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A Single-Arm, Non-Randomized Phase II Trial of Neoadjuvant Gemcitabine and Oxaliplatin in patients with Resectable Pancreas Adenocarcinoma

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Abstract

Objective—The role for neoadjuvant systemic therapy in resectable pancreas adenocarcinoma remains undefined. We evaluated the efficacy of gemcitabine and oxaliplatin administered as preoperative therapy in patients with resectable pancreas adenocarcinoma.

Methods—Eligible patients were screened using CT pancreas angiography, laparoscopy, endoscopic ultrasound and fine needle aspiration cytology, to identify 38 patients who received four cycles of neoadjuvant gemcitabine 1000mg/m² IV over 100 minutes and oxaliplatin 80 mg/m² IV over 2 hours, every 2 weeks. Patients whose tumors remained resectable at re-staging proceeded to operation and subsequently received 5 cycles of adjuvant gemcitabine (1000 mg/m² IV over 30 minutes day 1, 8, 15 every 4 weeks). The primary endpoint was 18-month overall survival and secondary endpoints included radiologic, tumor marker and pathologic response to neoadjuvant therapy, time to recurrence, patterns of failure and feasibility of obtaining pre-operative core biopsies.

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Results—Thirty-five of 38 (92%) patients completed neoadjuvant therapy. Twenty-seven patients underwent tumor resection (resectability rate 71%) of which 26 initiated adjuvant therapy for a total of 23 patients (60.5%) who completed all planned therapy. The 18-month survival was 63% (24 patients alive). The median overall survival for all 38 patients was 27.2 months (95% CI 17- NA) and the median disease-specific survival was 30.6 months (95% CI 19 - NA).

Conclusion—This study met its endpoint and provided a signal suggesting that exploration of neoadjuvant systemic therapy is worthy of further investigation in resectable pancreas adenocarcinoma. Improved patient selection and more active systemic regimens are key.

NCT00536874.

Introduction

Pancreatic adenocarcinoma is characterized by having a 5-year survival rate of less than 6%¹ due to late clinical manifestation and the systemic nature of the disease at presentation. Estimated 5-year survival rates following resection are between 15–20%². Resection alone is inadequate for cure, and, traditionally, systemic therapy and/or combined chemotherapy and radiation have been added to surgical treatment³. These latter modalities are typically administered in the post-operative adjuvant setting. Multiple studies have shown that adjuvant therapy improves overall survival,⁴⁻⁶ but up to 25% of patients cannot receive this treatment due to surgical morbidity.^{7, 8} Moreover, recent data suggest that in certain settings less than half of resected pancreatic cancer patients receive any form of adjuvant therapy.⁹

Neoadjuvant treatment offers several theoretical advantages over an initial resection and adjuvant therapy paradigm, including early delivery of systemic therapy for all patients, a higher negative margin resection rate (when radiation is included) and enhanced patient selection for surgery, collectively leading to potentially improved survival.¹⁰⁻¹² Conversely, neoadjuvant treatment carries the risk of disease progression during therapy because of unfavorable tumor biology and/or an ineffective treatment.¹⁰ A review of select trials for patients with localized pancreas cancer has suggested a benefit to neoadjuvant therapy by showing an increased median survival time^{12, 13} and potentially higher resectability rates^{14, 15} with neoadjuvant treatment.

However, neoadjuvant regimens for patients with resectable pancreatic cancer have been investigated in a few limited studies and have mostly examined combined chemoradiotherapy with/without systemic therapy and not systemic therapy alone.¹⁶⁻¹⁸ A single small phase II prospective trial evaluating neoadjuvant gemcitabine and cisplatin for resectable adenocarcinoma of pancreatic head origin demonstrated feasibility, tolerability and favorable overall and disease-free survival.¹⁹ Another neoadjuvant prospective phase II trial demonstrated significant metabolic and histological tumor response with a neoadjuvant gemcitabine and cisplatin regimen and feasibility of surgery after this treatment.²⁰

The phase II trial reported herein explores the efficacy of neoadjuvant therapy with gemcitabine and oxaliplatin in patients with radiographically resectable pancreatic adenocarcinoma. The rationale for this systemic regimen was based in part on a phase III trial that compared gemcitabine and oxaliplatin therapy to gemcitabine in treatment of advanced pancreatic cancer.²¹ This study reported that the combination was significantly

superior to gemcitabine alone in terms of tumor response (26.8% vs. 17.3%, $p=0.04$), progression-free survival (5.8 vs. 3.7 months, $p=0.04$) and clinical benefit (38.2% vs. 26.9%, $p=0.03$) and had a non-statistically significant trend to benefit in median overall survival (9.0 and 7.1 months, $p=0.13$).²¹ Additionally, pooled and meta-analysis data of combination platinum-based therapies in metastatic pancreatic cancer report improved outcomes compared to gemcitabine alone in patients with good functional status.⁷ Thus, we undertook an investigator-initiated, non-randomized, single-arm, phase II study of gemcitabine and oxaliplatin in patients with radiographically resectable pancreas adenocarcinoma.

Patients and Methods

Patient Population

Patients aged ≥ 18 years old with radiographically resectable pancreas cancer at Memorial Sloan-Kettering Cancer Center (MSKCC) were eligible. Pathologic confirmation of diagnosis by aspiration or biopsy was necessary prior to initiation of treatment but not mandated at time of enrollment. Radiographically resectable disease was defined as the following: no distant metastases; a clear fat plane around celiac and superior mesenteric arteries and a patent superior mesenteric vein and portal vein without primary tumor involvement; no encasement of the superior mesenteric vein or portal vein involvement; no encasement of the superior mesenteric artery or hepatic artery; no extra-regional nodal disease. All patients were discussed at a multidisciplinary conference with final eligibility adjudication determined by surgical investigators (PA, WJ), medical oncology (EO'R) and study radiologist (CW). Additional key inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, measurable disease by Response Evaluation Criteria in Solid tumors (RECIST 1.0); no major organ dysfunction; ANC $\geq 1,500$ cells/mm³; platelets $\geq 100,000$ cells/mm³; bilirubin ≤ 4.0 prior to initiation of therapy; serum creatinine ≤ 1.6 mg/dL; INR ≤ 1.5 , unless on therapeutic anticoagulation; no prior history of chemotherapy or radiation for pancreas cancer. Women of childbearing potential had to have a negative pregnancy test and men and women of childbearing potential had to be willing to consent to using effective contraception while on treatment and for at least three months thereafter.

Patients with histopathology other than adenocarcinoma as well as patients with borderline resectable or locally advanced pancreas adenocarcinoma were ineligible. Other exclusion criteria included a history of prior non-cutaneous malignancy within three years of entry; history of hypersensitivity to chemotherapy agents or hypersensitivity to computerized tomography (CT) intravenous contrast dye, not suitable for pre-medication; presence of active infection except resolving cholangitis and presence of peripheral neuropathy grade 2.

Trial Design and Treatment

The study design was of a single-institution, open-label, non-randomized phase II trial of neoadjuvant therapy with gemcitabine and oxaliplatin in patients with radiographically resectable pancreatic adenocarcinoma. The primary endpoint was 18-month overall survival.

Secondary endpoints included RECIST response to neoadjuvant therapy, tumor marker response and safety of neoadjuvant therapy, recurrence-free survival, failure patterns (first and all), disease-specific and overall survival. Exploratory correlative endpoints included assessment of pathologic response to neoadjuvant therapy and feasibility of obtaining endoscopic or laparoscopic core needle biopsies.

Potentially eligible patients were staged with a pancreas protocol CT including chest and pelvis at MSKCC followed by a staging laparoscopy to evaluate for sub-radiologic distant metastasis as well as to obtain laparoscopic core biopsies of the pancreas when feasible, for diagnostic and research purposes; Endoscopic ultrasonography (EUS) and fine needle aspiration (FNA) cytology were performed when not previously obtained. Endoscopic retrograde cholangiopancreatography (ERCP) was performed as clinically indicated for placement of a biliary stent (metal recommended) for palliation of obstructive jaundice. Neoadjuvant protocol therapy involved four cycles of gemcitabine dosed at $1000\text{mg}/\text{m}^2$ IV over 100 minutes and oxaliplatin $80\text{ mg}/\text{m}^2$ IV over 2 hours, with both drugs cycled every 2 weeks for 4 cycles. Oxaliplatin was supplied by Sanofi-Aventis.

After completion of neoadjuvant chemotherapy, all patients underwent a re-staging pancreas protocol CT at MSKCC. All patients eligible for pancreatic resection proceeded to surgery at MSKCC that was to be performed 2 weeks but no later than 6 weeks after the completion of neoadjuvant chemotherapy. A staging laparoscopy was conducted at the same operative procedure of definitive resection to re-confirm the absence of distant metastatic disease. Patients in whom distant metastasis was identified, or who were deemed to have locally advanced disease, were taken off the study, and further treatment was as recommended by the treating physicians. All patients who underwent either an R0/R1 surgical resection received five cycles of adjuvant gemcitabine ($1000\text{mg}/\text{m}^2$ day 1, 8, 15, every 4 weeks) for 15 doses. Adjuvant chemoradiotherapy was not planned in this trial; however, it was selectively considered for patients who had an R1 resection. Following completion of therapy all patients were followed every 4 months for years 1 and 2, then every 6 months for years 3-5 and annually thereafter with tumor markers and a CT chest/abdomen/pelvis with oral and IV contrast or MRI imaging of the abdomen and a non-contrast CT of the chest.

All patients provided written informed consent prior to enrollment. The MSKCC Institutional Review and Privacy Board reviewed this study. Clinical trials identification NCT00536874.

Biostatistical Plan

The primary study endpoint was 18-month overall survival (OS). The historical 18-month survival of patients resected at MSKCC between 1998 and 2003 who underwent laparoscopy and a pancreas protocol CT at MSKCC prior to resection, was 53%. Enrollment of 37 patients would allow differentiation of an 18-month overall survival (OS) of 53% and 73% with type I and II error rates of 10% each using a single-stage binomial design. The regimen was to be considered active if 24 patients were alive at 18 months. Patients were eligible for analysis of the primary endpoint if they received any dose of protocol specified therapy, even if unable to complete neoadjuvant therapy or subsequent surgery. Secondary

endpoints included RECIST 1.0 response and tumor marker response to neoadjuvant therapy, recurrence-free survival after surgery, failure patterns (first and all), safety (NCI CTCAE v3), and overall survival. Overall survival was defined as time from signing protocol consent to death and was estimated using Kaplan-Meier methodology and Greenwood's formula was used to calculate the standard error of the Kaplan-Meier estimate and 95% confidence interval. For patients that underwent resection, recurrence-free survival was defined as time from surgical resection to time of first recurrence, either local, distant or both, or death, whichever occurred first. Recurrence was defined as when definitive evidence of recurrence was present, i.e., mass and or biopsy confirmation and not on the basis of Ca 19-9 rise in isolation. Disease-specific survival was defined as time of signing protocol consent to death with patients censored if they died of another cause. The contribution of surgery to outcome was evaluating by comparing overall survival between the resected and unresected patients using the date of determination of nonresectability for the unresected patients as the reference date and by excluding patients that died early and thus were ineligible for resection.

Correlative objectives included feasibility of obtaining pre-operative core tissue samples by either laparoscopic or EUS-based approaches. Feasibility was achieved if 60% of patients had core samples obtained, and if 75% of samples were adequate for assessment. Pathologic response to treatment was determined based on the amount of residual viable carcinoma in relation to areas of fibrosis and fibro-inflammation in the gross lesion²². A 100% treatment response represented either fibrosis or fibro-inflammation within an entire gross lesion without microscopic evidence of carcinoma; a 0% response represented an entirely viable tumor in the absence of fibrosis/ fibro-inflammation.

Results

This trial enrolled 49 patients from July 2007 to December 2011. Eleven were excluded: six had metastases at staging laparoscopy; two had autoimmune pancreatitis; one patient withdrew consent and for two patients, a diagnosis of malignancy could not be confirmed. Thirty-eight patients received protocol specified therapy. The median age was 73 years, 23 (61%) were male, 24 (63%) had an ECOG PS of 1 and 31 (81.5%) had the primary tumor located in the head of the pancreas. Patient flow for the study is illustrated in Figure 1 and demographic information is summarized in Table 1. The data analysis cut-off point was 12/31/12.

Neoadjuvant therapy, Safety and Radiological Response

Of 38 patients who initiated neoadjuvant therapy, 35 (92%) completed all 4 cycles of treatment. Preoperative therapy was mostly well tolerated (Table 2). One patient (2.6%) experienced a grade 3 hypersensitivity reaction to oxaliplatin with the second dose, and was not re-challenged with oxaliplatin. There were three unexpected fatalities during preoperative therapy (7.9%). Two patients with a history of underlying heart disease had grade 5 cardiac events, myocardial infarction and a fatal arrhythmia. Both were deemed unrelated to therapy. One additional patient had a cerebrovascular accident after the second dose of therapy and was removed from the study and died shortly thereafter. One patient

experienced a grade 3 hemorrhage from the primary tumor site due to erosion into the duodenum after the second cycle of therapy and proceeded to surgery early.

Response to Preoperative Therapy: Radiologic and Tumor Marker

A low objective radiologic response rate was observed with four (10.5%) partial responses and the majority of patients having stable disease (28, 73.7%). Three patients (7.9%) had progression of disease. Minor changes in CEA and Ca 19-9 were observed. Data are summarized in Table 3.

Surgical and Pathological Outcomes

Following pre-operative therapy, 35 patients were surgical candidates and proceeded to operation of whom 27 (77%) underwent an R0/R1 resection. Eight of 35 (23%) were found to have unresectable disease at the time of operation (3 metastases; 5 locally unresectable). Twenty-six patients (96%) had adenocarcinoma. The median resected tumor size was 2.8 cm, 9 (33.5%) had negative lymph nodes and 20 (74%) underwent an R0 resection. The majority, 18 (66.5%) had AJCC stage IIB disease. These data are summarized in Table 4 and surgical morbidity is summarized in Supplemental Table 1s.

Adjuvant therapy

Of 27 who underwent tumor resection, 26 (96%) proceeded to adjuvant therapy. One patient with adenosquamous cancer had new liver metastases on baseline postoperative CT scan. Twenty-three patients (60.5%) completed all protocol-specified therapy. Three (11%) patients developed metastatic disease during adjuvant therapy. Adjuvant therapy was generally well-tolerated with no unexpected toxicity. Three patients (11%) received adjuvant chemoradiation following protocol therapy in view of an R1 resection. Data are summarized in Supplemental Table 2s.

Survival, Recurrence Outcomes and Patterns of Failure

The median follow-up time is 39.6 months, range 12.3- 57.7 months. For the primary study endpoint of 18-month OS, 24 patients are alive (Kaplan-Meier estimate of 63% with 95% CI 45- 76%). One patient is completing therapy at 12 months from diagnosis. For all 38 patients the median OS is 27.2 months, 95% CI 17 – NA (Figure 2). The median disease-specific survival was 30.6 months (95% CI 19 months – NA) with four patients censored; Figure 2s. For the 27 who underwent surgery, the median recurrence-free survival after surgery was 22 months, 95% CI 11- 27 (Supplemental Figure 1s). For the 27 resected patients, five are alive without recurrence, 19 have recurred with metastases as the first site of recurrence (liver 7, peritoneum 6, nodes 3, lung 3), and one patient had recurrence at both local and systemic sites concurrently and one patient had a lung only site of first failure. One patient developed a 2nd pancreas primary (T3, N0) and underwent a completion pancreatectomy and remains free of recurrence from both pancreas primaries. One patient died of unrelated causes following hip surgery complications.

Of 11 unresected patients, 3 experienced early death and 8 died of pancreatic cancer with an overall survival range of 5-32 months. Two of these eight, who experienced local progression during pre-operative therapy, subsequently received chemoradiation and

subsequently underwent surgery, both recurred and died at 13 and 20 months following surgery.

Patients who underwent resection had a significantly improved overall survival compared to those that did not, p -value = 0.0006. Supplemental Figure 3s.

Correlative Endpoints

A key exploratory endpoint was to evaluate the feasibility of obtaining preoperative core tissue samples at either laparoscopy or EUS for the purpose of xenograft implantation and comparison of pre-operative to postoperative specimens with regard to pathologic tumor response. Five pre-operative cores were obtained, all from body/tail primary tumors by either laparoscopic biopsy (3) and endoscopic biopsy (2). Xenograft implantation was successful in one sample. Feasibility was not demonstrated. Operative specimens were banked in 27 patients for future study.

In view of the inability to obtain pre-treatment core biopsies in the majority of patients, pathologic response was determined by evaluation of the operative specimen. Modest pathologic treatment effect was evident (Table 4).

Pre and post neoadjuvant sera were obtained from all patients for multi-analyte protein expression profiling and will be reported separately.

Discussion

Despite strong theoretical rationale the role of neoadjuvant therapy in resectable pancreatic cancer remains undefined.^{23, 24} Although the potential benefits of neoadjuvant therapy are supported by some studies^{12-15, 25}, there is no current consensus on whether it should be a standard option for patients with resectable pancreas adenocarcinoma²⁶⁻²⁸. There are many limitations in the published literature pertaining to neoadjuvant therapy. First, most are single-institution experiences and very few studies report data for resectable pancreas cancer with systemic therapy alone. Secondly, many studies have not clearly defined the patient population under study and thirdly the relative contribution of systemic therapy versus chemoradiation versus both modalities has not been defined. Selected single institution experiences, e.g., a 2008 MD Anderson phase II study²⁹ has shown that preoperative combined chemo-radiotherapy using gemcitabine was associated with favorable survival duration for patients who were able to complete all planned therapy; it remains unclear whether this reflects treatment impact or patient selection. Data from a recent large pooled and meta-analysis review in 2010²⁶ does not suggest a significant advantage of neoadjuvant therapy with respect to resectability and survival rates when compared to upfront surgical resection and adjuvant therapy in treatment of resectable pancreatic cancer; however, improved survival was associated with preoperative therapy for patients initially regarded as locally advanced and/or unresectable.²⁶

Our phase II trial explored the efficacy of neoadjuvant therapy with gemcitabine and oxaliplatin in patients with resectable pancreatic adenocarcinoma. Our study met its primary endpoint and provided a signal with a median overall survival of 27.2 months in the face of

a median age of study participants of 73 years in contrast to usual pancreas trials typically reporting a median age in the low 60's. With respect to secondary endpoints, there was a low RECIST, tumor marker and pathologic response to gemcitabine and oxaliplatin. These observations are explained by the relatively modest cytotoxic activity of gemcitabine and oxaliplatin. Arguably more active combinations such as FOLFIRINOX³⁰ or gemcitabine and albumin-bound-paclitaxel³¹ may increase the number of objective responses to preoperative therapy. Nonetheless response evaluation can be challenging and, in part, the visible mass may contain components of inflammation and desmoplastic stroma and RECIST criteria may over/underestimate response³². A correlative objective was to obtain sufficient pre-therapy tissue at either EUS evaluation or laparoscopy for the creation of human xenografts and for comparison to the resected specimen. This proved to be particularly challenging with success obtained in a limited number of patients and only in those with body or tail tumors with the retrieval of very small core biopsies. Recent advances in endoscopic tools may permit larger micro-core biopsies to be obtained from head tumors, which will hopefully offer enhanced opportunities for obtaining pre-treatment tissue in sufficient quantity to permit more than just diagnostic evaluation.

A prospective randomized controlled trial is the most effective way to compare the benefits of a neoadjuvant strategy versus upfront surgery followed by adjuvant approach, recognizing that there are many challenges to undertaking such a trial.²³ It is also plausible that some of the observed outcome improvement over reported experience from recent adjuvant phase III trials results (ESPAC-3, CONKO-001, RTOG 97-04, JASPAC-01)^{4, 33-35} reflects high quality multidisciplinary care. Learning points from the study were the requirement of timely collaboration to facilitate expeditious diagnostic work-up with the goal of having patients commence neoadjuvant therapy within 2-3 weeks of their entry point to the system along with improved patient selection.

In summary, our phase II trial demonstrated that neoadjuvant gemcitabine and oxaliplatin was active and provided an interesting survival signal. Institutionally, we are committed to developing further neoadjuvant therapy as a research direction in resectable pancreas cancer building on the observations from this trial in the context of more active regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Patient disposition (N= 49)

Figure 2.
Kaplan-Meier Overall Survival (N= 38)
Median follow-up time: 39.6 months (range 12.3- 57.7 months).
Median overall survival: 27.2 months, 95% CI 17- NA.

Table 1

Baseline Patient Demographics (N= 38)

Characteristic	No. (Percentage)
Gender	
Male	23 (61%)
Female	15 (39%)
Race	
Black/African-American	2 (5%)
White	32 (84.5%)
Hispanic	4 (10.5%)
Median Age	
Years (range)	73 (42-91)
ECOG Performance Status	
ECOG 0	14 (37%)
ECOG 1	24 (63%)
Primary Tumor Location	
Head/Neck	31 (81.5%)
Body	3 (8%)
Tail	4 (10.5%)
Histology	
Adenocarcinoma	38 (100%)

Table 2

Safety: Neoadjuvant Therapy with Gemcitabine and Oxaliplatin (N= 38)

Toxicity	Grade 2	Grade 3	Grade 4	Grade 5
I. Hematologic Toxicity				
Anemia	11 (29%)	4 (11%)		
Neutropenia	1 (2%)	2 (5%)		
Leukopenia	4 (11%)	2 (5%)		
Coagulopathy (PT/PTT/INR)		1 (2%)		
Platelets	2 (5%)			
AST/ALT	25 (66%)	16 (42%)		
Hyperbilirubinemia	15 (39%)	5 (13%)		
Alkaline phosphatase	10 (26%)	6 (16%)		
Hypoalbuminemia	11 (29%)			
Electrolyte abnormalities ¹	8 (21%)	8 (21%)		
Hyperglycemia	11 (29%)	18 (47%)		
Hypoglycemia	1 (3%)			
Amylase		3 (8%)		
Lipase		1 (3%)		
II. Non-Hematologic Toxicity				
Gastrointestinal symptoms				
Abdominal pain	4 (10.5%)			
Ascites (non-malignant)		1 (3%)		
Constipation	1 (3%)			
Nausea/vomiting	2 (5%)			
Infection (cholangitis/abscess)	2 (5%)	1 (3%)	1 (3%)	
Hemorrhage, Lower GI tract ²		1 (3%)		
Hemorrhoids	1 (3%)			
Constitutional Symptoms				
Fatigue/Lethargy	3 (8%)			
Weight loss	1 (3%)			
Other Toxicities				
Atrial fibrillation		1 (3%)		
Hypersensitivity reaction ³		1 (3%)		
Anxiety	1 (3%)			
Cerebrovascular accident				1 (3%)
Edema (limb)	1 (3%)			
Hypertension	1 (3%)			
Injection Site reaction (extravasation)	1 (3%)			
Fever/infection (normal ANC)	7 (18%)	1 (3%)	1 (3%)	
Neuropathy	1 (3%)			
Rash, erythema multiforme	1 (3%)			

Toxicity	Grade 2	Grade 3	Grade 4	Grade 5
Renal/GU	1 (3%)		1 (3%)	
Sudden death (cardiac) ⁴				2 (5%)

¹ Electrolyte abnormalities, including hyper/hyponatremia, hyper/hypokalemia, hyper/hypomagnesemia, hyper/hypophosphatemia.

² Patient had hemorrhage from primary tumor site related to erosion into the duodenum after the 2nd cycle of therapy and proceeded to surgery thereafter.

³ Infusion/hypersensitivity reaction to oxaliplatin after 2nd dose; no further oxaliplatin was administered. Neoadjuvant therapy was completed with gemcitabine alone.

⁴ Fatal myocardial infarction (N= 1); Fatal arrhythmia (N= 1).

Table 3**RECIST Radiologic and Tumor Marker Response to Neoadjuvant Therapy**

RECIST Response (N= 38)	No. Patients (%)			
Partial Response	4 (10.5%)			
Stable Disease	28 (73.7%)			
Progression of Disease	3 (7.9%)			
Inevaluable ¹	3 (7.9%)			

Tumor Marker Response (N= 35)²	Pre-Therapy	Post-Therapy	Median % change (range)
Median CEA level (range) in ng/mL	4.2 (0.8-149)	4.2 (0.8-82)	-5.1% (-68% to 203%)
Median Ca 19-9 level (range) in U/mL	133 (3-3816)	132 (5-2483)	-25.6% (-85% to 289%)

RECIST, Response Evaluation Criteria in Solid Tumors

¹ Excluded N= 3 who did not complete 4 cycles of neoadjuvant therapy (1 early MI, 1 CVA, 1 received only 2 cycles of therapy and went to surgery in view of gastrointestinal hemorrhage)

² Excluded N= 3: two patients with fatal cardiac events and one patient who did not have post-neoadjuvant tumor marker laboratory test

Table 4

Surgical and Pathologic Outcomes to Neoadjuvant Therapy (N= 35)

Surgical and Pathological Outcomes	No. Patients (%)
I. Resected Following Neoadjuvant Therapy	N= 27 (100%)
Median Length of Stay (range), days	6 (3-15)
Resection Type	
Whipple	20 (74%)
Distal pancreatectomy, splenectomy	7 (26%)
Tumor Location	
Head/neck	20 (74%)
Body	3 (11%)
Tail	4 (15%)
Histology^I	
Adenocarcinoma	26 (96%)
Adenosquamous	1 (4%)
T stage	
T1	1 (4%)
T3	26 (96%)
Median Tumor Size (range), cm	2.8 (1.7-4.6)
Nodal Status	
N0	9 (33.5%)
N1	18 (66.5%)
Resection Margin	
R0	20 (74%)
R1	7 (26%)
Differentiation	
Moderate	21 (78%)
Moderate-poor	6 (22%)
Lymphovascular/Perineural Invasion	
Lymphovascular invasion	13 (48%)
Perineural invasion	26 (96%)
TNM stage	
T1N0 (AJCC stage I)	1 (4%)
T3N0 (AJCC stage IIA)	8 (29.5%)
T3N1 (AJCC stage IIB)	18 (66.5%)
Pathologic Response to Neoadjuvant Therapy (Exploratory)	
0- 25%	17 (63%)
26- 50%	9 (33%)
51- 75%	1 (4%)

Surgical and Pathological Outcomes	No. Patients (%)
II. Unresectable Following Neoadjuvant Therapy	N= 8 (100%)
T4, locally advanced ²	4 (50%)
Varices/portal hypertension	1 (12.5%)
Metastases (N= 2 liver; N= 1 peritoneum)	3 (37.5%)

¹ N= 1 had incidentally detected primary mucinous well-differentiated ovarian neoplasm resected at time of Whipple surgery; N= 1 patient had an incidental neuroendocrine cancer resected concurrent with distal pancreatectomy.

² N= 2 superior mesenteric artery involvement, N=2 superior mesenteric vein-portal venous confluence invasion.