HIGHLIGHT ARTICLE

New Developments in the Treatment of Locally Advanced Pancreatic Cancer

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Laura R Triano, Bryan W Chang, Muhammad Wasif Saif

Yale Cancer Center, Yale University School of Medicine. New Haven, CT, USA

Summary

The results of the trials presented at this year's ASCO annual meeting underline the challenges of not only treating but also studying locally advanced pancreatic cancer, with any appreciable effect of treatment gained at the cost of considerable toxicity. That response was observed in small numbers of patients in the presented trials speaks to the importance of rational selection of treatment in individual patients in order to achieve maximal survival with minimal treatment-associated morbidity. Further understanding of tumor biology and identification of both prognostic and predictive factors will help define personalized treatment approaches for individual patients.

Introduction

Locally advanced pancreatic cancer is defined as the presence of a surgically unresectable tumor (involving the celiac axis or the superior mesenteric artery) without evidence of distant metastases [1]. While surgery is the only means of cure for pancreatic cancer, fewer than 10% of patients are eligible for resection based on the extent of disease at presentation. According to the Surveillance, Epidemiology and End Results (SEER; http://seer.cancer.gov/statfacts/html/pancreas.html) database, 26% of pancreatic cancer cases are locally advanced at the time of diagnosis, with a 5-year survival rate of 8.7% [2].

What Did We Know before ASCO 2009?

Chemoradiotherapy with 5-fluorouracil (5-FU) and radiotherapy to a total dose of 50 Gy increases overall

survival and quality of life of patients with locally advanced pancreatic cancer, as supported by the Gastrointestinal Tumor Study Group (GITSG) [3] and the Eastern Cooperative Oncology Group (ECOG) 8282 [4] trials. Most studies have investigated 5-FU-based chemotherapy regimens with radiotherapy. Over the last 10 years, gemcitabine has become the standard of chemotherapy in advanced pancreatic carcinoma and is also a potent radiosensitizer of epithelial cells. Many phase I and II trials have demonstrated the feasibility of combining radiotherapy (to total doses ranging from 24 to 61 Gy) with gemcitabine at weekly doses ranging from 100 to 1,000 mg/m^2, however results of randomized phase II studies are not sufficient or consistent to recommend such a regimen. Therefore, 5-FU is still the reference chemotherapy in association with radiotherapy for locally advanced pancreatic cancer. The optimal protocol to deliver 5-FU has not been evaluated in comparative trials, and multiple administration schedules have been reported, including weekly bolus (250 to 600 mg/m^2), bolus on the first three days of radiotherapy (350 to 600 mg/m^2), continuous infusion on the first and fifth weeks of radiotherapy (1,000 mg/m^2), and continuous infusion (200 to 300 mg/m^2/day).

Even if chemoradiotherapy were widely used to treat patients with locally advanced pancreatic cancer, its superiority compared to chemotherapy has never been proven. In the Federation Francophone de Cancerologie Digestive-Societe Francaise de Radiotherapie Oncologique (FFCD-SFRO) trial [5], although the chemoradiotherapy regimen used was not optimal (5-FU and cisplatin with 60 Gy external beam radiation

therapy) and produced unacceptable toxicity rates, results of this trial were consistent with older studies published in the 1980s. The results of the ECOG E4201 phase III trial [6] were in favor of chemoradiotherapy, however these results should be considered cautiously because of the insufficient number of patients included.

Table 1 summarizes selected phase III randomized clinical trials of chemotherapy and radiation in the treatment of locally advanced pancreatic cancer.

What Did We Learn at ASCO 2009?

Table 2 summarizes the findings of studies presented at this year's ASCO annual meeting.

Abstract #4610. Final analysis of a multicenter, randomized phase II trial comparing three different chemoradiotherapy regimens in the treatment of patients with locally advanced, nonmetastatic pancreatic cancer. [7]

Wilkowski *et al*. reported the final analysis of a phase II multicenter trial in Germany comparing three different concurrent chemoradiotherapy regimens for locally advanced pancreatic cancer [7]. All patients received 50 Gy of EBRT in combination with one of three chemotherapy regimens: 1) 5-FU as a 24-hour infusion (350 mg/m^2 on each day of radiation); 2) low-

dose gemcitabine 300 mg/m^2 and cisplatin 30 mg/m^2 on days 1, 8, 22, and 29; or 3) the same low-dose gemcitabine and cisplatin regimen followed by sequential chemotherapy with full-dose gemcitabine 1,000 mg/m^2 and cisplatin 50 mg/m^2 every two weeks until disease progression or unacceptable toxicity. Seventy patients were evaluable out of a total of 95 who were recruited. There was no difference among the three treatment arms with respect to the primary endpoint of overall survival at nine months (P=0.61). Response rate, a secondary endpoint, was 19% in the radiotherapy/5-FU arm, 22% in the radiotherapy/low dose gemcitabine/cisplatin arm, and 13% in the radiotherapy/low dose gemcitabine/cisplatin with sequential full dose gemcitabine/cisplatin arm. Grade 3 and 4 hematologic toxicities as well as rates of nausea and vomiting were higher in the two gemcitabine/cisplatin arms compared to 5-FU. The authors concluded that radiotherapy with gemcitabine/cisplatin was not more clinically efficacious than radiotherapy with 5-FU. The findings of this trial, as with previously reported studies, should be interpreted with caution due to the small sample size. Although combined modality therapy was not associated with improved outcome in this trial, the rates of increased hematologic and nonhematologic toxicities remain important observations.

Table 1. Selected phase III clinical trials of chemotherapy and radiation for the treatment of locally advanced pancreatic cancer.

Trial Author, year	No. of patients		Chemotherapy	Radiation	Median overall survival (months)	Median time to progression (months)	Grade 3-4 toxicity
GITSG Moertel *et al*., 1981 [3]	194	**Arm A**	None	60 Gy [a]	5.3	2.9	
		Arm B	5-FU 500 mg/m^2/wk bolus days 1-3 + maintenance 5-FU bolus 500 mg/m^2/wk until progression	40 Gy [a]	7.0	7.0	
		Arm C	5-FU 500 mg/m^2/wk bolus days 1-3 + maintenance 5-FU bolus 500 mg/m^2/wk until progression	60 Gy	7.6	7.6	
					A *vs*. B: P<0.1; A *vs*. C: P<0.1; B *vs*. C: P=0.19	A *vs*. B: P<0.1; A *vs*. C: P<0.1; B *vs*. C: P=0.14	
ECOG 8282 Cohen *et al*., 2005 [4]	108	**Arm A**	None	59.4 Gy	7.1	5.0	24.5%
		Arm B	5-FU 1,000 mg/m^2/day c.i. days 2-5 and days 28-31 + mitomycin-C 10 mg/m^2 day 2	59.4 Gy	8.4	5.1	32.7%
					P=0.16	P=0.19	P=0.049
FFCD-SFRO Chauffert *et al*., 2008 [5]	119	**Arm A**	Gemcitabine 1,000 mg/m^2/wk + maintenance gemcitabine until progression	None	13	32% at 1 year	Induction: 27% heme; 18% non-heme Maintenance: 27% heme; 24% non-heme
		Arm B	5-FU 300 mg/m^2/day c.i. 5 days/wk + cisplatin 20 mg/m^2/day days 1-5 and days 29-33 + maintenance gemcitabine 1,000 mg/m^2/wk until progression	60 Gy	8.6	14% at 1 year	Induction: 31% heme; 44% non-heme Maintenance: 71% heme; 30% non-heme
					P=0.03		Induction: P=0.008 Maintenance: P=0.001
ECOG 4201 Loehrer *et al*., 2008 [6]	74	**Arm A**	Gemcitabine 1,000 mg/m^2/wk on days 1, 8, 15	None	9.2	6.1	5.7%
		Arm B	Gemcitabine 600 mg/m^2/wk + maintenance gemcitabine 1,000 mg/m^2/wk on days 1, 8, 15	50.4 Gy	11.0	6.3	41.2%
					P=0.044	P=0.34	P<0.0001

[a] split course
c.i.: continuous infusion

Table 2. Summary of new developments for the treatment of locally advanced pancreatic cancer presented at ASCO, 2009.

Author Abstract #	No. of patients		Chemotherapy	Radiation	Median overall survival (months)	Progression free survival (months)	Grade 3-4 toxicity
Wilkowski #4610	95	**Arm A**	5-FU 350 mg/m^2/day c.i.	50 Gy	9.6	4.0	Hematological toxicities higher in gemcitabine/cisplatin arms; no febrile neutropenia
		Arm B	Gemcitabine 300 mg/m^2 + cisplatin 30 mg/m^2 days 1, 8, 22, 29	50 Gy	9.3	5.6	
		Arm C	Gemcitabine 300 mg/m^2 + cisplatin 30 mg/m^2 days 1, 8, 22, 29 with radiotherapy then gemcitabine 1,000 mg/m^2 + cisplatin 50 mg/m^2 every 2 wks	50 Gy	7.3	6.0	Nausea/vomiting more frequent in gemcitabine/cisplatin arms. Diarrhea more frequent in 5-FU arm
					P=0.61		
Goldstein #4616	48	**Induction**	Gemcitabine 1,000 mg/m^2 days 1 and 15 + oxaliplatin 100 mg/m^2 days 2 and 16x1 cycle every 28 days	None	15.4. Only 29% of patients received more than 80% planned treatment, an endpoint of the study	9.9	Grade 3: Liver toxicity 23%; anemia 10%; nausea 8%; fatigue 8%
		Concurrent	5-FU 200 mg/m^2/day over 6 wks	54 Gy			Grade 4: Liver toxicity 6%; thrombocytopenia 2%; late radiation toxicity 2%
		Consolidation	Gemcitabine 1,000 mg/m^2 days 1 and 15 + oxaliplatin 100 mg/m^2 days 2 and 16x3 cycles every 28 days	None			
Viret #4625	51		Docetaxel 20 mg/m^2/wk + cisplatin 20 mg/m^2/wk for 6 wks	54 Gy	9.6	5.8	59% had at least one episode of grade 3 or 4 toxicity
Ben-Josef #4602	27		Gemcitabine 1,000 mg/m^2 days -22, -15, 1, 8, 22, 29	IMRT [a]	23.1 whole cohort	7.2 whole cohort	19% Grade 3 gastrointestinal; 4% Grade 3 duodenal bleeding
Chang #4605	185	**Arm A**	5-FU 200 mg/m^2/day with radiation TNFerade 4x10^{11} PU intratumoral every wk	50.4 Gy	Parametric lognormal: TNFerade: 11.1; Standard: 8.7. Nonparametric: 9.9 both arms		Increased pyrexia and chills in TNFerade arm. Pain, biliary obstruction, cholangitis, hemorrhage, intestinal obstruction, neutropenia and thrombosis similar both arms
		Arm B	5-FU 200 mg/m^2/day with radiation				
		Both arms	Gemcitabine ± erlotinib after chemoradiotherapy				

[a] IMRT: intensity-modulated radiotherapy (50, 52.5, 55, 57.5, 60 Gy/25 fractions)
c.i.: continuous infusion

Abstract #4616. GOFURTGO trial (GFG): An AGITG multicenter phase II study of fixed dose rate gemcitabine-oxaliplatin (Gem-Ox) integrated with concomitant 5-FU and 3-D conformal radiotherapy (5-FU-3-DRT) for the treatment of locally advanced pancreatic cancer. [8]

Goldstein *et al*. reported the findings of a phase II multicenter trial of fixed dose rate gemcitabine and oxaliplatin integrated with concomitant 5-FU and three-dimensional conformal radiotherapy [8]. The authors previously published the results of a regimen consisting of induction gemcitabine followed by continuous 5-FU with concurrent radiotherapy followed by consolidation gemcitabine [9]. The phase II trial presented this year used this same paradigm and added oxaliplatin to gemcitabine induction and consolidation. Forty-eight patients were enrolled and received induction treatment with gemcitabine 1,000 mg/m^2 days 1 and 15 and oxaliplatin 100 mg/m^2 days 2 and 16 of a 28-day cycle, followed by 5-FU 220 mg/m^2/day over 6 weeks during radiotherapy of 54 Gy. Three consolidation doses of gemcitabine and oxaliplatin (as given for induction) were administered four to six weeks after completion of 5-FU/radiotherapy. The study endpoints were feasibility (defined as more than 80% patients completing treatment), safety/toxicity, regimen activity as defined by objective response, progression free survival, and overall survival, as well as quality of life. Only 24 patients (50%) completed all planned cycles of treatment, with 29% completing more than 80% of all treatment. Treatment was discontinued due to toxicity (16%), progressive disease (21%), or doctor/patient preference (4%/2%). The most common treatment-related toxicity affected liver function (grade 3: 23%; grade 4: 6%). Grade 3 cytopenias, fatigue, and GI effects including nausea were also observed. Median progression free survival was 9.9 months, and median overall survival was 15.4 months at a median follow up of 29.7 months. The authors concluded that the addition of oxaliplatin to the previously described gemcitabine-5FU/radiotherapy-gemcitabine regimen improved progression free survival (previously 7.1 months) and overall survival (previously 11.7 months) without significant offset by toxicity. Despite the observed improvement in these parameters compared to the authors' prior study, it should be noted that less than a third of enrolled patients completed more than 80% of the planned treatment, primarily due to progressive disease or toxicity, thus making it difficult to generalize these findings.

Abstract #4625. A phase II study of radiation and docetaxel and cisplatin in the treatment of locally advanced pancreatic carcinoma: FNCLCC-ACCORD 09/0201 trial [10].

Viret *et al*. presented the results of a phase II trial evaluating the efficacy and toxicity of radiation with docetaxel and cisplatin for the treatment of locally advanced pancreatic cancer [10]. Fifty-one patients were enrolled and received a total of 54 Gy EBRT in 1.8 Gy fractions with docetaxel and cisplatin 20 mg/m^2 each weekly for six weeks. The objective response rate was 16%, with a median duration of 7.6 months. Nearly 60% of patients experienced at least one episode of grade 3 or 4 toxicity, with asthenia, anorexia, vomiting, and nausea being the most common adverse effects. Median progression free survival was 5.8 months. Median overall survival was 9.6 months with a median of 21 months of follow up. The authors concluded that the combination of docetaxel and cisplatin with radiotherapy had limited effect in patients with locally advanced pancreatic cancer. As observed in other trials, the rates of significant treatment-related toxicities were quite high.

Abstract #4602. Phase I radiation dose-escalation trial of intensity-modulated radiotherapy with concurrent fixed dose-rate gemcitabine for unresectable pancreatic cancer [14].

Intensity-modulated radiotherapy is a radiation therapy technique that allows for dose intensification with concurrent improved sparing of normal tissues. By dividing the radiation beams into thousands of "pencil beams" of varying intensities, concave dose distributions and very sharp regions of dose fall-off can be created. Gemcitabine is known to be a potent radiation sensitizer, with potential for both enhanced anti-tumor effects and increased toxicity. Early studies of concurrent gemcitabine and radiotherapy for locally advanced pancreatic cancer showed substantial dose-related gastrointestinal toxicity [11]. More recent studies have demonstrated the feasibility of treating only the gross tumor volume with full-dose weekly gemcitabine, omitting the uninvolved lymph node beds and thereby decreasing the amount of normal tissue treated, as summarized in Table 3 [12, 13].

At this year's ASCO annual meeting, Ben-Josef *et al*. presented results from a radiation dose-escalation study using intensity-modulated radiotherapy and fixed dose rate gemcitabine [14]. Patients with unresectable localized pancreatic cancer were treated with fixed dose-rate gemcitabine 1,000 mg/m^2 in a 100-minute infusion on days -22 and -15 and then days 1, 8, 22, and 29. Radiation was started on day 1. Gross tumor volume was defined using a pancreas-protocol CT scan and expanded by 1 cm to create a planning target volume. Active breathing control or 4D simulation was used to account for organ motion. The radiation dose levels were 50, 52.5, 55, 57.5, and 60 Gy, all delivered in 25 fractions. Up to four cycles of fixed dose-rate gemcitabine were given after chemoradiotherapy. The objective was to determine the maximum tolerated radiation dose with concurrent intensity-modulated radiotherapy and fixed dose-rate gemcitabine. Twenty-seven patients were enrolled, and the median overall survival was 23.1 months, with a median progression-free survival of 7.2 months and a response rate of 52.4%. Grade 3 dose-limiting toxicities were seen in six patients, including five patients with nausea, vomiting, dehydration or anorexia and one patient with a duodenal bleed. Only one patient had local progression, and two patients underwent R0 resections, revealing complete and near-complete pathological responses respectively. The authors concluded that high dose intensity-modulated radiotherapy with concurrent fixed dose-rate gemcitabine was tolerable and produced encouraging response rates and survival in locally advanced pancreatic cancer.

Using sophisticated radiotherapy techniques to minimize the dose to normal tissues and account for organ motion, the authors were able to reach a dose of 60 Gy, significantly above the tolerance of the small bowel, which is 45-50 Gy, although further follow-up is needed to accurately evaluate late effects. A detailed account of failure patterns was not included, but local control seems to be quite good. The 23-month median survival is encouraging, given that historically, patients with locally advanced pancreatic cancer survive only 10 months even with chemoradiotherapy. Attempts to intensify local therapy in locally advanced pancreatic cancer by combining hypofractionated stereotactic body radiotherapy (25 Gy in one fraction) and gemcitabine resulted in increased duodenal toxicity without an improvement in survival [15]. Combining fractionated intensity-modulated radiotherapy with concurrent fixed dose-rate gemcitabine may represent a more tolerable and effective approach.

Table 3. Selected results of tumor-only radiation and gemcitabine for pancreatic cancer.

Author year	Radiation dose	Patient No.	Gemcitabine dose	Toxicity	Results
Talamonti *et al*., 2006 [12]	36 Gy in 15 fractions	20 preoperative	1,000 mg/m^2/wk	5% grade 3 GI toxicity 24% surgical complication rate	5% complete response 15% microscopic residual 65% pathologically node negative
Murphy *et al*. 2007 [13]	36 Gy in 15 fractions	74 inoperable	1,000 mg/m^2/wk	22% grade 3+ GI toxicity	5% local failure in nodes 64% 1-year freedom from local progression

Table 4. Insulin-like growth factor receptor (IGFR) inhibitors in clinical trials for pancreatic cancer.

Agent	Type	Clinical development stage
MK0646	Monoclonal antibody	Phase 2 with gemcitabine ± erlotinib for metastatic pancreatic cancer
AMG 479	Monoclonal antibody	Phase 2 with gemcitabine for metastatic pancreatic cancer

Abstract #4605. Multicenter randomized controlled phase III clinical trial using TNFerade (TNF) with chemoradiation in patients with locally advanced pancreatic cancer: interim analysis of overall survival [18].

Tumor necrosis factor alpha (TNF-alpha) is a multifunctional tumoricidal cytokine that is released by macrophages. TNF-alpha can induce cell death through several mechanisms, including caspase-triggered apoptosis, obliteration of tumor vasculature, and augmentation of immune response to tumor cells. TNF-alpha has also been found to be a radiosensitizing agent [16]. TNFerade is a nonreplicating adenovirus vector that delivers human tumor necrosis factor. A phase II dose-escalation trial of TNFerade in combination with 50.4 Gy radiation and 200 mg/m^2/day continuous infusion 5-FU demonstrated that the maximum tolerated dose of TNFerade was 4x10^{11} particle units (PU) [17]. The median survival was 9.8 months, although three of eleven patients survived over 18 months. Chang and colleagues presented an interim analysis of a phase III study of TNFerade [18]. Patients with locally advanced pancreatic cancer were randomized 1:2 to either a standard arm with chemoradiotherapy to 50.4 Gy with concurrent continuous infusion 5-FU or the same regimen with the addition of weekly intra-tumoral injections of 4x10^{11} PU TNFerade. Both arms received adjuvant gemcitabine with the option of erlotinib. A total of 330 patients were enrolled, and an interim analysis of overall survival was planned to occur after 92 deaths. Of the number of patients enrolled, 185 were evaluable for survival analysis, with 117 in the TNFerade arm and 68 in the standard arm. A parametric lognormal analysis showed a median survival of 11.1 months for the TNFerade arm, compared to 8.7 months for the standard arm. A nonparametric analysis showed a median survival of 9.9 months for both arms, with a "late effect" seen in the TNFerade arm. Toxicity was similar in both arms with the exception of increased pyrexia and chills in the TNFerade arm. The authors concluded that there was an encouraging trend in favor

TNFerade use. A second interim analysis is planned after 184 deaths have occurred.

TNFerade represents a novel approach to intensifying local therapy in locally advanced pancreatic cancer. Although the concept of combining radiation with a locally targeted radiosensitizing and tumor necrosing agent is appealing, the interim analysis presented did not demonstrate a significant survival benefit with the addition of TNFerade to standard chemoradiotherapy. Although the trial planned to enroll 330 patients, only 185 subjects were available for the interim analysis. TNFerade appears tolerable; however there is no evidence at this point that it represents an improvement over standard therapies. Results of the next interim analysis are expected in 2010.

Abstract #4500. The prognostic value of polymorphisms in the insulin-like growth factor receptor (IGFR) pathway in patients with locally advanced pancreatic cancer [23].

The IGFR pathway is upregulated in pancreatic cancer and represents an important potential therapeutic target. In normal cells as well as cancer cells, the insulin-like growth factors IGF-I and IGF-II and their regulatory binding proteins influence cell growth and metabolism. By binding to the IGFR, IGF-I and IGF-II modulate cell survival and progression through the cell cycle via the PI3/AKT pathway as well as through extracellular signal-regulated kinase pathways by means of insulin receptor substrate, Src homology and collagen adapter proteins [19]. IGFR is expressed at high levels in pancreatic cancers [20], and recent preclinical studies have shown that inhibition of IGFR can inhibit growth and survival of pancreatic cell lines [21]. IGFR inhibitors have also demonstrated anti-tumor synergy with gemcitabine against pancreatic cancer xenografts [22]. Table 4 shows IGFR inhibitors currently in clinical trials for pancreatic cancer.

At this year's ASCO meeting, Shroff *et al.* presented results of a study of the prognostic value of single nucleotide polymorphisms (SNPs) of the IGFR pathway in locally advanced pancreatic cancer [23].

Table 5. Genotype effect on overall survival of patients with locally advanced pancreatic cancer [23].

Single nucleotide polymorphism	Genotype	Patient No.	Median survival (months)	P value (log rank)	Hazard ratio (95% CI)	P value
IGF1R	GG	73	16.8	0.018	1 (reference)	-
IVS20431A>G	GA/AA	31	11.1		1.62 (1.03-2.55)	0.039
IRS1	GG	90	15.8	0.006	1 (reference)	-
G971R	GA/AA	14	8.6		1.99 (1.10-3.60)	0.023
IGF2*4352A>G	GA/GG	30	18.8	0.015	1 (reference)	-
	AA	73	13.9		1.66 (0.99-2.79)	0.054
Number at risk genotype	0-1	19	21.3	<0.001	1 (reference)	-
	2	53	16.3		1.78 (0.94-3.36)	0.078
	3	29	10.0		3.66 (1.80-7.42)	<0.001

Thirty-nine SNPs from seven candidate genes from the IGFR pathway were investigated using DNA samples extracted from 105 patients with locally advanced pancreatic cancer. Genotyping was performed using the Sequenom method. Kaplan-Meier, log-rank, and Cox regression analyses were used to compare overall survival of patients with different genotypes, taking into account clinical factors including performance status, CA 19-9, induction chemotherapy, LDH, albumin, and hemoglobin. The median survival time for the cohort was 15 months. Three SNPs were significantly associated with survival, and two remained significant after Cox regression analysis. Patients who were heterozygous and homozygous with regard to these polymorphisms had lower median survival than those who did not have the polymorphism. In addition, patients with two or three deleterious alleles had poorer survival than those who had none or only one (Table 5). These results were validated in an additional cohort of 42 patients. The authors suggested that SNPs in the IGFR pathway may have prognostic value in locally advanced pancreatic cancer. While the findings of this study are interesting, they will take on added significance if the SNPs that were identified can predict response to therapy in addition to offering prognostic information. Further investigation is required to determine whether a panel of SNPs can select patients with locally advanced pancreatic cancer who will respond to IGFR inhibitors.

Discussion

The treatment of locally advanced pancreatic cancer remains a formidable challenge in oncology due to the aggressive nature of the disease as well as the, at best, modestly effective treatments, which are in many cases limited by significant toxicities. The use of chemoradiotherapy for locally advanced pancreatic cancer is based on data from studies with relatively small numbers of patients and with varying methodologies. Thus, the use of an evidence-based standard approach remains controversial. Chemoradiotherapy is superior to best supportive care and exclusive radiotherapy alone and leads to a similar outcome when compared to modern chemotherapy with gemcitabine but with added toxicity. Induction chemotherapy before concurrent chemoradiotherapy improves survival of patients with locally advanced pancreatic cancer. In addition to sparing patients with rapidly progressive disease from potentially toxic radiotherapy, such a therapeutic strategy may help to define the subset of patients benefiting from chemoradiotherapy.

The value of induction chemotherapy before chemoradiotherapy needs to be validated in prospective
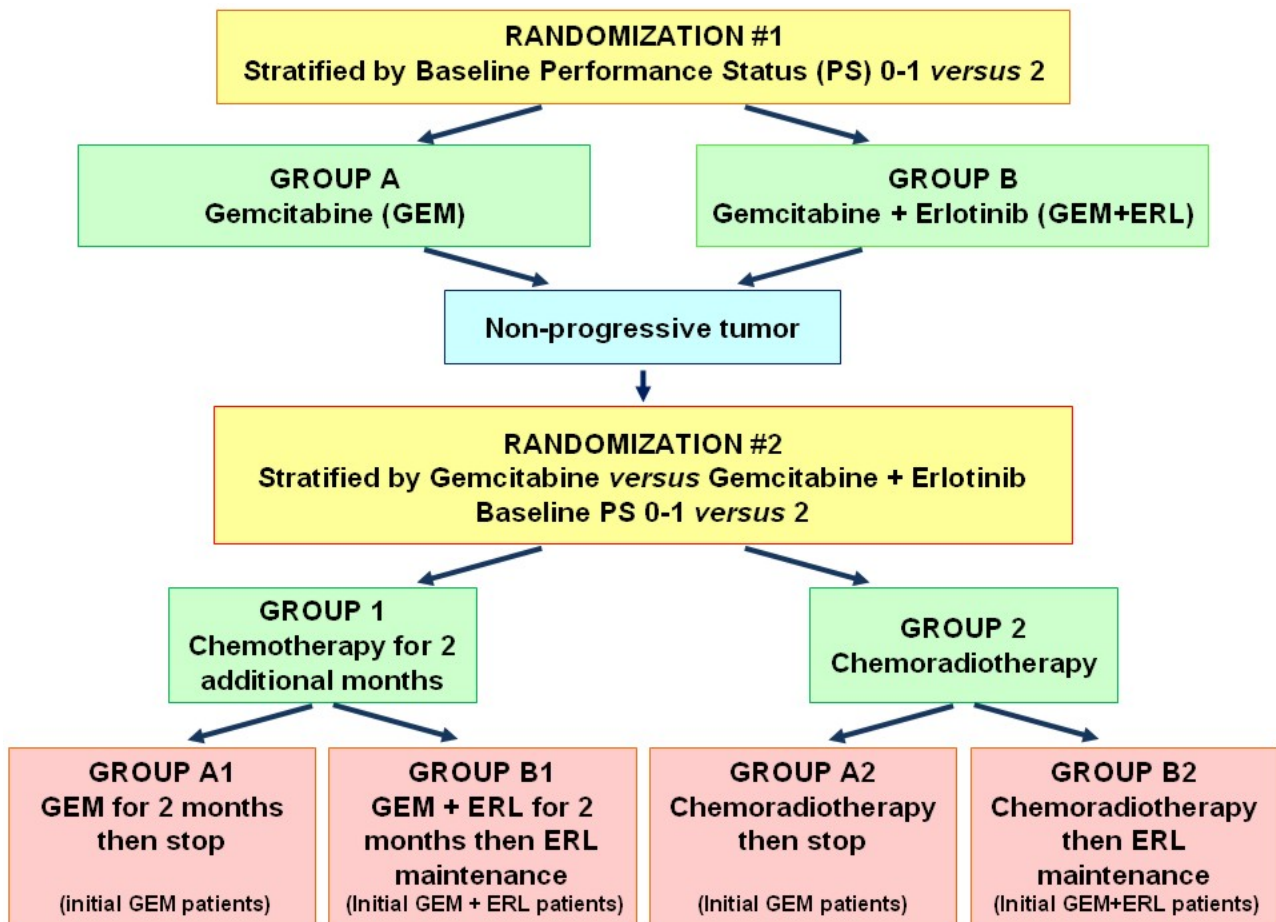

Figure 1. Schema for GERCOR LAP07 trial.

controlled trials, and the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) LAP07 phase III trial has been designed to evaluate this therapeutic approach. LAP07 is an international trial in which patients receive induction chemotherapy (randomly assigned to gemcitabine or gemcitabine plus erlotinib) for the first 4 months of treatment. Patients with a controlled tumor after this first phase of treatment will be randomly assigned to two additional cycles of chemotherapy or chemoradiotherapy (conformal radiotherapy to a total dose of 54 Gy in five fractions of 1.8 Gy per week and concomitant oral capecitabine with a total dose of 1,600 mg/m^2 per day, 5 days a week). After the end of this second phase, patients who have received erlotinib during induction chemotherapy will continue erlotinib as maintenance treatment until progression (Figure 1).

Conflict of interest The authors have no potential conflicts of interest

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