

A Phase I Study of Cetuximab in Combination With Gemcitabine and Radiation for Locally Advanced Pancreatic Cancer

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ABSTRACT

BACKGROUND: Cetuximab is a monoclonal antibody against the epidermal growth factor receptor (EGFR). The primary goal of this phase I study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of gemcitabine when combined with cetuximab plus radiation in patients with locally advanced pancreatic cancer.

PATIENTS AND METHODS: Patients with locally unresectable adenocarcinoma of the pancreas were treated with gemcitabine (200 mg/m²/week before dose escalation) plus cetuximab (400 mg/m² loading dose, 250 mg/m² weekly maintenance dose) concurrent with radiation (50.4 Gy).

RESULTS: Nine patients were enrolled in the study. One withdrew due to declining performance status before receiving any therapy. Grade 4 allergic reactions to cetuximab caused the withdrawal of 2 patients. Another patient had elevated liver function test results and a stroke after his loading dose of cetuximab. Grade 3 or 4 toxicity developed in 3 of the remaining 5 patients treated with the level 1 dose. Therefore, no further dose escalations were planned. Grade 3 toxicities included nausea, vomiting, ileus, and pneumonitis. One patient had grade 4 diarrhea.

CONCLUSIONS: The combination of cetuximab, gemcitabine, and radiation resulted in significant toxicity. A recommended phase II dose could not be determined.

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Pancreatic cancer is the fourth leading cause of cancer deaths in the United States. In 2012, it is estimated that there will be 43,920 new cases and 37,390 deaths, with an overall 5-year survival rate of less than 4%.¹ Gemcitabine, the standard agent used for treatment of metastatic disease, is a potent radiosensitizer. Results of phase I studies in patients with pancreatic cancer who are on a once-weekly gemcitabine dose schedule suggested that, with conventional radiotherapy regimens, the maximum tolerated dose (MTD) is in the range of 250 to 350 mg/m².^{2,3} Late toxicities, including ulceration, bleeding, strictures, and fistulas, have been observed with once-weekly gemcitabine when higher doses or larger fraction sizes of radiation were used.⁴

To improve local–regional control, additional agents or biologics have been com-

bined with gemcitabine-based chemoradiation trials. The epidermal growth factor receptor (EGFR) is a member of the ErbB receptor tyrosine kinase family, whose signal transduction network plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, metastasis, and protection from apoptosis. EGFR is overexpressed in pancreatic cancers and may be vital to their growth.⁵ Thus, the combination of anti-EGFR antibodies and chemoradiation therapy could increase therapeutic efficacy, given these agents' diverse cellular targets and mechanisms of action.

Cetuximab is a monoclonal antibody that binds specifically to EGFR on both normal and tumor cells, competitively inhibiting the binding of EGF and TGF- α . In vitro assays and in vivo animal studies have shown that anti-EGFR antibodies inhibit the

growth and survival of tumor cells that over-express EGFR.⁶ In nude mice with orthotopically implanted pancreatic tumors, treatment with anti-EGFR antibodies plus gemcitabine resulted in improved efficacy with increasing concentrations of the drug.⁷ Thus, we hypothesized that the combination of anti-EGFR antibodies and gemcitabine would produce a synergistic cytotoxic effect, decreasing tumor angiogenesis, inhibiting cancer cell proliferation, and increasing apoptosis.

When cetuximab was combined with gemcitabine, without radiation therapy, both agents could be delivered at full doses

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(400 mg/m² initial dose followed by 250 mg/m²/week maintenance dose for cetuximab and 1000 mg/m² weekly for gemcitabine) for treating advanced pancreatic cancer.⁸ For head and neck cancer, the combined therapy of cetuximab (full dose, 400 mg/m² initial dose followed by 250 mg/m²/week) and radiation (full dose, 2 Gy/day to up to 76.8 Gy/day) also showed good tolerance.⁹ When gemcitabine was given with concurrent radiation but without cetuximab for unresectable pancreatic cancer, the maximum tolerated dose was 440 mg/m²/week when administered in a 30-minute infusion.¹⁰

We designed this phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of gemcitabine, when combined with cetuximab and radiation therapy in patients with locally advanced pancreatic cancer.

PATIENTS AND METHODS

Eligibility

To be eligible for the study, patients had to have unresectable adenocarcinoma of the pancreas or the periampullary region. Tumors were declared unresectable after appropriate imaging and consultation with an experienced pancreatic surgeon. In general, tumors that encase the superior mesenteric artery or celiac trunk, invade or encase the aorta or inferior vena cava, occlude the superior mesenteric vein or portal vein, or involve

lymph nodes outside the field of resection are considered unresectable. In addition, the patients were required to have adequate hematologic, renal, and hepatic function (bilirubin, ≤ 2.0 mg/dL; aspartate aminotransferase [AST] and alanine aminotransferase [ALT], ≤ 5 times upper limits of normal) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Patients were ineligible if they had any of the following: evidence of metastatic disease outside the planned irradiation field, another malignancy or chemotherapy within the past 5 years (except for resected nonmelanoma skin cancer and carcinoma in situ of the cervix), prior therapy that targeted the EGFR pathway, prior radiation of any area within the planned field of treatment, or medical conditions that could be significantly worsened by the treatment. Women with childbearing potential were required to have a negative pregnancy test before treatment and to agree to the use of effective contraception during therapy (Table 1).

Cetuximab

The patients were scheduled to receive an initial loading dose of 400 mg/m² cetuximab at week 1, followed by a weekly dose of 250 mg/m² from weeks 2 to 7. They were continuously observed during the infusion.

Gemcitabine

There were three planned dose escalations of gemcitabine (200, 300, and 400 mg/m²)

at a fixed-dose rate of 10 mg/m²/min. The starting dose of gemcitabine was 200 mg/m², with planned dose escalations of 100-mg/m² increments at each dose level. The patients were grouped in cohorts of 3. If no DLTs were seen in a cohort, the dose would be escalated. If 1 of 3 patients experienced a DLT, a second cohort of 3 patients would be enrolled at the same dose level. If 2 or more of the 6 patients experienced a DLT, that dose level was deemed to be above the MTD, and the previous dose level was the recommended phase II dose level.

Radiation Therapy

The minimum interval between surgery and the first dose of radiation was 14 days for those who underwent a biopsy and 28 days for those who underwent any bypass procedure. The planned total dose was 50.4 Gy, delivered over 28 fractions in 5.5 weeks (1.8 Gy/day). A conedown after 45 Gy was designed to encompass gross disease with a margin of 1 to 1.5 cm. The prescription point was designated at the intersection of multiple beams. No planned interruption of more than 3 days was allowed.

Simulation of the gross tumor volume (GTV), which included only the gross tumor and radiologically involved regional lymph nodes, was performed by using contrast computed tomography (CT). Planning target volume (PTV1) included the GTV plus 2-cm margins in all directions. The boost planning target volume (PTV2) included

Table 1. Treatment schema

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Cohort 1							
Cetuximab (250 mg/m ²)	x* (400 mg/m ²)	x	x	x	x	x	x
Gemcitabine (200 mg/m ²)		x	x	x	x	x	x
Radiation (50.4 Gy)		x x x x x	x x x x x	x x x x x	x x x x x	x x x x x	x†
Cohort 2							
Cetuximab (250 mg/m ²)	x* (400 mg/m ²)	x	x	x	x	x	x
Gemcitabine (300 mg/m ²)		x	x	x	x	x	x
Radiation (50.4 Gy)		x x x x x	x x x x x	x x x x x	x x x x x	x x x x x	x†
Cohort 3							
Cetuximab (250 mg/m ²)	x* (400 mg/m ²)	x	x	x	x	x	x
Gemcitabine (400 mg/m ²)		x	x	x	x	x	x
Radiation (50.4 Gy)		x x x x x	x x x x x	x x x x x	x x x x x	x x x x x	x†

*Induction dose of 400 mg/m².

†Boost dose of 5.4 Gy.

the GTV with a 1- to 1.5-cm margin and radiologically involved nodes. The exact borders were designed based on all relevant data from preoperative CT scans, endoscopic retrograde cholangiopancreatography or ultrasound. For patients who had undergone an attempted resection, surgical clips placed by the surgeon were used to outline the target volume.

Treatments were carried out with a linear accelerator with photon beams of 10 MV or higher energy and were individualized on the basis of the volume and location of the tumor. The uniformity requirement was $\pm 5\%$ of the total dose at the prescription point within the PTV. In general, a 3-field (anterior and 2 laterals) or 4-field (anterior, posterior, and left and right lateral) technique was used with the patient supine. Other techniques, including multi-field 3D conformal therapy, were used to cover the PTV, provided that normal tissue constraints were maintained.

Fields were selected to minimize the dose to adjacent critical normal structures, such as kidney, spinal cord, and liver, outside the clinical target volume. The equivalent of at least one kidney received no more than 20 Gy, or the equivalent of at least two-thirds kidney was spared from the radiotherapy fields. The spinal cord dose was limited to 45 Gy at any contour level. No more than one-half of the liver volume received more than 30 Gy. While undergoing concurrent chemoradiation, the patients were evaluated weekly for toxicity by an attending physician.

Dose-Limiting Toxicity

The patients were evaluated with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.¹¹ A DLT was defined as any of the following: (1) any nonhematologic toxicity of grade 3 or higher, except nausea, vomiting, and hypertension; (2) nausea or vomiting requiring hospitalization despite at least 2 different antiemetic regimens; (3) grade 4 neutropenia for ≥ 5 consecutive days or neutropenic fever; (4) grade 4 thrombocytopenia for ≥ 5 consecutive days or bleeding with grade 3 to 4 thrombocytopenia; (5) any study-related toxicity that required radiation to be interrupted for more than 14 days; and (6) inability to deliver $>75\%$ of the planned chemotherapy dose during the 6-week treat-

ment period. An infusion reaction was not considered a DLT. To enable full evaluation for DLTs, we observed all patients for 4 weeks following completion of the last dose of radiation.

Dose Modification

Unplanned treatment breaks of more than 3 days required dose modification by 1 dose level, and breaks of more than 7 days required dose modification by 2 levels. Patients were withdrawn from the study if the break lasted more than 14 days. Adjustments of radiation dose were made independent of chemotherapy modifications. In general, radiation was not interrupted for chemotherapy-induced side effects. If radiotherapy was interrupted because of gastrointestinal toxicity, chemotherapy was delayed until radiotherapy was resumed.

Withdrawal of Patients

Patients were withdrawn from the study if any of the following conditions occurred: (1) disease progression based on radiographic evidence, clinical signs, and/or tumor marker; (2) intolerable cetuximab-related grade 3 acne or acneiform rash that did not respond to dose modifications or other interventions; (3) other unacceptable toxicity, as assessed by the physician; or (4) patient refusal of or nonadherence to therapy.

Toxicity Evaluation and Follow-Up

Adverse events were coded according to the NCI CTCAE version 3.0.¹¹ Each adverse event was categorized as unknown, related, possible, probable, or definite, according to the likelihood that the event was caused by the therapy. The patients were observed for at least 30 days after onset of the adverse event or discontinuation of treatment, to assure sufficient safety follow-up.

After completion of the study, the patients returned for follow-up visits. CT scans of the abdomen and pelvis, chest X-rays, CA19-9 levels, complete blood counts, and basic metabolic panels were obtained at 4 weeks after completion of chemoradiation and every 3 months thereafter. If a patient did not have disease progression at 2 years after completing therapy, CT scans would be reduced to every 6 months.

Response Assessment

Complete response was defined as disappearance of all target lesions. Partial response was at least a 30% decrease in the sum of the longest diameters of all measurable disease and without new lesions or progression. Progression was defined as at least a 20% increase in the sum of the longest diameter of the target lesions or development of any new lesions. Stable disease had neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression.

RESULTS

Patient Characteristics

Nine patients were enrolled in the study from December 2005 through July 2007. One patient was withdrawn before receiving the initial dose of cetuximab because of a decline in performance status. All of the remaining 8 patients (6 men, 2 women) were Caucasian. The median age at enrollment was 58 years (range, 47–75). All patients had histologically proven adenocarcinoma of the pancreas that was deemed unresectable by the attending surgeon. The median baseline CA19-9 value was 355 U/mL (range, 62–8703). One patient had undergone an unsuccessful attempt at resection before enrolling in the study. Another had a history of colon cancer 17 years before the study and had received 5-FU/leucovorin adjuvant therapy at that time. Baseline ECOG performance status varied among the 8 patients, as follows: 0 ($n = 2$), 1 ($n = 5$), and 2 ($n = 1$).

Treatment Assignment

Two of the 8 patients had cetuximab-related infusion reactions: 1 with grade 4 anaphylactic reaction and 1 with a grade 3 allergic reaction to the loading dose of cetuximab, with severe flushing and hypotension. Both of these patients were withdrawn from the study. As these were clearly infusion reactions, they were not defined as DLTs of combination therapy. A third patient had elevated liver function tests and a stroke after the loading dose of cetuximab. Only 5 patients received more than the loading dose of cetuximab.

One patient at the first dose level had grade 3 nausea and vomiting, despite the use of antiemetic drugs, and the cohort was

therefore expanded to 6 patients. A second patient had grade 4 diarrhea. Since 2 of 6 patients had DLTs at the first dose level, no further dose escalations were planned. Given the unexpectedly severe toxicity at dose level 1, the planned de-escalation to dose level -1 of 150 mg/m² of gemcitabine did not occur.

Toxicity

Table 2 lists the treatment-related side effects in each of the 5 patients who received more than the loading dose of cetuximab. Of the 5 patients, 4 completed 70% or more of the scheduled chemoradiation, but only 1 finished all doses of chemotherapy and radiation (patient 5).

Patient 2 received 3 weeks of chemotherapy and a total of 12.6 Gy of radiation. Five days after his third week of therapy, he was hospitalized twice for nausea, vomiting, and dehydration. Up-

per endoscopy during hospitalization showed evidence of severe erosive esophagitis. He was also found to have biliary stent occlusion with obstructive jaundice, line infection, and *Klebsiella* bacteremia. A CT scan showed disease progression and possible liver metastasis. Thus, he was withdrawn from the study and started on single-agent gemcitabine chemotherapy. He died of disease progression 575 days (18.9 months) after his first dose of induction cetuximab.

Patient 5 completed all the scheduled treatments and experienced only grade 1 toxicities (rash, skin fissures, fatigue, low hemoglobin, low white blood cell [WBC] counts, low potassium, and fatigue) throughout the treatment course. An abdominal CT scan at 1 month after completing the treatment demonstrated stable disease. The patient later had biopsy-proven metastasis to the cervical spine 6 months after completion of the study.

Lung metastases developed subsequently, and he died 752 days (24.7 months) after study enrollment.

Patient 3 had the only grade 5 toxicity that occurred during the study. He completed the radiation therapy of 50.4 Gy and missed only 1 dose (week 3) of cetuximab because of a grade 1 rash. However, 27 days after completing his last dose of chemoradiation, he was hospitalized for severe and intractable nausea, vomiting, and abdominal pain. He died of aspiration pneumonia 45 days after the study closed, before his scheduled follow-up and restaging visit.

Patient 4 had grade 4 diarrhea, along with grade 3 pneumonitis and pulmonary infiltrates, dyspnea, and hypoxia. She completed 36 Gy of radiation and approximately 5 weeks of chemotherapy (with 25% reduction of gemcitabine dose due to thrombocytopenia). A week after her week 5 dose of chemother-

Table 2. Treatment-related side effects

Patient	Age	Sex	Total dose received	Treatment-related side effects			
				Grade 1/2	Grade 3/4	Grade 5	Comments
1	70	F	Cetuximab x3	Anorexia	Rash		Treatment interrupted due to grade 3 rash; withdrew because of poor performance status.
			Gemcitabine x5	Dysphagia			Died of disease progression 349 days after first dose.
			50.4 Gy	Dysarthria, fatigue, weight loss			
2	75	M	Cetuximab x2	Rash			Withdrew because of central line infection, dehydration, and biliary obstruction.
			Gemcitabine x2	Anorexia			Died of disease progression 575 days after first dose
			12.6 Gy	Odynophagia, low Mg			
3	69	M	Cetuximab x5	Rash	Vomiting, infection	Aspiration pneumonia	Died of aspiration pneumonia, 45 days after completing study.
			Gemcitabine ×6 5	Low platelets, nausea, constipation, ileus			
			4 Gy				
4	58	F	Cetuximab x4	Rash	Diarrhea		Withdrew because of intractable nausea and vomiting. Alive, with radiologically stable disease, 1586 days after first dose.
			Gemcitabine ×4 (150 mg/m ²)	Skin fissures	Pneumonitis (HSV)		
			36 Gy	Fatigue, low Hgb, low platelets, constipation, nausea, vomiting, esophagitis, neuropathy, low K, low Mg, low Na, low HCO ₃	Dyspnea, hypoxia		
5	54	M	Cetuximab ×6	Rash			Died with bone and lung metastases 752 days after first dose.
			Gemcitabine ×6	Skin fissures			
			50.4 Gy	Fatigue, low Hgb, low WBC, low K			

apy, she was hospitalized for intractable diarrhea. Her hospital course was prolonged by numerous complications, including acute renal failure, heparin-induced thrombocytopenia, ascites, interstitial pneumonitis (herpes simplex virus type 1), and hypoxemic respiratory failure. She was removed from the study and remains alive at this writing, 52.1 months after her first dose of cetuximab. However, her CA19-9 level has gradually increased to 4177 U/mL after reaching a nadir of 5 U/mL in 2008.

Patient 1 had grade 3 rash and desquamation. She had to skip 2 doses of cetuximab due to grade 3 dermatologic toxicity. She also did not receive week 7 doses of cetuximab and gemcitabine because of declining performance status. A posttreatment CT scan of the abdomen found possible liver and bone metastases, and she was started on palliative gemcitabine and zoledronic acid. She died of disease progression at 349 days (11 months) after her first dose of cetuximab.

Table 3 shows the most common treatment-related adverse events by body system. Overall, the most common nonhematologic toxicities were acneiform rash and fatigue. All 5 patients had dermatologic toxicity: 4 were grade 1 and 1 was grade 3. Fatigue was also a common nonhemato-

logic adverse event. The most common gastrointestinal toxicities included nausea, vomiting, constipation, and anorexia. At this writing, 1 of the 8 patients remains alive. Survival ranged from 45 to 1586 days.

DISCUSSION

Since EGFR is often overexpressed in pancreatic cancer, the use of EGFR inhibitors such as cetuximab seems to be an ideal therapeutic approach to controlling tumor cells. However, the evidence has not been straightforward. A phase III study failed to show a significant overall survival benefit of this combination, compared with gemcitabine alone, for locally advanced or metastatic pancreatic adenocarcinoma.¹² Another phase III randomized study found that the combination of a different EGFR inhibitor, erlotinib (100 mg/day), and gemcitabine was superior to gemcitabine alone in both response and survival, with a 1-year survival of 23% vs.17% ($P = .02$).¹³ Although the survival benefit was modest, it provided proof of principle that a biologic added to cytotoxics can improve survival in pancreatic cancer.

The approach of combining cetuximab with radiotherapy was initially tested in patients with locally advanced squamous cell

carcinoma of the head and neck. In a randomized, multicenter phase III study, radiotherapy with cetuximab resulted in significantly prolonged progression-free survival, duration of local control, and overall survival.¹⁴

Our phase I study was intended to test this concept in pancreatic cancer. The regimen of weekly cetuximab (250 mg/m²) and gemcitabine (200 mg/m²) delivered with concurrent radiation therapy (50.4 Gy within 6 weeks) resulted in unexpectedly severe toxicities among patients with locally advanced pancreatic cancer, including strong anaphylactic reactions to induction cetuximab ($n = 2$); grade 5 aspiration pneumonia, most likely secondary to grade 3 ileus, nausea, and vomiting ($n = 1$); grade 4 diarrhea; and grade 3 pneumonitis. A grade 3 rash developed in 1 patient, and his cetuximab infusion was interrupted for 2 weeks.

Our results differ markedly from those of a recently published phase I study evaluating the use of cetuximab with gemcitabine and radiation for locally advanced pancreatic cancer.¹⁵ In that study, dose escalation was performed, with gemcitabine (0–300 mg/m²) given concurrently with cetuximab (400 mg/m² loading dose and 250 mg/m² maintenance dose) and abdominal radiation (50.4 Gy). Although of the 16 patients enrolled, 96% experienced grade 1–2 adverse effects and 9% experienced grade 3–4 adverse effects, these were not regarded as serious treatment-related events, and no patient deaths were attributed to drug toxicity. The authors concluded that cetuximab could be safely administered with concurrent gemcitabine (up to 300 mg/m²/week) and abdominal radiation in patients with locally advanced adenocarcinoma of the pancreas. It is unclear why these studies have such major differences in toxicity.

A disproportionately high percentage of participants in our study experienced infusion reactions (2/8, 25%) compared with <2% observed by Cunningham et al.¹⁶ A high prevalence of hypersensitivity reactions to cetuximab has been reported in the southeastern United States and has been associated with preexisting IgE antibodies against an oligosaccharide present on the recombinant molecule.^{17,18} However, hypersensitivity reactions were not reported in

Table 3. Most common treatment-related adverse effects by body system

Adverse effect (occurred in ≥ 2 patients)	Grade 1 or 2 (n)	Grade 3 or 4 (n)
Patients with ≥ 1 adverse event	5	3
Body as a whole		
Anaphylaxis to induction cetuximab	0	2
Acneiform rash	4	1
Skin fissures	2	0
Infection	0	2
Fatigue	3	0
GI/digestive		
Nausea	2	0
Vomiting	1	1
Constipation	2	0
Anorexia	2	0
Hematology/lymphatics		
Low hemoglobin	2	0
Low platelet	2	0
Respiratory		
Pneumonitis	0	2

another study in the southeast that was conducted at the University of Alabama at Birmingham.¹⁵

Rash was the most common toxicity among patients treated with cetuximab in our study. All 5 patients who received more than 1 dose of cetuximab had an acneiform rash (1 grade 3 and 4 grade 1). The adverse effects were comparable to those reported in a study of cetuximab therapy in metastatic colorectal cancer, in which rash occurred in 88% of the treated patients, with 12% of the incidences being grade 3 or 4.¹⁶ The severity of acneiform rash induced by an EGFR antagonist may be associated with better responses to treatment in patients with refractory colorectal or pancreatic cancer.^{8,16}

In a phase I study reported in abstract form, gemcitabine (300 mg/m²) and cetuximab (loading dose 400 mg/m², followed by 250 mg/m²/week) were given weekly during radiation for locally advanced pancreatic adenocarcinoma.¹⁹ The authors concluded that this combined treatment was well tolerated and appeared to be active. Toxicity was clearly increased for the maximum schedule without significant increase of efficacy, but the MTD was not reached. The study ultimately recommended 45 Gy radiation with gemcitabine (300 mg/m²) and cetuximab (loading dose 400 mg/m², followed by 250 mg/m²/week).

In addition, a phase II study showed that initial treatment consisting of radiotherapy with weekly gemcitabine (300 mg/m²) plus cetuximab (loading dose 400 mg/m² day 1, followed by 250 mg/m² concomitant with radiotherapy) was well tolerated. Radiation was given using intensity-modulated radiation therapy to a total dose of 5400 cGy. This treatment was followed by gemcitabine (with and without cetuximab) as adjuvant therapy.²⁰ A possible explanation as to why our study had greater toxicity may have been the difference in radiation dose delivery. We used traditional radiotherapy treatment volumes, which included the primary tumor as well as the prophylactic nodal basins in the treatment volume, resulting in a larger volume of normal tissue. Intensity-modulated treatment approaches that limit the volumes to gross tumor with a margin and do not include prophylactic nodal treatment may be better tolerated.

Therefore, despite promising preclinical and clinical studies suggesting that the combination of cetuximab and radiation would be both tolerable and possibly synergistic, the results of our phase I trial indicated substantial toxicity from the doses administered in this combination. Our results show that the toxicities may have been more tolerable had a lower dose or different dose schedule been used. A phase II study combining cetuximab, gemcitabine plus oxaliplatin, and radiation in locally advanced pancreatic cancer was found to be effective and had acceptable toxicity. The study was designed to deliver 4 doses of gemcitabine and oxaliplatin at 2-week intervals, along with weekly cetuximab, followed by concurrent capecitabine twice daily on the days of radiation therapy along with weekly cetuximab. Limiting the chemotherapy to capecitabine alone during the radiation component may have helped to make this a more tolerable regimen.²¹

For future studies, it may also be important to identify patients who could benefit most from the therapy, such as those with EGFR mutations or overexpression. For example, patients with non-small-cell lung cancer and specific mutations in the EGFR tyrosine kinase domain were found to have a better response rate to EGFR inhibitors than were those without the mutations.^{22,23} Unfortunately, a phase III study of the use of gemcitabine plus cetuximab vs. gemcitabine alone in patients with advanced pancreatic adenocarcinoma showed no difference in treatment response between those patients with and those without EGFR expression.¹² K-ras has also been identified as predictive of cetuximab response in treatment of metastatic colorectal cancer, with studies showing that using cetuximab in patients with K-ras mutations has no significant benefit, whereas using it in patients with wild-type K-ras has significant benefit.^{24,25} As pancreatic cancers are frequently (80%–90%) associated with mutations in K-ras,²⁶ future studies that examine this combination should correlate the response to K-ras status.

In conclusion, we found that the combination of weekly cetuximab (250 mg/m²), gemcitabine (200 mg/m²), and concurrent radiation therapy (1.80 Gy fractions to 50.4 Gy) caused significant toxicity. A recommended phase II dose could not be deter-

mined. Given the therapy's toxicity profile, further investigations of this combination therapy should be approached with caution.

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Disclosures of Potential Conflicts of Interest

Dr. Berlin serves on the advisory board of Bristol-Myers Squibb and ImClone.