may prove to be effective.
Chemotherapy regimens. Fluorouracil (5-FU; Adrucil)-based regimens have been the standard treatment for the disease with an objective response rate (ORR) of 0 to 7 percent. Gemcitabine (Gemzar) therapy has been reported to be superior to 5-FU and became the first-line treatment for the disease in 1997. Combination therapy with 5-FU and gemcitabine has been found to be tolerable, but no randomized studies have demonstrated the combination to be of greater benefit than gemcitabine monotherapy. Capecitabine (Xeloda) has shown activity for patients with metastatic pancreatic cancer in phase 2 clinical trials. Its oral administration and lack of overlapping toxicity make it an ideal agent to pair with gemcitabine. A recent phase 3 trial of gemcitabine/capecitabine vs. gemcitabine alone showed the combination to significantly improve the ORR (19.1 percent vs. 12.4 percent; \( p = 0.034 \)), progression-free survival (HR [hazard ratio] 0.78; 95 percent CI, 0.66-0.93; \( p = 0.004 \)) and a trend toward improved overall survival (HR 0.86; 95 percent CI, 0.72-1.02 months; \( p = 0.08 \)). The objective of this study was to evaluate the efficacy and safety of standard dose capecitabine and gemcitabine as first-line therapy for treatment of patients with advanced pancreatic cancer.

**Methods:** Patients with histologically confirmed unresectable locally advanced or metastatic adenocarcinoma of the pancreas who had not received prior chemotherapy or radiation were eligible. Additional eligibility criteria included ages 18-80, ECOG performance status 0-2, a life expectancy of > 3 months, a measurable lesion and adequate end-organ function. Patients received gemcitabine 1,000 mg/m² intravenously over 30 minutes on days one, eight and 15, and 1,660 mg/m² of capecitabine orally on days 1-21 every four weeks. Treatment continued until disease progression, development of severe toxicity or withdrawal of patient consent. Dose reductions due to toxicity were established. The primary end point of the study was response rate with the secondary end point being the toxicity associated with the regimen.

**Results:** A total of 50 patients were evaluable for response on an intention-to-treat basis. The median age was 53 years (range 39-76). Twenty-nine patients had metastatic lesions with the other 21 having unresectable locally advanced disease. The response rate was 48 percent (95 percent CI, 22.5-57.1 percent) with all responders having a partial response. An additional 20 patients (40 percent) had stable disease. The median time to progression was 6.5 months (95 percent CI, 2.3-8.7 months) and the one-year survival rate was 45 percent. The median overall survival was 11.5 months (95 percent CI, 8.68-14.0 months) for patients with stage III disease and 9.4 months (95 percent CI, 3.56-14.2 months) for those patients with stage IV disease. Grade 3-4 toxicities associated with the combination therapy included neutropenia (22 percent), thrombocytopenia (6 percent) and hand-foot syndrome (10 percent).

**Conclusion:** The combination of gemcitabine and capecitabine was well-tolerated and demonstrated promising efficacy in the treatment of advanced pancreatic cancer.

**Managed Care Implications:** While intravenous 5-FU has shown limited activity in the treatment of advanced pancreatic cancer, the administration of oral capecitabine daily for 21 days may lead to an increase in response
rate, particularly when combined with other active chemotherapeutic agents such as gemcitabine.

**Title:** A multi-institutional phase 2 study of imatinib mesylate and gemcitabine for first-line treatment of advanced pancreatic cancer.

**Authors:** Moss RA, Moore D, Mulcahy ME, et al.

**Reference:** Gastrointest Cancer Res. 2012;5:77-83.

**Purpose:** Pancreatic cancer carries a dismal prognosis and remains a significant cause of cancer morbidity and mortality. Gemcitabine (Gemzar) has replaced fluorouracil (5-FU; Adrucil) as the standard treatment for patients with the disease, showing a modest but statistically significant improvement in overall survival when the two drugs were compared. In multiple trials, single-agent gemcitabine has achieved a median overall survival of six months in patients with advanced-stage disease. New treatment strategies are needed. One strategy is for more effective therapy to improve the access of chemotherapy to the interior of the tumor. Inhibition of platelet-derived growth factor receptors (PDGFRs) may decrease tumor interstitial fluid pressure (IFP) and allow better penetration of gemcitabine. Imatinib mesylate (Gleevec) is an oral small molecule that inhibits PDGF, as well as the tyrosine kinases associated with BCR-ABL and c-kit. The rationale for using imatinib in anticancer therapy focuses on PDGFRs. PDGFRs are expressed on several tumor types, including pancreatic, are found in both tumor pericytes and tumor vasculature and are thought to play a role in the control of IFP. Several preclinical studies have demonstrated improved activity of cytotoxic chemotherapeutic agents, including gemcitabine, when combined with imatinib. Phase 1 trials using gemcitabine and imatinib in solid tumors have been reported. Due to significant toxicity with standard dosing, a schedule of imatinib 400 mg orally daily on days one to five and eight to 12 and gemcitabine at a fixed dose of 1,500 mg/m² was used. Partial responses were noted as was a striking degree of stabilization of disease (31 percent of patients at 12 weeks). Based on these promising results, this phase 2 study was undertaken.

**Methods:** Patients were required to have an ECOG performance status of 0 to 2, be at least 18 years of age and have measurable disease. Patients had to be deemed ineligible for curative resection and could not have had prior chemotherapy for metastatic disease, with the exception of patients with prior surgical resection and a history of adjuvant fluorouracil if at least six months had passed between the last dose of chemotherapy and the recurrence of the pancreatic cancer. Patients also needed to have adequate end-organ function. Therapy consisted of gemcitabine 1,200 mg/m²/120 minutes as an intravenous infusion on days three and 10. Imatinib, 400 mg orally, was given once a day with meals on days one to five and eight to 12. Cycles were repeated every 21 days. The primary endpoint of the study was progression-free survival (PFS). Secondary end points included overall response rate (ORR), toxicity, overall survival (OS) and one-year survival rate.

**Results:** A total of 42 patients were evaluable for response. The median number of cycles completed was three (range 0-17). One patient had a partial response, 16 had stable disease, 18 had progressive disease and seven were not assessed. The median PFS was 3.9 months (95 percent CI, 2.1-5.1 months). The median OS was 6.3 months (95 percent CI, 5.2-8.5 months) and the one-year survival rate was 26.5 percent (95 percent CI, 13.8-39.1 percent). Hematologic toxicity was significant, with 50 percent of patients having a grade 3 or higher neutropenia and 17 percent having a grade 3 or higher thrombocytopenia. This resulted in numerous dose reductions. Grade 3 or higher nonhematologic toxicity included dehydration (9 percent of patients), skin rash (9 percent) and fatigue (5 percent).

**Conclusion:** Imatinib in combination with gemcitabine is tolerated in locally advanced, metastatic or recurrent pancreatic cancer. However, the combination does not show a statistically significant improvement in PFS or OS when compared to single-agent gemcitabine.

**Managed Care Implications:** Drugs with unique mechanisms of action will be studied for the treatment of advanced pancreatic cancer. While this study was negative, imatinib may be used in other drug combinations in this particular patient population.