

## EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study

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**Background:** TNFeradeBiologic (AdGVEGR.TNF.11D) is a replication-deficient adenoviral vector that expresses tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) under the control of the Egr-1 promoter, which is inducible by chemotherapy and radiation.

**Objective:** This study was conducted to determine the maximal tolerated dose of TNFeradeBiologic with standard chemoradiotherapy and preliminary activity and safety of the combination in the treatment of locally advanced pancreatic cancer (LAPC).

**Design:** TNFeradeBiologic was injected into locally advanced pancreatic carcinomas by using EUS or percutaneous administration once a week for 5 weeks together with 50.4 Gy radiation and 5-fluorouracil (5-FU) 200 mg/m<sup>2</sup> daily over 5.5 weeks. Dose levels from  $4 \times 10^9$  to  $1 \times 10^{12}$  particle units (PU) were studied.

**Setting:** Multicentered, academic institutions.

**Patients:** Fifty patients with LAPC were treated.

**Interventions:** Doses of TNFerade Biologic were administered to patients.

**Main Outcome Measurements:** Tolerated of TNFerade Biologic was measured through toxicity and tumor response, by using the criteria of the Response Evaluation Criteria in Solid Tumors and the World Health Organization, and was reviewed by a central radiology facility. Overall survival and progression-free survival were also measured.

**Results:** Dose-limiting toxicities of pancreatitis and cholangitis were observed in 3 patients at the  $1 \times 10^{12}$  PU dose, making  $4 \times 10^{11}$  PU the maximum tolerated dose. One complete response, 3 partial responses, and 12 patients with stable disease were noted. Seven patients eventually went to surgery, 6 had clear margins, and 3 survived >24 months.

**Limitations:** This is a Phase1/2 non-randomized study.

**Conclusions:** Intratumoral delivery of TNFerade Biologic by EUS with fine-needle viral injection or percutaneously, combined with chemoradiation, shows promise in the treatment of LAPC. There appeared to be better clinical outcome at the maximal tolerated dose than at lower doses. The dose of  $4 \times 10^{11}$  PU TNFerade Biologic was generally well tolerated, with encouraging indications of activity, and will be tested in the randomized phase of this study. Delivery of TNFerade Biologic did not interfere with subsequent surgical resection. (Gastrointest Endosc 2012;75:332-8.)

Abbreviations: 5-FU, 5-fluorouracil; ANC, absolute neutrophil count; CRT, chemoradiation therapy; DLT, dose-limiting toxicity; DVT, deep vein thrombosis; EUS-FNI, EUS-guided fine-needle viral injection; FNI, fine-needle viral injection; LAPC, locally advanced pancreatic cancer; MTD, maximal tolerated dose; PU, particle units; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

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### Take-home Message

- Intratumoral delivery of TNFerade Biologic by EUS-fine-needle viral injections or percutaneous administration, combined with chemoradiation, shows promise in the treatment of locally advanced pancreatic cancer.
- Delivery of TNFerade Biologic did not interfere with subsequent surgical resection.

Pancreatic cancer is the fourth most common cause of cancer death in the United States, with over 34,000 patients expected to die from the disease this year.<sup>1</sup> At the time of diagnosis, most patients with pancreatic carcinoma have advanced disease either locally or with metastases.<sup>2</sup> Many of these patients have local complications, including pain and biliary or intestinal obstruction, and their median life expectancy is only 6 to 10 months.<sup>2</sup> Patients with locally advanced disease have traditionally been treated with systemic 5-fluorouracil (5-FU) and radiation, although more recently gemcitabine, alone or with erlotinib, has also become a standard of care for locally advanced pancreatic cancer (LAPC).<sup>3-5</sup> Recent data suggest that patients who achieve disease stabilization with induction chemotherapy benefit from consolidation chemoradiation therapy (CRT).<sup>6</sup> Despite these modest advances, life expectancy remains, however, short, and morbidity is high.<sup>7</sup> More effective modalities of treatment for LAPC are clearly needed.

Local treatment may ameliorate symptoms and improve outcome in patients with locally predominant pancreatic cancer. Direct intratumoral delivery has the theoretic potential to deliver high local concentrations of a therapeutic agent while minimizing systemic side effects. CT- or abdominal US-guided percutaneous intratumoral injection is feasible but may be limited by the inability to assess the entire extent of a pancreatic tumor.<sup>8</sup> The efficacy, tolerability, and safety of repeated EUS-guided fine-needle viral injection (EUS-FNI) of pancreatic tumors, especially when performed transgastroscopically, has been shown previously.<sup>9</sup>

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) has potent antitumor effects through its effect on tumor vasculature and a direct cytotoxic effect.<sup>10-13</sup> TNF- $\alpha$  may also function as a radiosensitizer by increasing the levels of hydroxyl radicals or other radical products, thereby enhancing the oxidative damage produced by radiation.<sup>14,15</sup> Clinical studies with TNF- $\alpha$ , however, have been limited by severe systemic toxicity.<sup>15,16</sup> TNFerade Biologic (AdGVEGR.TNF.11D) is a novel means of selective delivery of TNF- $\alpha$  to tumor cells that uses gene transfer.<sup>17</sup> TNFerade Biologic consists of a portion of the radiation-inducible Egr-1 promoter gene upstream to a TNF- $\alpha$  cDNA and incorporates this into an E1, E4, partial E3-, replication-deficient adenovirus type 5, providing spatial and temporal control of the radiosensitivity and cytotoxicity provided by TNF- $\alpha$ .<sup>17</sup> Preclinical xenograft studies have

demonstrated the potent anticancer properties of locally administered TNF- $\alpha$  gene therapy with minimal systemic therapy.<sup>17-20</sup> Phase I studies with percutaneous delivery of TNFerade Biologic combined with adjunctive radiation therapy in a mixed population of patients with solid tumors, including 4 patients with pancreatic cancer, demonstrated objective responses.<sup>8</sup> Therefore, a dose-escalation study was performed to evaluate the dosing, feasibility, and tolerability of intratumoral injection of TNFerade Biologic with 5-FU and radiation therapy as first-line therapy for LAPC.

## PATIENTS AND METHODS

### Patient selection

Patients with histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas that was not considered resectable for potential cure at the study site because of locally advanced disease involving major arteries (superior mesenteric artery, hepatic artery, aorta) or veins (portal vein, superior mesenteric vein) and without evidence of metastatic disease were eligible. No central radiology reading was performed at the time of enrollment. Additional criteria included Karnofsky performance status of  $>70\%$ , life expectancy of  $>3$  months, age 18 to 79 years, and measurable disease. Exclusion criteria included history of other malignancy in the past 2 years other than carcinoma in situ of the cervix or bladder, or early-stage localized prostate cancer; previous chemotherapy or radiation for pancreatic cancer or previous radiation to the target field; evidence of metastatic disease; history of pancreatitis or pancreatic pseudocyst; contraindication to EUS and percutaneously guided delivery; evidence of active infection; liver enzymes more than threefold of the upper limit of normal; evidence of coagulopathy (international normalized ratio  $>1.5$  or partial thromboplastin time ratio  $>1.5$ ); renal insufficiency (serum creatinine  $>2.0$  mg/dL), hematocrit  $<28\%$  or hemoglobin  $<9$  mg/dL, platelet count  $<100,000/\mu\text{L}$ , leukocyte count  $<3000/\mu\text{L}$ , absolute neutrophil count (ANC)  $<1500/\mu\text{L}$ ; pregnancy or lactation; long-term immunosuppressive medication; and investigational medications or other concurrent anticancer therapy within the 4 weeks before day 1 of the study. Written informed consent was required, and the protocol was reviewed and approved by each institution's institutional review board.

### Treatment plan

The study was an open-label extended dose-escalation study designed to assess the safety, feasibility, and tolerability of intratumoral injection of TNFerade Biologic in patients undergoing first-line CRT for LAPC. The secondary and exploratory objectives included measuring the antitumor efficacy, comparing the different modes of delivery, and studying the effect of treatment on surgical downstaging.

Patients were injected immediately before radiation with TNFerade Biologic once a week for 5 weeks. Radiation and chemotherapy with 5-FU was started on day 1 and continued

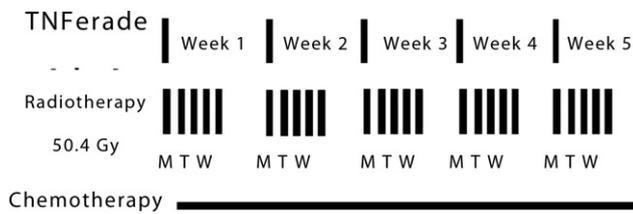


Figure 1. Treatment schedule.

concomitantly with TNFerade Biologic for 5.5 weeks (Fig. 1). Four dosage levels were evaluated:  $4 \times 10^9$  PU,  $4 \times 10^{10}$  PU,  $4 \times 10^{11}$  PU, and  $1 \times 10^{12}$  PU. Three to 6 patients were enrolled per dose depending on toxicity. In this phase I study of a novel agent in combination with CRT and an unusual means of delivery, additional patients were added to each cohort because of toxicities, technical issues, and Data Safety Monitoring Board requests. If no or only 1 dose-limiting toxicity (DLT) developed, dose escalation continued. A DLT was defined as any grade 3 or greater nonhematologic toxicity (except alopecia, nausea, vomiting and diarrhea, asymptomatic hyperamylasemia, or hyperlipasemia) or grade 4 hematologic toxicity (thrombocytopenia [platelets  $<10,000/\text{mm}^3$ ], neutropenia [leukocytes  $<0.5 \times 10^9/\text{L}$ ], or anemia [hemoglobin  $<6.5 \text{ g/dL}$ ]) related to the combination of TNFerade Biologic, 5-FU, and radiation therapy observed during the treatment period and for up to 2 weeks after the last administration of TNFerade Biologic.

A total volume of 2 mL TNFerade Biologic-containing solution was injected via EUS or percutaneously on days 1, 8, 15, 24, and 32. The mode of delivery was left to the discretion of the individual study sites. In patients receiving endoscopic injection, after conscious sedation, the entire target tumors were visualized on EUS with a linear array echoendoscope, by using either a gastric or a duodenal approach, and were injected with 4 0.5-mL injections into different areas of the tumor with a protocol similar to that previously described by Hecht et al.<sup>9</sup> Percutaneous injections consisted of a single injection of 2.0 mL TNFerade Biologic into the tumor by using CT or ultrasound guidance.

External-beam radiation therapy was administered as 50.4 Gy 5 days a week in 1.8-Gy fractions for a total of 5.5 weeks or 28 days. Patients received concurrent 5-FU by continuous infusion (200 mg/m<sup>2</sup>/day for Monday through Friday) for the duration of the radiation therapy (5.5 weeks).

**Safety and efficacy evaluations**

Patients were monitored for adverse events, hematologic abnormalities including abnormal levels of lipase and amylase, changes evident on physical examination, plasma TNF- $\alpha$  levels, anti-TNF- $\alpha$  neutralizing antibody titers, viral genome shedding in urine and as shown by a throat swab, serial CA19-9 levels, and tumor size by CT scan. An external data safety monitoring board reviewed the patient safety data throughout the study.

Efficacy parameters were based on objective tumor response. Contrast medium-enhanced 3-mm slice helical CT

Table 1. Patient baseline characteristics

Characteristic	All patients	
	(N = 50)	%
Age (y)		
Median	59	
Range	35.0-79.0	
Sex (%)		
M	31	62
F	19	38
Race (n [%])		
White, non-Hispanic	41	82
Black, non-Hispanic	2	4
Hispanic	2	4
Asian or Pacific Islander	5	10
Karnovsky Performance Scale (%)		
Median	90	
Range	70.0-100.0	

scans were performed at baseline and 4 and 12 weeks after treatment. Objective tumor response was calculated based on the tumor area defined as the product of bidimensional measurements at each assessment. Tumor response was also determined by using Response Evaluation Criteria in Solid Tumors and World Health Organization criteria and was reviewed by a central radiology facility.<sup>21</sup> Other efficacy parameters included overall survival and progression-free survival.

**RESULTS**

**Patient characteristics**

A total of 50 patients were enrolled in this multicenter study. The characteristics of the entire cohort of patients are listed in Table 1. The median age was 59 years (range, 35-79 years), and the median Karnofsky performance status was 90 (range, 70-100). No patient had evidence of metastatic disease at the time of enrollment. Twenty-three patients were treated by percutaneous injection, and 27 patients received their injections by EUS-guided delivery.

**Dose escalation**

Ten patients received  $4 \times 10^9$  PU without treatment virus-related DLTs. Twenty additional patients were treated at the  $4 \times 10^{10}$  PU dose with a single DLT resulting in a hypotensive episode. Eleven patients were subsequently treated with  $4 \times 10^{11}$  PU without any DLTs. However, at the  $1 \times 10^{12}$  PU dose, 9 patients were treated and 3 experienced associated

**Table 2. All grade 3 and 4 toxicities by dose level**

Toxicity	(patients)	N			
		$4 \times 10^9$ PU	$4 \times 10^{10}$ PU	$4 \times 10^{11}$ PU	$1 \times 10^{12}$ PU
GI bleeding	6	1	3	0	2
Deep vein thrombosis	6	2	2	2	0
Pulmonary embolism	2	0	2	0	0
Abdominal pain	9	1	3	2	3
Pancreatitis	2*	0	0	0	2
Cholecystitis	1	0	1	0	0
Nausea, vomiting, anorexia	4	1	3	0	0
Biliary obstruction	8	0	3	3	2
Cholangitis	6†	0	3	2	1
Anemia	2	0	2	0	0
Electrolyte abnormalities	5	1	1	2	1
Coagulopathy	3	1	0	1	1
Hypotension	2‡	0	1	0	1
Bradycardia	1	0	0	0	1
Supraventricular tachycardia	1	1	0	0	0
Intestinal ischemia	1	1	0	0	0
Staphylococcal infection	1	1	0	0	0
Mental status change	1	0	1	0	0
Cerebrovascular accident	1	0	1	0	0
Death	2§	0	1	1	0
Cardiopulmonary arrest	1¶	0	0	1	0

PU, particle units.

\*Includes two DLTs at  $1 \times 10^{12}$  PU.

†Includes one DLT at  $1 \times 10^{12}$  PU.

‡Includes one DLT at  $4 \times 10^9$  PU.

§Two deaths unrelated to treatment.

¶Cardiopulmonary arrest after pancreaticoduodenectomy surgery.

DLTs (2 cases of pancreatitis and 1 of ascending cholangitis). All DLTs occurred after the administration of the first dose of TNFerade Biologic and resulted in termination of treatment in those 3 patients. Hence, the maximum tolerated dose (MTD) was set at  $4 \times 10^{11}$  PU.

## Toxicity

In general the treatment was well tolerated. Overall grade 3 and 4 toxicities included GI bleeding, deep vein thrombosis (DVT), pulmonary emboli, pancreatitis, and cholangitis (Table 2). Two of the 10 patients receiving the  $4 \times 10^9$  PU dose missed a prescribed dose because they had flulike symptoms and a prolonged partial thromboplastin time. One patient at this dose developed intestinal ischemia, which was thought by the investi-

gator to be unrelated to the study drug. Of the 20 patients in the  $4 \times 10^{10}$  PU treatment group, 3 missed a prescribed TNFerade Biologic dose because they had pain, flulike symptoms, and progression in disease. Only 2 of the prescribed TNFerade Biologic doses were missed in 2 patients in the  $4 \times 10^{11}$  PU group because of patient preference and the diagnosis of a DVT. However, in the  $1 \times 10^{12}$  PU group, 2 cases of pancreatitis and a single case of cholangitis resulted in termination of treatment for those 3 patients, and an additional episode of hypokalemia and hypotension resulted in missed doses in another patient.

Two patients died within 30 days of the end of treatment. One death was ascribed to progressive disease and the other

Table 3. Tumor objective response	
	<b>N=50</b>
<b>Best response (n [%])</b>	
Complete response	1 (2)
Partial response	3 (6)
Minor response	4 (8)
Stable disease	12 (24)
Progressive disease	19 (38)
Not applicable/nondiagnostic	8 (16)

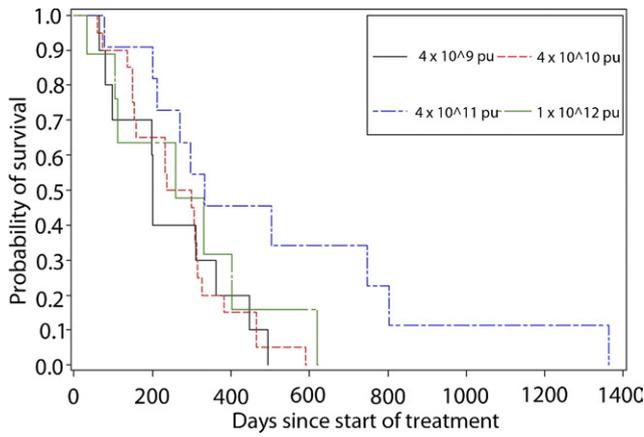


Figure 2. Overall survival by treatment group. PU, particle units.

to splenic artery thrombosis. Neither was thought by the investigators to be related to the treatment. Grade 3 and 4 toxicities are listed in Table 2.

**Efficacy**

The results of the effect of treatment on the target tumor are summarized in Table 3. A single complete response was seen in 1 patient ( $4 \times 10^{10}$  PU cohort), and a partial response was seen in 3 patients (2 patients from the  $4 \times 10^{11}$  PU cohort and 2 from the  $1 \times 10^{12}$  PU cohort.) Twelve patients (24%) had stable disease, and 19 (38%) had progressive disease. The median time to tumor progression was 108 days (95% CI, 67–198 days) (Fig. 2). Twenty patients (40%) were free from local progression at 3 months. Determining radiographic response in pancreatic tumors is made difficult by the desmoplastic nature of these tumors and surrounding chronic pancreatitis.<sup>22</sup> In other studies, reduction in serum levels of the tumor marker CA 19-9 have been correlated with outcome in pancreatic cancer patients undergoing treatment.<sup>22-24</sup> At the end of treatment, 15 of 46 patients had decreases of at least 50% from their baseline CA 19-9 level, which has been correlated with significantly better outcome.<sup>24</sup>

The overall median survival was 297 days (95% CI, 201-316 days). However, the best median survival was

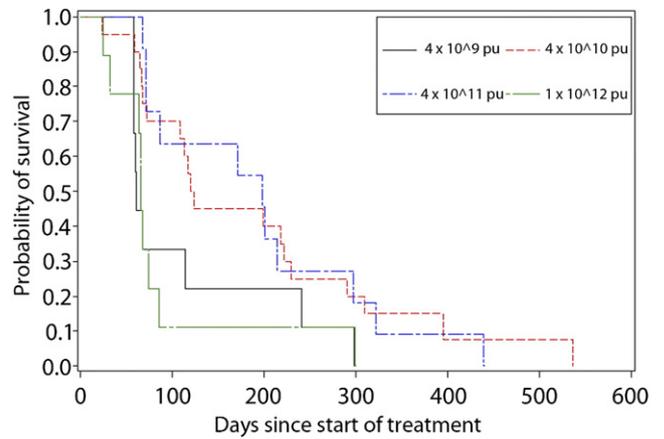


Figure 3. Progression-free survival by treatment group. PU, particle units.

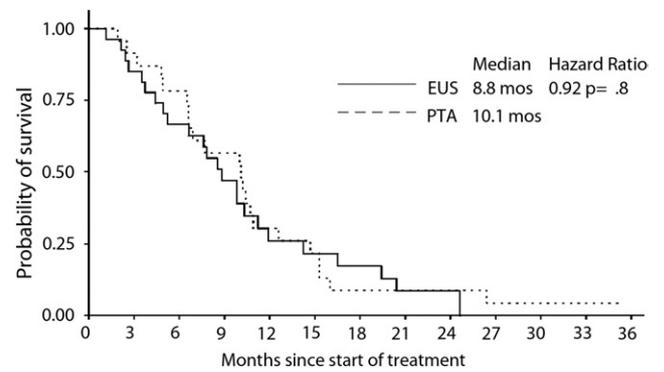


Figure 4. Comparison of overall survival by method of TNFerade administration: EUS- vs. percutaneously guided intratumoral injection. PTA, percutaneous administration.

seen in the  $4 \times 10^{11}$  PU cohort of 332 days (95% CI, 154-316 days) (Fig. 3). On long-term follow-up of the 50 patients enrolled in this study, 1 was still alive 396 days after enrollment in the study. This patient was initially staged as having T4N1M0 disease, received  $4 \times 10^{11}$  PU, underwent surgical resection after treatment, and was found to have a partial pathologic response. Further exploratory analysis studied the impact of mode of delivery on outcome. The method of TNFerade Biologic administration (either by EUS or by the percutaneous route) did not influence overall outcome (Fig. 4).

A planned analysis (per protocol amendment) of the effect of treatment on tumor downstaging and eventual surgical resection was performed. All patients were initially thought to be unresectable. Seven patients underwent surgical resection some time after treatment, and 6 had negative surgical margins. One patient had a complete pathologic response.

**DISCUSSION**

We demonstrated the feasibility and safety of intratumoral gene therapy by either EUS-guided FNI or percutaneous

injection for the treatment of LAPC. Evidence of clinical efficacy was based on the tumor responses and surgical downstaging. The MTD of TNFerade Biologic was identified as  $4 \times 10^{11}$  PU in combination with standard 5-FU and radiotherapy for further study in a randomized clinical trial. This study has limitations, including the small size, the lack of standardization for criteria for locally advanced unresectability, and the nonrandomized study design.

Overall, the combination of chemotherapy, radiotherapy, and TNFerade Biologic was relatively well tolerated. Grade 3 or 4 nausea and vomiting was seen in 4 patients in this study, which is not uncommon with CRT alone. Gastrointestinal bleeding was seen in 6 patients in this study, although it is unclear whether it was related to treatment or to the underlying disease. Occluded biliary stents were the cause of non-treatment-related grade 3 and 4 nonhematologic toxicities in 8 patients, and cholangitis was observed in 6 patients. These toxicities quickly resolved after stent exchange. This result is comparable to a report showing stent occlusion in 15 of 100 patients undergoing CRT.<sup>25</sup> Grade 3 or 4 abdominal pain was seen in 9 patients and included 2 cases of pancreatitis (both of which were DLTs at the maximum dose) and a single case of acute cholecystitis. Although abdominal pain is a common symptom in patients with LAPC, severe pancreatitis is not. It is unclear from this study whether these cases represent the effect of the disease or the treatment.

Similarly, pancreatic cancer is also associated with an increased prothrombotic risk. Both chemotherapy treatment and pancreatic cancer are thought to be independent strong risk factors for the development of DVT.<sup>26</sup> In the current study, 6 patients developed DVTs, with 2 showing evidence of a pulmonary embolism, but no associated deaths. In a retrospective study of thrombotic events in patients with pancreatic adenocarcinoma, venous thrombosis was observed in 27%, and a pulmonary embolism occurred in 4% of patients, with 2% mortality.<sup>27</sup> In summary, the use of locally injected TNFerade Biologic with CRT did not appear to cause significant increased toxicity in this trial.

Responses to CRT are difficult to measure radiographically because of the surrounding pancreatitis and the pronounced desmoplastic reaction of this tumor.<sup>22,23</sup> Nevertheless, 4 patients had a complete response (1 patient) or partial response (3 patients) based on CT radiology criteria. Although overall survival and progression-free survival were not primary endpoints of this dose escalation study, the results are comparable with those of larger phase III randomized studies in LAPC in which external-beam radiation and 5-FU chemotherapy were used for a similar patient profile based on age and functional status.<sup>3,28,29</sup> In those studies, the median progression-free survival ranged from 2.9 to 6.2 months and median survival from 8.2 to 11.4 months. This compares with the median progression-free survival of 3.6 months and overall survival in the current study of 9.8 months, with an overall survival in the MTD group ( $4 \times 10^{11}$  PU) of 10.9 months.<sup>3,29-32</sup>

The incidence of surgical resection in those patients initially deemed unresectable was examined in an unplanned

exploratory analysis. Seven patients (14%) in this study subsequently underwent surgical resection, 6 with completely negative surgical margins and 1 with a complete pathologic response. This result hints at the local effect of TNFerade Biologic combined with CRT. Historical series of CRT for LAPC have reported secondary resectability rates in the range of 1% to 13% of patients.<sup>33,34-36</sup> Predicting which patients may become resectable with treatment would be extremely helpful for future studies.

The role of CRT in the treatment of LAPC remains unclear. Although the combination of 5-FU and radiation historically has been a standard treatment, the trial by the Fédération Francophone de la Cancérologie Digestive and the Société Française de Radiothérapie Oncologique of "intensive induction" with 5-FU, cisplatin, and high-dose radiotherapy followed by gemcitabine compared with gemcitabine alone brought the utility of this approach into question.<sup>37</sup> The gemcitabine arm alone had superior outcomes, although the CRT arm was clearly nonstandard, with excessive toxicity. More recently, however, Loehrer et al presented the results of the Eastern Cooperative Oncology Group 4201 trial, which randomized patients with LAPC to gemcitabine with radiotherapy or gemcitabine alone.<sup>38</sup> Although once again the trial used nonstandard CRT and also closed early because of poor accrual, there was a significant improvement in survival compared with chemotherapy alone. Until large randomized trials comparing standard CRT with gemcitabine-based chemotherapy alone, 5-FU and radiotherapy will be a reasonable basis for the addition of biologic agents and comparator arm.

In summary, this dose escalation study demonstrated the safety and feasibility of EUS-guided and percutaneously guided intratumoral TNFerade Biologic with standard CRT in the treatment of LAPC and identified a maximal tolerated dose. Encouraging activity has prompted the prospective randomized phase III Pancreatic Cancer Trial, which compares standard 5-FU plus radiotherapy with and without TNFerade Biologic. Recent reports have indicated that this trial was stopped for lack of efficacy. New molecular markers such as DPC4 or trial designs such as run-in chemotherapy may prospectively identify a subset of patients who have predominantly locoregional complications from their cancer and would benefit from a localized approach.<sup>39</sup>

## REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010;58:71-96.
2. Schneider G, Siveke JT, Eckel F, et al. Pancreatic cancer: basic and clinical aspects. *Gastroenterology* 2005;128:1606-25.
3. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981;48:1705-10.
4. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-13.

5. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960-6.
6. Huguet F, Thierry A, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326-31.
7. Lockhart AC, Rothenberg ML, Berlin JD. Treatment for pancreatic cancer: current therapy and continued progress. *Gastroenterology* 2005;128:1642-54.
8. Senzer N, Mani S, Rosemurgy A, et al. TNFerade biologic, an adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene: a phase I study in patients with solid tumors. *J Clin Oncol* 2004;22:592-601.
9. Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003;9:555-61.
10. Old LJ. Tumor necrosis factor (TNF). *Science* 1985;230:630-2.
11. Bevilacqua MP, Stengelin S, Gimbrone MA, Jr., et al. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 1989;243:1160-5.
12. Carswell EA, Old LJ, Kassel RL, et al. An endotoxin induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* 1975;72:3666-70.
13. Koga S, Morris S, Ogawa S, et al. TNF modulates endothelial properties by decreasing cAMP. *Am J Physiol* 1995;268:C1104-13.
14. Hallahan DE, Beckett MA, Kufe D, et al. The interaction between recombinant human tumor necrosis factor and radiation in 13 human tumor cell lines. *Int J Radiat Oncol Biol Phys* 1990;19:69-74.
15. Hallahan DE, Vokes EE, Rubin SJ, et al. Phase I dose-escalation study of tumor necrosis factor-alpha and concomitant radiation therapy. *Cancer J Sci Am* 1995;1:204-9.
16. Fraker DL, Thom AK, Doherty GM, et al. Tumour necrosis factor mediates the survival benefit of interleukin 2 in a murine pulmonary metastases model. *Surg Oncol* 1992;1:1-9.
17. Hallahan DE, Mauceri HJ, Seung LP, et al. Spatial and temporal control of gene therapy using ionizing radiation. *Nat Med* 1995;1:786-91.
18. Mauceri HJ, Hanna NN, Wayne JD, et al. Tumor necrosis factor alpha (TNF-alpha) gene therapy targeted by ionizing radiation selectively damages tumor vasculature. *Cancer Res* 1996;56:4311-4.
19. Staba MJ, Mauceri HJ, Kufe DW, et al. Adenoviral TNF-alpha gene therapy and radiation damage tumor vasculature in a human malignant glioma xenograft. *Gene Ther* 1998;5:293-300.
20. Chung TD, Mauceri HJ, Hallahan DE, et al. Tumor necrosis factor-alpha-based gene therapy enhances radiation cytotoxicity in human prostate cancer. *Cancer Gene Ther* 1998;5:344-9.
21. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 2006;42:1031-9.
22. Willett CG, Daly WJ, Warshaw AL. CA 19-9 is an index of response to neoadjuvant chemoradiation therapy in pancreatic cancer. *Am J Surg* 1996;172:350-2.
23. Massucco P, Capussotti L, Magnino A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. *Ann Surg Oncol* 2006;13:1201-8.
24. Wong D, Ko AH, Hwang J, et al. Serum CA19 9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. *Pancreas* 2008;37:269-74.
25. Pisters PW, Hudec WA, Lee JE, et al. Preoperative chemoradiation for patients with pancreatic cancer: toxicity of endobiliary stents. *J Clin Oncol* 2000;18:860-7.
26. Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost* 2002;87:575-9.
27. Mitry E, Taleb-Fayad R, Deschamps A, et al. Risk of venous thrombosis in patients with pancreatic adenocarcinoma. *Gastroenterol Clin Biol* 2007;31:1139-42.
28. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988;80:751-5.
29. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373-8.
30. Moertel CG, Childs DS, Jr., Reitemeier RJ, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 1969;2(7626):865-7.
31. Gastrointestinal Tumor Study Group. Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. *Cancer* 1985;56:2563-8.
32. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988;80:751-5.
33. Snady H, Bruckner H, Cooperman A, et al. Survival advantage of combined chemoradiotherapy compared with resection as the initial treatment of patients with regional pancreatic carcinoma. An outcomes trial. *Cancer* 2000;89:314-27.
34. Jessup JM, Steele G, Jr., Mayer RJ, et al. Neoadjuvant therapy for unresectable pancreatic adenocarcinoma. *Arch Surg* 1993;128:559-64.
35. White R, Lee C, Anscher M, et al. Preoperative chemoradiation for patients with locally advanced adenocarcinoma of the pancreas. *Ann Surg Oncol* 1999;6:38-45.
36. Kim HJ, Czischke K, Brennan MF, et al. Does neoadjuvant chemoradiation downstage locally advanced pancreatic cancer? *J Gastrointest Surg* 2002;6:763-9.
37. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008; 19:1592-9.
38. Loehrer PJ, Powell ME, Cardenes HR, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 4506).
39. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009;27:1806-13.

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