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ORIGINAL REPORT

Gemcitabine in Combination With Oxaliplatin Compared With Gemcitabine Alone in Locally Advanced or Metastatic Pancreatic Cancer: Results of a GERCOR and GISCAD Phase III Trial

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ABSTRACT

Purpose
Gemcitabine (Gem) is the standard treatment for advanced pancreatic cancer. Given the promising phase II results obtained with the Gem-oxaliplatin (GemOx) combination, we conducted a phase III study comparing GemOx with Gem alone in advanced pancreatic cancer.

Patients and Methods
Patients with advanced pancreatic cancer were stratified according to center, performance status, and type of disease (locally advanced *v* metastatic) and randomly assigned to either GemOx (gemcitabine 1 g/m^2 as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2 every 2 weeks) or Gem (gemcitabine 1 g/m^2 as a weekly 30-minute infusion).

Results
Three hundred twenty-six patients were enrolled; 313 were eligible, and 157 and 156 were allocated to the GemOx and Gem arms, respectively. GemOx was superior to Gem in terms of response rate (26.8% *v* 17.3%, respectively; $P = .04$), progression-free survival (5.8 *v* 3.7 months, respectively; $P = .04$), and clinical benefit (38.2% *v* 26.9%, respectively; $P = .03$). Median overall survival (OS) for GemOx and Gem was 9.0 and 7.1 months, respectively ($P = .13$). GemOx was well tolerated overall, although a higher incidence of National Cancer Institute Common Toxicity Criteria grade 3 and 4 toxicity per patient was observed for platelets (14.0% for GemOx *v* 3.2% for Gem), vomiting (8.9% for GemOx *v* 3.2% for Gem), and neurosensory symptoms (19.1% for GemOx *v* 0% for Gem).

Conclusion
These results confirm the efficacy and safety of GemOx, but this study failed to demonstrate a statistically significant advantage in terms of OS compared with Gem. Because GemOx is the first combined treatment to be superior to Gem alone in terms of clinical benefit, this promising regimen deserves further development.

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INTRODUCTION

Pancreatic cancer accounts for 3% of all cancers, but it is the fifth leading cause of cancer death in Western countries.[1] At the time of diagnosis, approximately half of the patients have metastases, and their median survival does not exceed 6 months; whereas approximately one third of patients diagnosed with locally advanced disease have median survival times ranging between 6 and 9 months.[2] Thus, only a small proportion of patients are eligible for surgery at diagnosis, and there is a strong need for active systemic treatments for this cancer.

Most of the studies with single chemotherapeutic agents or combinations performed in pancreatic cancer achieved low

response rates and had low impact on survival. The publication by Burris et al,[3] by showing superiority of gemcitabine (Gem) as a single agent over fluorouracil (FU) monotherapy, established Gem as the reference treatment in advanced or metastatic pancreatic cancer. On the basis of published preclinical in vitro synergy data[4] between Gem and oxaliplatin (Ox), which is a platinum analog with demonstrated activity in several gastrointestinal tumors,[5-8] the French Multidisciplinary Clinical Research Group in Oncology (GERCOR) has conducted a phase II study in 64 patients with advanced or metastatic pancreatic cancer.[9] The encouraging results observed with the GemOx combination prompted the initiation of a phase III trial, conducted by both GERCOR and the Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD), to further explore this regimen and compare it to the standard Gem treatment. We report here the final results of this study.

PATIENTS AND METHODS

Eligibility Criteria

The study was designed to enroll patients with nonresectable, pathologically proven, locally advanced or metastatic adenocarcinoma of the exocrine pancreas. Other eligibility criteria included age between 18 and 75 years, WHO performance status (PS) of 0 to 2, measurable disease, no previous chemotherapy or radiation therapy, no clinical CNS involvement, no previous peripheral neuropathy, and adequate biologic parameters (neutrophil count $> 1,500/mL$, platelet count $> 100,000/mL$, serum creatinine $< 1.5 \times$ the upper limit of normal value [ULN], alkaline phosphatase $< 3 \times$ ULN, and bilirubin $< 1.5 \times$ ULN). Pain and biliary obstruction had to be controlled in all patients before inclusion onto the study. Written informed consent was required from all patients, and the study was approved by the ethics committees of the participating centers. Eligible patients were randomized centrally to receive either Gem alone or the GemOx combination.

Treatment Plan and Dose Adaptations

The GemOx regimen was strictly identical to the regimen tested in our phase II study.[9] Each cycle of treatment comprised a 100-minute infusion of gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) 1,000 mg/m^2 (10 mg/m^2/min) on day 1 and a 2-hour infusion of oxaliplatin (Eloxatin; Sanofi-Synthelabo, Paris, France) at a dose of 100 mg/m^2 administered on day 2. Treatment was repeated every 2 weeks. In the Gem arm, gemcitabine was administered at a dose of 1,000 mg/m^2 in a 30-minute intravenous infusion, as initially described by Burris et al.[3] Treatment was repeated weekly for 7 out of 8 weeks and then weekly for 3 out of 4 weeks.

Dose reductions were made on the basis of the worst toxicity observed during the previous cycle. In case of nonneurologic toxicity (National Cancer Institute Common Toxicity Criteria version 2) more than grade 2, the subsequent cycle was administered after recovery, with the Gem dose decreased to 800 mg/m^2 (80-minute infusion in the GemOx arm and 30-minute infusion in the Gem arm) and the Ox dose decreased to 85 mg/m^2 in the GemOx arm. Ox dose was reduced to 85 mg/m^2 in case of grade 2 sensory peripheral neuropathy and temporarily discontinued in case of grade 3 sensory peripheral neuropathy. Patients would then continue to receive Gem monotherapy according to the same biweekly schedule until recovery to grade 1 neuropathy. In case of laryngopharyngeal dysesthesia, Ox infusion was prolonged to 6 hours and eventually stopped if further symptoms occurred during the following cycles.

Patients with metastatic disease received chemotherapy until evidence of disease progression, patient refusal, or unacceptable toxicity. Patients with locally advanced disease received at least 3 months of treatment. Then, concomitant radiochemotherapy (45 Gy in 25 fractions for 5 weeks, associated with a daily FU 250 mg/m^2 continuous infusion, and a boost of 10 Gy in 8 fractions restricted to the initial tumor volume) was recommended, but decisions regarding continuation of chemotherapy alone, surgery, or concomitant radiochemotherapy were decided on a case by case basis at the investigators' discretion.

Treatment Evaluations

Baseline assessment involved medical history, physical examination including evaluation of clinical symptoms, biologic analyses (CBC count, serum creatinine, bilirubin, AST, ALT, alkaline phosphatase, and CA-19.9 levels) performed within the week preceding treatment initiation, and tumor measurement (computed tomography scan) performed within 21 days of the start of treatment. During the treatment period, blood counts, evaluation of toxicity, and physical examination as well as record of PS, weight, pain assessment using a visual analog scale, and analgesic consumption to evaluate the clinical benefit were to be performed before each cycle of chemotherapy.

Tumor assessment by the same imaging method throughout the follow-up period, defined according to the WHO, was required in both arms every 2 months or earlier if clinically indicated. Because survival was the primary end point of the study, tumor response assessments were determined by the investigators and were not expert reviewed (unlike in the phase II trial). Clinical benefit was evaluated according to Andersen and Rothenberg's definition[10]; patients with less pain (at least $\geq$ 50% improvement from baseline) on a visual analog scale and/or decreased analgesic consumption ($\geq$ 50% reduction compared with baseline consumption) and/or improved Karnofsky PS ($\geq$ 20 points compared with baseline evaluation) without any worsening of any of these parameters for at least 4 consecutive weeks were considered as having a clinical benefit. If a patient was stable on both primary measures of clinical benefit (pain and PS), he or she was then classified as either a responder (weight gain $\geq$ 7% from baseline sustained for $\geq$ 4 weeks) or a nonresponder. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2. Progression-free survival (PFS) was calculated from the day of randomization until death or evidence of clinical progression or tumor progression as assessed by computed tomography scan measurement. Overall survival (OS) was calculated from the day of randomization until the date of death.

Statistical Analysis

Randomization was performed centrally, and the minimization method was used to balance treatment allocation according to center, stage of disease (locally advanced *v* metastatic), and PS (0 or 1 *v* 2). A total of 300 assessable patients was needed to demonstrate a 20% difference in OS at 8 months, from 30% of patients alive in the Gem arm (based on the experience of Burris et al[10]) to 50% of patients alive in the GemOx arm (based on our previous phase II experience), using a log-rank test at the two-sided 0.05

level with a power of 90%. All patients who received any study medication (Gem or GemOx) were included in the safety population. The per protocol population consisted of all randomized and eligible patients.

The primary efficacy variable was OS, which was defined as the time from randomization to death from any cause. Hazard ratios (HRs) and 95% CIs were calculated using the Cox proportional hazards model. Survival curves were drawn using the Kaplan-Meier method. The cutoff date used for the analysis was 1 year after the inclusion of the last patient (March 1, 2004). Secondary end points of the trial were response rate, clinical benefit response, PFS, and safety, according to investigator's assessment.

Log-rank tests and Kaplan-Meier estimations were performed for the analysis of both PFS and OS. Objective response and clinical benefit response rates were calculated with 95% CIs. χ^2 or Fisher's exact tests, when suitable, were used to compare qualitative data. Differences were assumed to be significant when $P < .05$. Cox proportional hazards modeling was used to examine the effect of various prognostic factors on OS according to the results of the univariate analysis.

RESULTS

Enrollment and Patient Characteristics

Between March 2001 and February 2003, a total of 326 patients were enrolled. Patients were randomly assigned equally between the Gem and GemOx treatment arms (163 patients each). A total of 13 patients were considered ineligible at inclusion. Reasons for ineligibility were neuroendocrine tumor (two patients), death before treatment initiation (two patients), high bilirubin level at baseline (eight patients), and withdrawal of consent before first cycle (one patient). Therefore, 313 patients (156 in the Gem arm and 157 in the GemOx arm) were both eligible and treated and were included in the per protocol population for both efficacy and safety analysis. Patient characteristics were well matched across treatment arms (Table 1). Of note, 30% and 32% of patients presented with a locally advanced disease in the Gem and GemOx arms, respectively.

Table 1. Baseline Characteristics of Patients

Characteristic	Gem Arm (n = 156)	GemOx Arm (n = 157)
Age, years		
Mean	60.1	61.3
Range	22-75	35-77
Sex, %		
Male	53	60
Female	47	40
PS, %		
0	28	31
1	54	52
2	18	17
Disease, %		
LA	30	32
M	70	68
T4 stage, %	10.2	9.9
Primary tumor, %		
Head	50	54
Body	37	27
Tail	13	19
Median CA-19.9 serum level, U/mL	1,424	965
Baseline pain, %		
VAS 0-2	47	49
VAS 2-4	27	24
VAS > 4	26	27

Abbreviations: Gem, gemcitabine; GemOx, gemcitabine and oxaliplatin; PS, performance status; LA, locally advanced; M, metastatic; VAS, visual analog scale.

Dose-Intensity

The median number of cycles received in the Gem arm was nine (standard deviation [SD], 6.4 cycles; range, one to 31 cycles), corresponding to a median duration of exposure of 11.2 weeks (SD, 10.3 weeks; range, 1 to 55 weeks); in the GemOx arm, the median number of cycles received was eight (SD, 4.8 cycles; range, one to 22 cycles), corresponding to a median duration of exposure of 17.3 weeks (SD, 11.1 weeks; range, 2 to 53 weeks). The relative dose-intensity of Gem was 81.1% in the Gem arm (SD, 16.4%; range, 1.7% to 106%) and 90.6% in the GemOx arm (SD, 11.8%; range, 56.4% to 110.6%); the relative dose-intensity of Ox in the GemOx arm was 87.1% (SD, 17.0%; range, 34.4% to 110.0%).

Safety

Neurosensory symptoms were experienced by 95% of patients but remained of mild to moderate intensity (grades 1 to 2) in 76% of patients. Grade 3 peripheral sensory neuropathy (Ox-limiting toxicity) was experienced by 19.1% of patients treated with GemOx. Regarding other toxicities, the overall tolerance of the GemOx combination versus Gem was acceptable, with a significant increase in toxicity observed only in the percentage of patients with grade 3 to 4 thrombocytopenia (14.0% *v* 3.2%, respectively) and vomiting (8.9% *v* 3.2%, respectively; Table 2). At least one episode of grade 3 to 4 toxicity was reported in 39.7%

Table 2. Summary of NCI-CTC Grade 3 to 4 Toxicities Per Patient

Toxicity	Gem Arm (%)	GemOx Arm (%)	*P*
Neutropenia	27.6	20.4	NS
Febrile neutropenia	1.3	1.3	NS
Thrombocytopenia	3.2	14.0	.0007
Anemia	10.3	6.4	NS
Nausea	5.8	10.2	NS
Vomiting	3.2	8.9	.03
Diarrhea	1.3	5.7	NS
Alopecia, grade 2	3.2	5.7	NS
Peripheral sensory neuropathy	0.0	19.1	.0001

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; Gem, gemcitabine; GemOx, gemcitabine and oxaliplatin; NS, not significant.

and 52.2% of patients in the Gem and GemOx arms, respectively ($P = .03$). No toxic death occurred. Two Gem-related interstitial pneumopathies were reported (one in each arm). Serious adverse events related to therapy were observed in 15 and 19 patients in the Gem and GemOx arms, respectively ($P = .50$). Serious adverse events not related to therapy were observed in 88 and 76 patients in the Gem and GemOx arms, respectively ($P = .16$).

Efficacy

Efficacy results for the per protocol population are listed in Table 3.

Response rate. GemOx was found to be significantly superior to Gem in terms of response rate (per protocol population, n = 313: 26.8% ± 7.1% *v* 17.3% ± 6.1%, respectively; $P = .044$; and assessable patients, n = 304: 28.2% ± 7.4% *v* 17.4% ± 6.1%, respectively; $P = .025$). This superiority of GemOx over Gem was observed in both the metastatic (26.4% *v* 18.3%, respectively) and locally advanced (27.4% *v* 14.9%, respectively) populations.

Clinical benefit response. GemOx was found to be significantly superior to Gem in terms of clinical benefit response (assessable patients, n = 292: 42.3% ± 8.3% *v* 28.0% ± 7.3%, respectively; $P = .01$; and per protocol population, n = 313: 38.2% ± 7.7% *v* 26.9% ± 7.1%, respectively; $P = .03$). This superiority of GemOx over Gem was observed in both the metastatic (34.9% *v* 23.9%, respectively) and locally advanced (45.1% *v* 34.0%, respectively) populations.

PFS. GemOx was found to be significantly superior to Gem in terms of median PFS (5.8 *v* 3.7 months, respectively; $P = .04$; HR, 1.287; 95% CI, 1.014 to 1.688; Fig 1. This superiority of GemOx over Gem was observed in both the metastatic (4.6 *v* 3.0 months, respectively) and locally advanced (7.4 *v* 5.3 months, respectively) populations.

OS. Median follow-up time at the date of analysis was 21 months; 136 patients (87.2%) and 133 patients (84.7%) were dead at that time in the Gem and GemOx arms, respectively; Fig 2. The 8-month survival probability, which served as a basis for the sample size calculation, was 45.3% in the Gem arm and 56.5% in the GemOx arm ($P = .05$). One-year survival probability was 27.8% in the Gem arm and 34.7% in the GemOx arm ($P = .22$). For the per protocol population (n = 313), median OS time was 7.1 months for Gem alone and 9.0 months for GemOx ($P = .13$; HR, 1.20; 95% CI, 0.95 to 1.54). For the intent-to-treat

Table 3. Summary of Efficacy Results (per protocol population)

Response and Survival	Gem (n = 156)	GemOx (n = 157)	*P*
RR, % of patients			
All patients, N = 313	17.3	26.8	.04
LA, n = 98	14.9	27.4	
M, n = 215	18.3	26.4	
CBR, % of patients			
All patients, N = 313	26.9	38.2	.03
LA, n = 98	34.0	45.1	
M, n = 215	23.9	34.9	
Median PFS, months			
All patients, N = 313	3.7	5.8	.04
LA, n = 98	5.3	7.4	
M, n = 215	3.0	4.6	
Median OS, months			
All patients, N = 313	7.1	9.0	.13
LA, n = 98	10.3	10.3	
M, n = 215	6.7	8.5	
8-Month survival, % of patients	45.3	56.5	.05
1-Year survival, % of patients	27.8	34.7	.22

Abbreviations: RR, response rate; LA, locally advanced; M, metastatic; CBR, clinical benefit response rate; PFS, progression-free survival; OS, overall survival; Gem, gemcitabine; GemOx, gemcitabine and oxaliplatin.

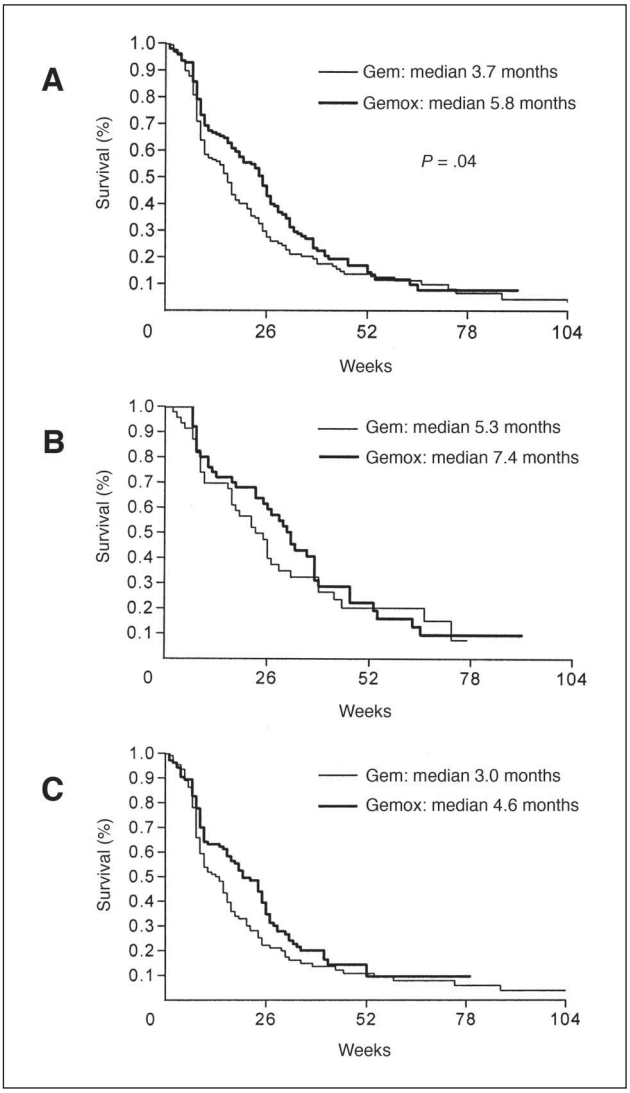

Fig 1. Progression-free survival curves. Gem, gemcitabine; GemOx, gemcitabine and oxaliplatin.

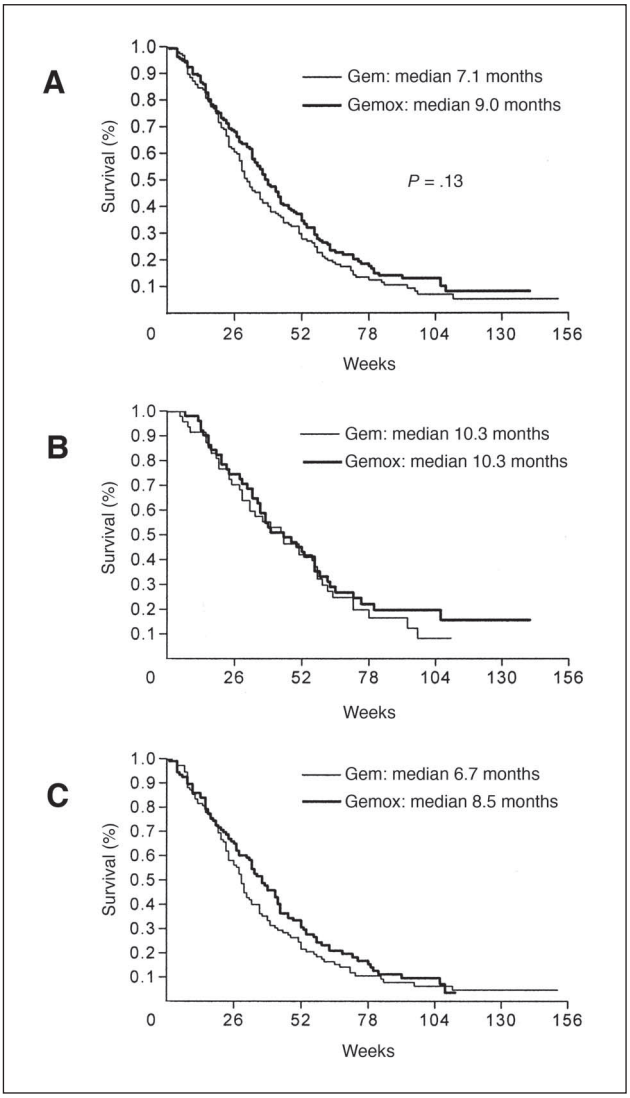

Fig 2. Overall survival curves. Gem, gemcitabine; GemOx, gemcitabine and oxaliplatin.

population (n = 326), median OS time was 6.9 months for Gem alone and 8.8 months for GemOx ($P = .15$; HR, 1.18; 95% CI, 0.94 to 1.51). For locally advanced patients (30% of total population), median survival times were identical in both arms (10.3 months), whereas for metastatic patients (70% of the total population), the median survival time was 6.7 months in the Gem arm and 8.5 months in the GemOx arm ($P = .17$; HR, 1.21; 95% CI, 0.91 to 1.63).

Radiation therapy. For locally advanced cancer patients, chemoradiotherapy was recommended after 3 months of chemotherapy in both arms in case of stable disease or response. The decision concerning chemoradiotherapy was at the discretion of each investigator. After chemoradiotherapy, no further treatment was to be administered. A total of 14 (29.8%) of 47 and 11 (21.6%) of 51 locally advanced patients in the Gem and GemOx arms, respectively, presented with progressive disease after 3 months or earlier and were not concerned by the chemoradiotherapy decision. For the remaining patients (with stable disease or tumor response), 11 (33.3%) of 33 and 16 (40.0%) of 40 patients in the Gem and GemOx arms, respectively, received chemoradiation.

Surgery. Two patients with locally advanced disease who responded after Gem and further chemoradiotherapy underwent surgery with curative intent. Both patients were in the Gem arm. One patient was still disease free more than 110 weeks after diagnosis, and the other patient relapsed 80 weeks after surgery.

Second-line therapy. At the time of disease progression, second-line chemotherapy was administered in 55.0% of the Gem patients and in 55.4% of the GemOx patients. The majority of Gem patients (74.0%) received a true cross-over (with Ox) or cross-over–like regimen (with platinum), whereas 31.1% of GemOx patients received a cisplatin-based regimen as second-line therapy.

Prognostic Factor Analysis

In a univariate analysis, CA-19.9 serum level more than 350 U/mL, metastatic disease, and PS of 2 at baseline were found to be adverse prognostic factors for survival. In the multivariate analysis, T4 stage (relative risk, 1.364; $P = .04$), CA-19.9 serum level more than 350 U/mL (relative risk, 1.383; $P = .02$), metastatic disease (relative risk, 1.394; $P = .018$), and PS of 2 (relative risk, 1.735; $P < .001$) were considered independent adverse prognostic factors for survival.

DISCUSSION

The demonstration by Burris et al[3] that single-agent Gem, compared with FU, provides clinical benefit (23.8% *v* 4.8%, respectively) and slightly improves OS (5.65 *v* 4.41 months, respectively) of patients with advanced pancreatic cancer has established this drug as standard treatment in this severe disease. Consistency of such results in terms of OS was later confirmed by randomized studies comparing Gem to other single agents.[11,12] Several trials have tested either the combination of this drug with other cytotoxics or the modulation of its duration of infusion, due to the saturable intercellular metabolism of Gem, which intracellular metabolism is saturable. This hypothesis was investigated in a randomized phase II trial that compared a 2,200 mg/m^2 dose of Gem as a 30-minute conventional infusion (days 1, 8, and 15 every 4 weeks) with a 1,500 mg/m^2 dose as a prolonged infusion (10 mg/m^2/min on days 1, 8, and 15 every 4 weeks). The prolonged infusion of Gem, compared with the conventional infusion, was associated with an improved efficacy (1-year survival rate, 28.8% *v* 9%, respectively; 2-year survival rate, 18.3% *v* 2.2%, respectively) at the price of higher rates of hematologic toxicity.[13] The

synergism observed between both Ox and Gem on cancer cell lines as well as the known activity of cisplatin in this indication have led the GERCOR group to conduct a phase II trial to evaluate the efficacy and tolerance of the GemOx combination in advanced pancreatic cancer.[9] In an attempt to optimize the combination, Gem was administered on day 1 and Ox was administered on day 2 after the observation that better activity was obtained in vitro with this schedule of administration.[4] In addition, the infusion of Gem was prolonged according to the results published by Tempero et al.[13] The expert reviewed response rate (30.6%) as well as the palliative effects (40% clinical benefit response) and survival (median survival, 9.2 months) observed with the GemOx combination have led us to further explore the efficacy of this combination in a phase III trial in which the control arm is the standard treatment of advanced or metastatic pancreatic cancer (weekly 30-minute intravenous administration of Gem). As a matter of fact, the Eastern Cooperative Oncology Group was discussing, at the same time, the design of a large phase III trial comparing Gem to GemOx in which a third arm of prolonged infusion of Gem alone was added to better define the role of the Gem mode of administration in the combination. This trial, the results of which are expected in 2006, will permit defining the respective contributions of prolonged Gem infusion and Ox addition in the GemOx combination. Other authors have also reported phase II data on various regimens of GemOx or FU and Ox.[14-18]

The results of the GemOx arm correlate completely with the results observed in the phase II study for all parameters, although tumor assessments were reviewed externally in the phase II study only. Clinical benefit, which was the primary end point of the Burris et al[3] study that had conferred to Gem the status of standard treatment, was superior in the GemOx arm in the current study, and tolerance of GemOx seems better than for other platinum-based combinations in this poor prognosis and rather fragile population. Nevertheless, despite the 9-month median OS observed with the GemOx combination, the OS difference between the two arms was not statistically significant. This could be partly explained by the lack of power resulting from the difference observed between the statistical assumptions and actual results obtained (OS of 7.1 *v* 9 months instead of the 6 *v* 8 months assumed in the protocol for Gem and GemOx, respectively). Furthermore, the high percentage of second-line therapies received might have confused the results; the same proportion of patients (> 50%) was able to receive second-line therapy in both arms, but possibly more active regimens, based on platinum compounds, were essentially administered in the Gem arm. Details on second-line therapies and their possible influence on OS will be provided in a separate article.

Other efficacy parameters (response rate, clinical benefit response, and PFS) were significantly in favor of GemOx, which was not the case for all three parameters in other reported phase III trials[19-25] (Table 4). However, direct comparison of these results cannot be made because of the difference in subpopulations enrolled (locally advanced and metastatic). As a matter of fact, the percentage of locally advanced patients in our trial is among the highest reported (but still in the range of European trials), and the benefit of treatment is not of the same magnitude in both subsets of patients. In metastatic patients, the 1.6-month improvement in median PFS translated into a 1.8-month advantage

Table 4. Summary of Phase III Trials Comparing Gemcitabine Alone to Combination With Another Compound

Study	Design	No. of Patients	Stage (%)		RR		PFS/TTP		OS	
			III	IV	%	*P*	Months	*P*	Months	*P*
Berlin et al[19]	Gem	327	10	90	5.6	NS	2.2	.022	5.4	NS
	Gem + FU				6.9		3.4		6.7	
Rocha-Lima et al[20]	Gem	360	13	81	4.4	< .001	3.0	NS	6.6	NS
	Gem + CPT-11		15	82	16.1		3.4		6.3	
Heinemann et al[21]	Gem	195	27	73	NA	—	2.5	.016	6.0	NS
	Gem + cisplatin				NA		4.6		7.6	
O'Reilly et al[22]	Gem	349	NA	NA	6.3	NS	3.8	NS	6.2	NS
	Gem + exatecan				8.2		3.7		6.7	
Richards et al[23]	Gem	565	10	90	9.1	.006	3.9	NS	6.3	NS
	Gem + pemetrexed		9	91	18.3		3.3		6.2	
Van Cutsem et al[24]	Gem	688	33	77	6	NS	3.6	NS	6.0	NS
	Gem + tipifarnib		34	76	8		3.7		6.4	
Bramhall et al[25]	Gem	239	NA	NA	11	NS	NA	—	5.5	NS
	Gem + marimastat				16		NA		5.5	
Present study	Gem	313	30	70	16.3	.044	3.7	.038	7.1	NS
	GemOx		32	68	26.8		5.8		9.0	

Abbreviations: Gem, gemcitabine; GemOx, gemcitabine and oxaliplatin; RR, response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival; NS, not significant; NA, not available.

in OS, whereas in locally advanced patients, median survivals were identical (10.3 months) despite a 2.1-month difference in median PFS (Figs 1 and 2). This could be explained, at least in part, by the chemoradiotherapy administered in nonprogressive locally advanced patients in both arms. Thus, one might question the interest of splitting these different populations in separate trials in the future.

Results of two phase II trials combining both Gem and inhibitors of either epidermal growth factor receptor (cetuximab) or vascular endothelial growth factor (bevacizumab) were recently reported.[26,27] Both trials showed interesting results on survival (9-month median survival, 37% 1-year survival rate for Gem plus bevacizumab and 32% 1-year survival rate for Gem plus cetuximab) that were in the range of what was observed with the GemOx combination. However, these interesting results are pending confirmation through randomized phase III trials. Results of the first of these phase III studies, which compares Gem plus erlotinib versus Gem alone, were recently released and showed a modest but statistically significant advantage in OS for the combination arm (median survival, 6.37 *v* 5.91 months, respectively; HR, 0.81; $P = .025$).[28]

Given the promising results of GemOx in metastatic pancreatic cancer patients (including a median survival of 8.5 months, which has never been observed in any previous phase III study) and in attempt to simplify its way of administration, the GERCOR is currently conducting a randomized phase II trial comparing the 2-day GemOx administration regimen to the same combination administered on day 1 only. A recently reported experience showed that the pharmacokinetic profile of both drugs did not show statistically significant differences between the alternate schedules of Gem administered before Ox and Ox administered before Gem.[29] Considering the interesting results of biologic agents, the next GERCOR randomized phase II will explore the addition of bevacizumab, erlotinib, or both to the GemOx combination.

Appendix

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The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Thierry André, Roche; Aimery de Gramont, Sanofi-Aventis. Honoraria: Christophe Louvet, Eli Lilly, Sanofi-Aventis; Roberto Labianca, Sanofi-Aventis; Pascal Hammel, Eli Lilly, Sanofi-Aventis; Gérard Lledo, Merck, Roche, Sanofi-Aventis; Thierry André, Eli Lilly, Sanofi-Aventis; Michel Ducreux, Sanofi-Aventis; Aimery de Gramont, Eli Lilly, Sanofi-Aventis. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

REFERENCES

1. Rosewicz S, Wiedenman B: Pancreatic carcinoma. Lancet 349:485-489, 1997

2. Evans DB, Abbruzzese JL, Rich TA: Cancer of the pancreas, in De Vita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed 5). Philadelphia, PA, Lippincott-Raven, 1997, pp 1054-1087

3. Burris HA, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15:2403-2413, 1997

4. Faivre S, Raymond E, Woynarowski JM, et al: Supraadditive effect of 2′,2′-difluorodeoxycytidine (gemcitabine) in combination with oxaliplatin in human cancer cell lines. Cancer Chemother Pharmacol 44:117-123, 1999

5. Culy RC, Clemett D, Wiseman LR: Oxaliplatin: A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. Drugs 60:895-924, 2000

6. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000

7. Louvet C, André T, Tigaud JM, et al: Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 20:4543-4548, 2002

8. Hoff PM, Fuchs CS: The experience with oxaliplatin in the treatment of upper gastrointestinal carcinomas. Semin Oncol 30:54-61, 2003

9. Louvet C, André T, Lledo G, et al: Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: Final results of a GERCOR multicenter phase II study. J Clin Oncol 20:1512-1518, 2002

10. Rothenberg ML, Moore MJ, Cripps MC, et al: A phase II trial of gemcitabine in patients with 5 FU-refractory pancreas cancer. Ann Oncol 7:347-353, 1996

11. Moore MJ, Hamm J, Dancey J, et al: Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21:3296-3302, 2003

12. Cheverton P, Friess H, Andras C, et al: Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naïve patients with advanced pancreatic cancer (APC). Proc Am Soc Clin Oncol 23:314s, 2004 (abstr 4005)

13. Tempero M, Plunkett W, Ruiz Van Haperen V, et al: Randomized phase II comparison of dose-intense gemcitabine: Thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402-3408, 2003

14. Alberts SR, Townley PM, Goldberg RM, et al: Gemcitabine and oxaliplatin for metastatic pancreatic adenocarcinoma: A North Central Cancer Treatment Group phase II study. Ann Oncol 14:580-585, 2003

15. Heinmann V, Golf A, Seipelt G, et al: Randomized trial of capecitabine plus oxaliplatin versus capecitabine plus gemcitabine plus oxaliplatin in advanced pancreatic cancer. J Clin Oncol 22:340s, 2004 (suppl 14, abstr 4108)

16. Van Laethem JL, Polu M, Marechal R, et al: Gemcitabine and oxaliplatin in gemcitabine-refractory advanced pancreatic cancer: A phase II study. J Clin Oncol 22:343s, 2004 (suppl 14, abstr 4119)

17. Ciruelos Gill EM, Castellano D, Paz-Ares L, et al: A phase II study of gemcitabine plus oxaliplatin in advanced pancreatic/ductal biliary adenocarcinoma administered every 2 weeks. Proc Am Soc Clin Oncol 22:366, 2003 (abstr 1469)

18. Ducreux M, Mitry E, Ould-Kaci M, et al: Randomized phase II study evaluating oxaliplatin alone oxaliplatin combined with infusional 5-FU and infusional 5-FU alone in advanced pancreatic carcinoma patients. Ann Oncol 15:467-473, 2004

19. Berlin J, Catalano P, Thomas J, et al: Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group trial E2297. J Clin Oncol 15:3270-3275, 2000

20. Rocha-Lima CMS, Green MR, Rotche R, et al: Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 22:3776-3783, 2004

21. Heinemann V, Quietzsch D, Gieseler F, et al: A phase III trial comparing gemcitabine plus cisplatin vs gemcitabine alone in advanced pancreatic carcinoma. Proc Am Soc Clin Oncol 22: 250, 2003 (abstr 1003)

22. O'Reilly M, Abou-Alfa G, Letourneau R, et al: A randomized phase III trial of DX-8951f (exatecan mesylate; DX) and gemcitabine (GEM) vs gemcitabine alone in advanced pancreatic cancer (APC). J Clin Oncol 22:314s, 2004 (suppl 14, abstr 4006)

23. Richards D, Kindler H, Oettle H, et al: A randomized phase III study comparing gemcitabine + pemetrexed versus gemcitabine in patients with locally advanced and metastatic pancreas cancer. J Clin Oncol 22:314s, 2004 (suppl 14, abstr 4007)

24. Van Cutsem E, Van de Velde H, Karasek P, et al: Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 8:1430-1438, 2004

25. Bramhall SR, Schulz J, Nemunaitis J, et al: A double blind placebo controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer 87:161-167, 2002

26. Xiong HQ, Rosenberg A, LoBuglio A, et al: Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: A multicenter phase II trial. J Clin Oncol 22:2610-2616, 2004

27. Kindler HL, Friberg G, Stadler WM, et al: Bevacizumab (B) plus gemcitabine (G) in patients with advanced pancreatic cancer: Updated results of a multi-center trial. J Clin Oncol 22:315s, 2004 (suppl 14, abstr 4009)

28. Moore MJ, Goldstein D, Hamm J, et al: Erlotinib improves survival when added to gemcitabine in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG). Proc 2005 Gastrointestinal Cancers Symposium, Orlando, FL, January 27-29, 2005 (abstr 77)

29. Airoldi M, Cattel L, Passera R, et al: Clinical and pharmacokinetic study of gemcitabine-oxaliplatin association in metastatic or locally advanced pancreatic adenocarcinoma. J Clin Oncol 22:141s, 2004 (suppl 14, abstr 2059)