Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301)

Laetitia Dahan,[1] Frank Bonnetain,[2] Marc Ychou,[3] Emmanuel Mitry,[4] Mohamed Gasmi,[5] Jean-Luc Raoul,[6] Stéphane Cattan,[7] Jean-Marc Phelip,[8] Pascal Hammel,[9] Bruno Chauffert,[10] Pierre Michel,[11] Jean-Louis Legoux,[12] Philippe Rougier,[4] Laurent Bedenne,[2] Jean-François Seitz,[1,13] for the Fédération Francophone de Cancérologie Digestive

See Commentary, p 1454

For numbered affiliations see end of article.

Correspondence to
Laetitia Dahan, Service d'Oncologie Digestive, Pôle Oncologie-Spécialités, CHU Timone, 264 rue Saint Pierre, 13385 Marseille cedex 5, France; laetitia.dahan@mail.ap-hm.fr

Presented at the 44nd annual meeting of the American Society of Clinical Oncology, 2009, Chicago.

L D and F B contributed equally to this work.

Received 20 April 2010
Accepted 8 June 2010

ABSTRACT

Purpose Gemcitabine is the standard chemotherapy for patients with metastatic pancreatic adenocarcinoma. Although the 5-fluorouracil (5FU), folinic acid and cisplatin combination (LV5FU2-CDDP) is an option, the optimal order of the regimens must be determined. The first strategic phase III trial comparing LV5FU2-CDDP followed by gemcitabine versus gemcitabine followed by LV5FU2-CDDP was conducted.

Methods Patients with metastatic pancreatic adenocarcinoma, performance status (PS) 0–2, without prior chemotherapy were randomly assigned (1:1) to receive either LV5FU2-CDDP followed by gemcitabine at disease progression or toxicity (Arm A), or the opposite sequence (Arm B). 202 patients had to be included and 170 deaths had to be observed to detect an expected improvement in median overall survival (OS) from 6.5 to 10 months in Arm A (two-sided $\alpha = 5\%$ and $\beta = 20\%$).

Results 202 patients were included (Arm A, 102; Arm B, 100). Median age, male/female ratio, PS 0–1 and previous surgery were similar in the two arms. After a median follow-up of 44 months, median OS in Arm A was 6.6 months versus 8.0 months in Arm B ($p = 0.85$). Median progression-free survival was similar between Arms A and B. More grade 3/4 toxicities were observed when LV5FU2-CDDP was administered as a first-line treatment compared with gemcitabine: 79% versus 64% ($p = 0.018$).

Conclusion This trial did not show any strategic advantage to using LV5FU2-CDDP as a first-line treatment and suggests that gemcitabine remains the standard first-line treatment. Sixty-one per cent of patients were able to receive a second line of chemotherapy.

Significance of this study

What is already known about this subject?

- After the study by Burris *et al*, gemcitabine-based chemotherapy became the gold standard for systemic treatment of advanced pancreatic cancer.
- Most of the subsequent randomised trials comparing gemcitabine with gemcitabine combined with chemotherapy or biotherapy failed to demonstrate a clinical benefit.
- This study tries to answer the question of an intensified first-line treatment.
- The role of a second line of treatment for metastatic cancer remained debated and there is no standard in patients with metastatic pancreatic adenocarcinoma that progresses after gemcitabine-based first-line treatment.

What are the new findings?

- This is the first controlled trial to evaluate systematic second-line chemotherapy in patients with disease progression after the first line and its possible influence on overall survival (OS).
- This randomised multicentre phase III trial was designed to compare OS for both therapeutic sequences.
- No significant difference in either progression-free survival or OS was observed between the two treatment arms.

How might it impact on clinical practice in the foreseeable future?

- Gemcitabine was better tolerated when administrated as a first-line treatment and remains the standard first-line treatment.
- A high percentage of patients were able to receive second-line chemotherapy in this study.
- A platinum-based regimen could be used for second-line treatment.

INTRODUCTION

Pancreatic adenocarcinoma is a highly malignant disease, representing the fifth most common cause of death from cancer in western countries, with <5% of patients still living at 5 years. Only 10–20% of patients are eligible for surgery at diagnosis and approximately half of the remaining patients have a non-resectable tumour.[1]

After the study by Burris *et al*.[2] showing that gemcitabine-based chemotherapy was more effective than bolus 5-fluorouracil (5FU), the former became the gold standard for systemic treatment of advanced pancreatic cancer. However, the median survival is still only 5.6 months.[2] Numerous studies have tried to increase the efficacy of chemotherapy by combining gemcitabine with others drugs, but none of the regimens evaluated in phase III trials has shown an increase in overall survival (OS).[3–9] Only one randomised trial including 569 patients comparing gemcitabine with gemcitabine combined with erlotinib showed a modest but significant increase in OS in the erlotinib arm (6.24 months vs 5.91 months) when gemcitabine was combined with erlotinib.[10]

Cisplatin combined with 5FU appears promising in metastatic pancreatic carcinoma, with a 26% response rate with a median survival of 7 months in a phase II trial.[11] In a randomised trial comparing 5FU with 5FU plus cisplatin, FU-CDDP was better than FU for response and progression-free survival (PFS) but not OS.[12] However, this regimen had serious toxic side effects. A phase II study using a combination of 5FU plus cisplatin with a bimonthly LV5FU2-cisplatin schedule (LV5FU2-CDDP) was better tolerated with a promising OS (9 months).[13] As a result, we compared this regimen with gemcitabine alone as first-line treatment. In addition we wanted to explore the role of a second line of treatment for this cancer.

This paper reports the final results of this FFCD (Fédération Francophone de Cancérologie Digestive) phase III trial comparing two successive lines of chemotherapy.

PATIENTS AND METHODS

Patient selection

Eligibility criteria were: proven metastatic pancreatic adenocarcinoma by histological or cytological biopsy, at least one measurable metastasis ≥10 mm on CT or MRI or ≥20 mm with a conventional scan. The targeted metastasis should not have been treated by radiotherapy. All patients gave written informed consent to participate, were over 18, had a WHO performance status (PS) ≤2 and a life expectancy of >2 months. Adequate bone marrow (absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l), liver function (total bilirubin < 50 μmol/l, alkaline phosphatases < ×ULN (upper limit if normal), previous biliary stenting was allowed) and renal function (creatinine clearance >60 ml/min) were required.

Exclusion criteria were: previous palliative or adjuvant chemotherapy, prior radiotherapy <4 weeks, brain metastases, a medical history of malignant tumours, pregnant women or woman who were breast feeding, and locally advanced cancer with no evidence of metastases.

The protocol was approved by the Regional Ethics Committee (Marseille, France).

Study design and randomisation

Clinical and biological investigation

Pretreatment evaluation included a full medical history, physical examination, haematological and biochemical analysis, including quality of life (QoL) with the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30).

All eligible patients were randomised 1:1 through a minimisation program at the FFCD centre (Dijon): to either Arm A, LV5FU2-CDDP followed by gemcitabine after progression; or Arm B, gemcitabine followed by LV5FU2-CDDP after progression.

Patients were stratified according to WHO PS (0, 1 vs 2), tumour localisation (head vs other) and participating institutions (centre).

Treatment plan

LV5FU2-CDDP included a 2 h infusion of leucovorin (LV) 200 mg/m^2 followed by 5FU as a bolus 400 mg/m^2 then a 46 h infusion of 2400 mg/m^2 with cisplatin 50 mg/m^2 as a 2 h infusion on day 1, every 2 weeks.

Gemcitabine included 1000 mg/m^2 as a 30 min weekly infusion for 7/8 weeks and then a weekly infusion for 3/4 weeks according to a classic Burris regimen.

In the case of disease progression during the first line of treatment, second-line chemotherapy was initiated until progression occurred.

Dose adjustment

If grade 3 or 4 toxicity occurred treatment was interrupted until toxicity had decreased to ≤grade 2. Treatment was then begun again with a 25% reduction in the initial dosage. If grade 3 or 4 toxicity occurred again treatment was discontinued. Recovery of renal function to grade 0 was necessary to continue cisplatin with a 25% dose reduction.

Evaluation and follow-up

All toxicities were graded according to National Cancer Institute common toxicity (NCI-CTC) criteria (v3.0). Serious adverse events were also recorded within 24 h.

After randomisation, a complete clinical examination and full laboratory investigations were performed every 2 weeks. Platelets, white blood cells (WBC) and haemoglobin were collected each week from patients receiving gemcitabine.

Radiological assessment (abdominal and thoracic CT scan) and tumour marker (carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9) evaluations were performed every 8 weeks. The tumour response was classified according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria based on imaging results. After ending treatment, follow-up information including a clinical examination and QoL assessment was available for all patients every 8 weeks until disease progression or death.

Statistical methods

This randomised multicentre phase III trial was designed to compare OS as the primary end point. OS was defined as the interval between randomisation and death (all causes). To detect an expected improvement in median OS from 6.5 (Arm B) to 10 months in arm A (two-sided $\alpha = 5\%$ and $\beta = 20\%$), 202 patients had to be included over 32 months (including 5% of lost to follow-up) to observe 170 deaths. The minimum follow-up for the last included patient was 13 months.

Secondary end points included:

– PFS was defined as the interval between randomisation and the first disease progression or death (all causes). Patients alive without progression were censored.

– Second-line PFS (PFS2) was defined as the interval between randomisation and progression or death (all cause) during second-line treatment. Patients alive without progression during second-line treatment were censored. In patients receiving only one line of treatment, PFS2 was defined as the interval between randomisation and the first disease progression or death (all causes).

– Proportion of patients receiving a second line.

– Tolerance for each line.

– The results of QoL assessed by EORTC QLQ-C30 will be presented in a later publication.

All analyses were performed on a strict intent to treat principle. The safety population, defined as all patients receiving at

least one dose of treatment with an available toxicity report, was used to compare toxicities.

Qualitative and continuous variables were described using percentage, means (SD) and medians (minimum − maximum), respectively, and then compared using the χ^2 or Fisher exact test and the Mann–Whitney test, respectively. Median follow-up was calculated according to the reverse Kaplan–Meier estimates. Survival curves were plotted using Kaplan–Meier estimates and were compared using log-rank tests and stratified log-rank tests. The unstratified and stratified univariate Cox models were used to calculate the HR with a 95% CI. All analyses were performed using Stata software (V10; StataCorp, College Station, Texas, USA) at the 0.05 level of significance.

RESULTS

Between August 2003 and May 2006, in 33 French centres, 102 patients and 100 patients were included in Arm A (first-line LV5FU2-CDDP) and Arm B (first-line gemcitabine), respectively. Three patients in Arm B did not meet the major inclusion criteria and had received prior chemotherapy (two adjuvant and one palliative chemotherapy). Twenty-six patients and 24 patients did not meet minor biological or haematological eligibility criteria in Arms A and B, respectively, and three patients were lost to follow-up in Arm A. However, the 202 patients were included in the intent to treat analyses (figure 1). The median follow-up was 44 months.

Patient characteristics

Patient characteristics are summarised in table 1. Arms A and B were well matched. In Arms A and B the median age was 62 and 65 years and WHO PS 0–1 was 77% and 83%, respectively. Sex, biological markers, prior treatments, and sites of metastases were well balanced. However, one patient in Arm A and two patients in Arm B had received radiotherapy >4 weeks before randomisation. Mean CEA and CA 19-9 levels were also similar in each arm

Treatment delivery

One patient in Arm A and four patients in Arm B did not receive at least one dose of chemotherapy due to complications.

As shown in table 2, the median duration of first-line treatment was significantly longer in patients receiving gemcitabine than in those receiving LV5FU2-CDDP as the first-line treatment: 10 weeks versus 5 weeks ($p = 0.0001$). Furthermore, the median duration of second-line treatment was significantly longer in patients receiving gemcitabine than in those receiving LV5FU2-CDDP as a second-line treatment: 8 versus 4 weeks ($p = 0.044$)

Toxicity

The distribution of maximum grade 3/4 toxicities in each arm according to the line of chemotherapy is shown in table 3. This table shows significant differences in haematological grade 3/4 toxicities when LV5FU2-CDDP was administered as the first line of treatment compared with gemcitabine as the first line: 50% in Arm A versus 35% in Arm B ($p = 0.03$). While no differences were observed for non-haematological and nausea/vomiting grade 3/4 toxicities, the occurrence of all grade 3/4 toxicities was significantly more frequent when LV5FU2-CDDP rather than gemcitabine was administered as the first line of treatment: 79% in Arm A versus 64% in Arm B ($p = 0.018$).

Figure 1 CONSORT diagram.

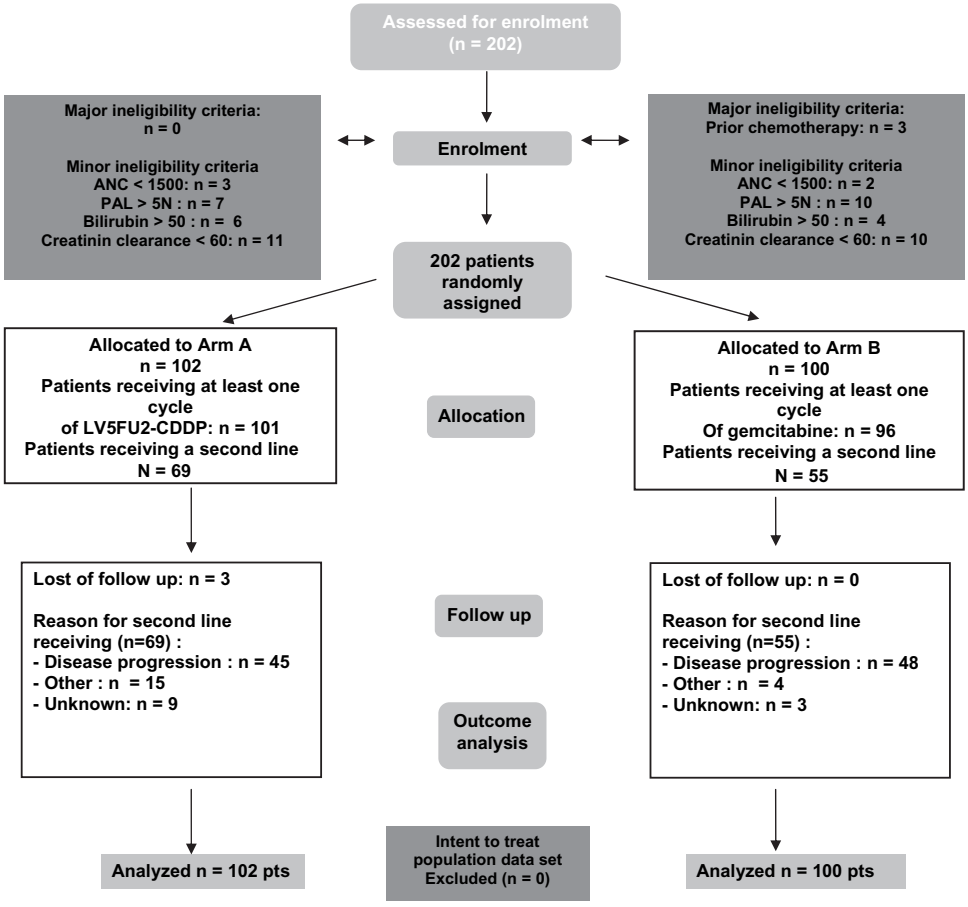

Table 1 Patients' demographics and clinical characteristics.

	Arm A (LV5FU2-CDDP in first line)		Arm B (gemcitabine in first line)	
	n	%	n	%
Patients	102		100	
Female sex	37	36	35	36
WHO PS				
0	28	27	30	30
1	51	50	53	53
2	22	21	14	14
Not determined	1	1	3	3
Primary tumour location				
Head	57	56	49	49
Other	44	43	50	50
Unknown	1	1	1	1
Site of metastases				
Liver	87	85	90	90
Lung	15	15	12	12
Lymph nodes	18	18	24	24
Peritoneum	11	11	17	17
Other	7	7	8	8
Prior treatment				
Chemotherapy	0	0	3	3
Radiotherapy	1*	1	2*	2
Surgery	23	23	27	27
Resection	13	57	14	40
Drainage	4	17	8	30
Others	6	26	6	22
Radiological/endoscopic drainage	22	22	11	11
Duodenal stenting	10	10	5	5
Age (years)	Median (min–max) 62 (40–84)		Median (min–max) 65 (39–81)	
Biological tumorous marker				
CEA (ng/ml)	9 (0–2224)		7(1–3604)	
CA 19-9 (UI/ml)	565(0–862200)		560(1–156649)	

*Radiotherapy >4 weeks before randomisation.
CA 19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination; PS, performance status.

Haematological grade 3/4 toxicities were increased when gemcitabine was administered as the second line compared with LV5FU2-CDDP: 58% in Arm A versus 33% in Arm B ($p = 0.004$) probably because of a decline of the bone marrow due an intensified first line. In contrast, nausea/vomiting grade 3/4 toxicities tended to be less frequent in Arm A: 4% versus 15% in Arm B ($p = 0.065$).

In patients receiving two lines of treatment (69 patients in Arm A and 55 patients in Arm B) significantly ($p = 0.007$) more grade 3/4 haematological toxicities were observed when gemcitabine was administered as the second line (arm A) (n=40, 58%) than with gemcitabine as the first line (Arm B) (n=19, 35%). Occurrence of all grade 3/4 toxicities was also significantly ($p= 0.017$) more frequent when gemcitabine was administered as a second line: 74% in Arm A (N=51) versus 55% in Arm B (N=30). However, no differences were observed for non-haematological or nausea/vomiting grade 3/4 toxicities.

In contrast, there were significantly ($p = 0.004$) more grade 3/4 haematological toxicities when LV5FU2-CDDP was administered as the first-line treatment (n=41, 59%) than with LV5FU2-CDDP administered as a second-line treatment (n=18, 33%). No differences were observed for non-haematological and nausea/vomiting grade 3/4 toxicities, resulting in no significant differences in grade 3/4 toxicities ($p = 0.16$) when LV5FU2-CDDP was administered as second or first line of treatment: 81% in Arm A (n=56) versus 69% in Arm B (n=38).

Table 2 Treatment administration

	LV5FU2-CDDP	Gemcitabine	p Value*
Line 1	Arm A	Arm B	
	N = 102	N = 100	
Patients with at least 1 administration	101(99%)	96 (96%)	0.21
Median duration of treatment in weeks (n = 96)	5 (0.1–96) (n = 96)	10 (1–64) (n = 93)	0.0001
Line 2	Arm B	Arm A	
	N = 100	N = 102	
Patients with at least one administration	55(55%)	69 (68%)	0.11
Median duration of treatment in weeks	4 (0.1–74) (n = 53)	8 (1–21) (n = 63)	0.044

*All two-sided Fisher exact tests or Wilcoxon rank-sum (Mann–Whitney) test.
LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination.

Table 3 Toxicities according to WHO criteria

N	LV5FU2-CDDP	Gemcitabine	p Value*
Line 1	Arm A	Arm B	
	N=101	N=96	
All toxicities	80 (79%)	61 (64%)	0.018
Haematological toxicities	50 (50%)	33 (35%)	0.03
Non-haematological toxicities	54 (53%)	44 (46%)	0.317
Nausea and vomiting	13 (13%)	8 (8%)	0.359†
Line 2	Arm B	Arm A	
	N=55	N=69	
All toxicities	38 (69%)	51(74%)	0.476
Haematological toxicities	18 (33%)	40 (58%)	0.004
Non-haematological toxicities	28 (51%)	35 (51%)	0.828
Nausea and vomiting	8 (15%)	3 (4%)	0.065†
Overall toxicities (lines 1 and 2)	Arm A	Arm B	
	N=101	N=96	
All toxicities	87 (86%)	77 (80%)	0.256
Haematological toxicities	60 (59%)	41 (43%)	0.015
Non-haematological toxicities	70 (69%)	60 (63%)	0.311
Nausea and vomiting	14 (14%)	15 (16%)	0.748
Toxicities grade 3/4	Line 1	Line 2	p
LV5FU2-CDDP	Arm A	Arm B	
	N=69	N=55	
All toxicities	56 (81%)	38 (69%)	0.16
Haematological toxicities	41 (59%)	18 (33%)	0.004
Gemcitabine	Arm B	Arm A	
	N=55	N=69	
All toxicities	30 (55%)	51(74%)	0.017
Haematological toxicities	19 (35%)	40 (58%)	0.007

*All two side Pearson tests without missing value modality.
†All two-sided Fisher exact tests.
LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination.

Number of patients receiving second-line treatment

Table 4 shows that 69 patients (68%) and 55 patients (55%) received a second line of chemotherapy in Arms A and B, respectively (non-significant). However, the reasons for the second line of chemotherapy were mainly ($p = 0.006$) due to progression in Arm B (48 patients, 87%) compared with Arm A (45 patients, 65%). Other reasons for changing the first line of treatment were toxicity in 12 patients in Arm A (17%) and 3 patients in Arm B (6%) ($p = 0.006$). Others reasons in Arm A were a poor general condition (1 patient), stroke (1patient), weight loss (1 patient) and unknown (9 patients). Other reasons in Arm B were pain (1 patient) and unknown causes (3 patients).

Table 4 Response and survival to treament according to the group of treatment

	LV5FU2-CDDP Arm A N=102		Gemcitabine Arm B N=100		
	n	%	n	%	p Value
Best tumorous response in second line	N= 69		N = 55		0.8*
Complete response (CR)	0	0	1	2	
Partial response	7	10	3	5	
Stable disease	19	28	21	38	
Progression	25	36	21	38	
Not evaluable	0	0	1	2	
Unknown	18	26	8	15	
Best tumorous response in first line	N = 102		N = 100		
Complete response (CR)	3	3	3	3	
Partial response	12	12	16	16	
Stable disease	33	32	29	29	
Progression	27	27	25	25	
Not evaluable	3	3	1	1	
Unknown	24	24	26	26	
Overall best tumorous response					
Complete response (CR)	3	3	4	4	
Partial response	16	16	18	18	
Stable disease	39	38	37	37	
Progression	24	23	17	17	
Not evaluable	2	2	1	1	
Unknown	18	18	23	23	
Progression-free survival (PFS)					
Median PFS in months (95% CI)	3.4 (2.4 to 4.4)		3.5 (2.4 to 4.1)		0.67†
Median PFS in months (95% CI) after second line	5.03 (4.3 to 5.9)		5.8 (4.3 to 7.8)		0.61†
Overall survival (OS):					
Median OS in months (95% CI)	6.7 (5.4 to 8.6)		8.03 (5.9 to 9.8)		0.83†
1 year OS	28.8% (20.4% to 37.8%)		32.7% (23.7% to 42.0%)		
2 years OS	7.5% (3.2% to 14.1%)		4.1% (1.3% to 9.4%)		
Death	94		92		98
Death without registered progression	30	29	32	32	
Alive without registered progression	3	3	0	0	
Second line					
Patients receiving a second line	69	68	55	55	0.13*
Second line due to progression	45	65	48	87	0.006*

*χ^2 or Fisher exact test.
†Log-rank test.
LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combinatio

The second-line treatment was stopped due to disease progression in 44 patients (64%) in Arm A and 34 patients (62%) in Arm B.

Best response during treatment

During the first line of treatment in Arm A, 15 patients had an objective response (3 complete responses and 12 partial responses). In arm B, 19 patients had an objective response (3 complete responses and 16 partial responses).(table 4)

During the second line of treatment, 7 patients had a partial response in Arm A and 4 patients had an objective response (1 complete response, 3 partial responses) in Arm B.

Overall, 19 patients had an objective response (3 complete responses, 16 partial responses) and 39 patients had stable disease in Arm A while 22 patients had an objective response (4 complete responses, 18 partial responses) and 37 patients had stable disease in Arm B. We observed 24 and 17 progressions in Arms A and B, respectively, as the best response. No differences were observed for tumour control according to first or second line of administration (table 4).

Overall survival

At the cut-off date, 192 patients had died, 94 (92%) and 98 (98%) in Arms A and B, respectively (table 4). As shown in figure 2, OS did not differ with the treatment sequence (HR 0.97 (95% CI 0.73 to 1.29), log-rank p = 0.83). Median OS was 6.7 months (95% CI 5.4 to 8.6) in Arm A and 8.03 months (95% CI 5.9 to 9.8) in Arm B (figure 2).

The 1 year OS rate was 28.8% (95% CI 20.4% to 37.8%) in Arm A and 32.7% (95% CI 23.7% to 42.0%) in Arm B, and the 2 year OS rate was 7.5% (95% CI 3.2% to 14.1%) in Arm A and 4.1% (95% CI 1.3% to 9.4%) in Arm B.

Progression-free survival

At the cut-off date, 69 patients (68%) and 68 patients (68%) had disease progression in Arms A and B, respectively. Moreover, 30 patients in Arm A and 32 patients in Arm B died without reported disease progression. The median PFS was 3.4 months (95% CI 2.4 to 4.4) in arm A and 3.5 months (95% CI 2.4 to 4.1) in Arm B (HR 1.06 (95% CI 0.8 to 1.4), log-rank p=0.67) (figure 3A).

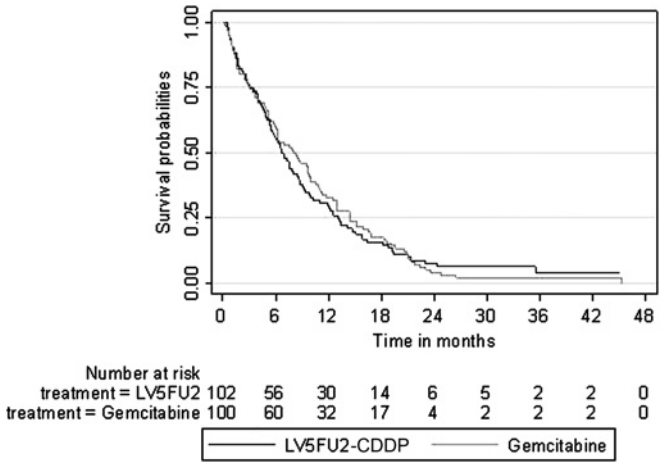

Figure 2 Overall survival according to treatment arm (Kaplan–Meier estimation); intent to treat population. LV5FU2-CDDP arm: 5-fluorouracil, folinic acid and cisplatin combination followed by gemcitabine. gemcitabine arm: gemcitabine followed by LV5FU2-CDDP.

PFS1 and PFS2 treatment

In patients receiving two lines of treatment due to progression, the median PFS1 was 2.6 months (95% CI 2.0 to 4.9) in Arm A and 3.6 months (95% CI 2.5 to 5.5) in Arm B (log-rank p=0.38). The univariate Cox HR was 0.76 (95% CI 0.51 to 1.18).

The median PFS2 was similar in the intent to treat population: 5.03 months (95% CI 4.3 to 5.9) in Arm A and 5.8 months (95% CI 4.3 to 7.8) in Arm B (log-rank p=0.61) (figure 3B). The univariate Cox HR was 0.93 (95% CI 0.70 to 1.22). When we explored PFS2 in patients receiving two lines, the median PFS2 was 6.03 months (95% CI 5.1 to 9.0) in Arm A and 8.8 months (95% CI 6.0 to 9.8) in Arm B (log-rank p=0.19 and stratified log-rank p = 0.03).

DISCUSSION

The study by Burris *et al*[2] showing that gemcitabine provides a clinical benefit compared wiht 5FU and improves OS in patients with advanced pancreatic cancer has established this regimen as the standard first-line treatment. We investigated alternative approaches due to the lack of effective combinations with gemcitabine when this trial was begun. Encouraging results observed with the combination of 5FU plus cisplatin in a phase II trial prompted the initiation of the present phase III trial.[13] The current study shows that OS and PFS were not different in the two arms. Moreover, gemcitabine was better tolerated when administrated as a first-line treatment, with significantly fewer cases of grade 3/4 haematological toxicity. This study confirms that gemcitabine is clearly the standard, with results in this study even better than those in the Burris study.

This is the first randomised phase III trial to evaluate a chemotherapy strategy with a second line of treatment in the treatment plan. At disease progression, the second line was administered in 68% of patients who received first-line LV5FU2-CDDP treatment (Arm A) and in 55% of patients in Arm B. Most Arm B patients received a second line of treatment for progression (87%); in contrast, toxicity was the cause of change in a significant percentage of patients in Arm A (33%), and this difference was statistically significant. The combination of 5FU plus cisplatin caused frequent and sometimes severe nausea and vomiting, even when adequate prophylactic antiemetic treatment was given, and these adverse side effects affected patient compliance and explained the higher percentage of second-line treatments in Arm A. Finally, our results do not support the role of 5FU plus cisplatin as a first line treatment, thus gemcitabine remains the standard of chemotherapy. This study is consistent with recent results published by Colucci *et al*[14] which showed that gemcitabine plus cisplatin was not superior to gemcitabine alone.

At present, there is no standard in patients with metastatic pancreatic adenocarcinoma that progresses after gemcitabine-based first-line treatment. Although several phase II trials evaluating second-line chemotherapy can be found in the medical literature, definitive conclusions cannot be drawn from these results.[15–31] Oxaliplatin, a platinum-based compound, is better tolerated than cisplatin which is active in several gastrointestinal tumours. A statistically significant increase in OS was found in the randomised CONKO 003 phase III trial with oxaliplatin combined with an 5FU regimen as the second line of treatment, compared with the best supportive care.[32] A randomised phase III study, presented at the annual ASCO 2008

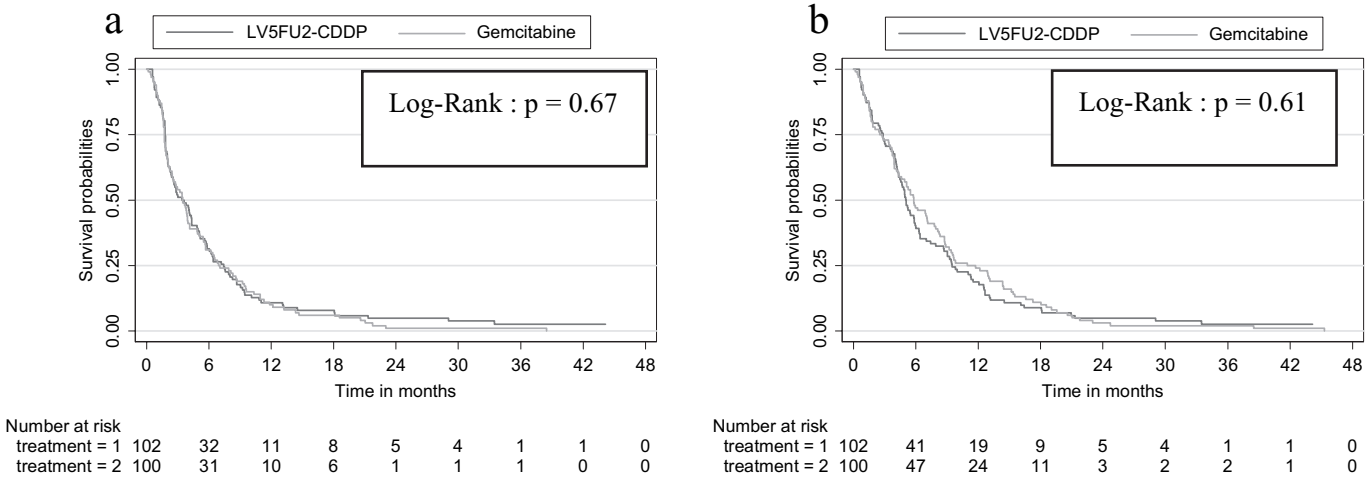

Figure 3 Progression-free survival (A) and progression-free survival in second line. (B) According to treatment arm (Kaplan–Meier estimation); intent to treat population. LV5FU2-CDDP arm: 5-fluorouracil, folinic acid and cisplatin combination followed by gemcitabine. Gemcitabine arm: gemcitabine followed by LV5FU2-CDDP.

meeting, compared 5FU with 5FU combined with oxaliplatin and showed a significant increase in OS (13 vs 26 weeks; $p = 0.014$).[33]

This is the first controlled trial to evaluate systematic second-line chemotherapy in patients with disease progression after the first line and its possible influence on OS. A high percentage of patients (61%) were able to receive second-line chemotherapy in this study. However, with only 69 and 55 patients in the respective arms receiving second-line treatment, a dedicated trial to assess specifically the efficacy of second-line treatment could be proposed.

The results seem interesting, with an OS of 8 months in the gemcitabine then LV5FU2-CDDP arm. These results were observed in a multicentre phase III study in unselected metastatic patients; however, in this setting, the association of 5FU andcisplatin may not be the best choice.

In conclusion this study did not show that LV5FU2-CDDP was better than gemcitabine as the first-line treatment in advanced pancreatic cancer. No significant difference in either PFS or OS was observed between the two treatment arms. Gemcitabine remains the standard for first-line chemotherapy in patients with unresectable metastatic tumours. A platinum-based regimen could be used for second-line treatment and oxaliplatin combined with 5FU seems to be the best candidate.

Author affiliations
[1]Assistance Publique-Hôpitaux de Marseille, Hôpital Timone, Université de la Méditerranée, Marseille, France
[2]Unité de Biostatistique et de Méthodologie FFCD, INSERM U866, Dijon, France
[3]Centre Val D'Aurelle, Montpellier, France
[4]Assistance Publique-Hôpitaux de Paris, Hôpital Ambroise Paré, Boulogne, UFR médecine PIFO, Université Versailles Saint-Quentin, France
[5]Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Université de la Méditerranée, Marseille, France
[6]Department of Medical Oncology, Centre E Marquis, Rennes and European University in Brittany, Rennes, France
[7]Hôpital Huriez, CHRU, Lille, France
[8]CHU Grenoble, France
[9]Hopital Beaujon, Clichy, France
[10]Centre François Leclerc, Dijon, France
[11]CHU, Rouen, France
[12]Centre Hospitalier Régional, Orléans, France
[13]CIC 9502, AP-HM, Marseille, France

Acknowledgements We are grateful to the patients who participated in this study. We thank all of the investigators who participated in this study: E Boucher, J L Jouve, O Bouché, P L Etienne, P Texereau, A Azzedine, D Auby, B Denis, T Aparicio, C Mariette, M Pauwels, J P Lagasse, C Lombard-Bohas, N Abdelli, P Brulet, D Gargot, D Pere Verge, J P Triboulet, H Perrier, A Patenotte, O Boulat, A M Queuniet, B Landi, K Imani, B Buecher, J Charneau and F Ghiringhelli. We also thank the CRAs of the FFCD: Ms C Choine, Mr H Fattouh, Ms F Guiliani, Ms A Kodjo, Mr N Le Provost, Ms M Moreau and Ms S Ngassam and Ms Cécile Girault, administrative executive of the FFCD. We thank Philip Bastable and Dale Lebrec for the help in revising the manuscript. We are grateful to Assistance Publique—Hôpitaux de Marseille which promoted the trial.

Competing interests None.

Ethics approval This study was conducted with the approval of the Regional Ethics Committee (Marseilles, France).

Contributors Manuscript writing: LD and FB. Review: LD, FB, JLR, EM, PR, JLL, SC, PH, BC, JFS. Data management: FB, LD. Protocol writing: JFS, JLL, PH, PR, LB, MY, EM, BC, LD, FB. Investigators: LD, MY, EM, MG, JLR, SC, JMP, PH, BC, PM, JLL, PR, LB, JFS. Administrative support: LB. Final responsibility for the decision to submit for publication: LD and FB.

Provenance and peer review Not commissioned; externally peer reviewed.

RÉFÉRENCES

1. **Gudjonsson B.** Cancer of the pancreas. 50 years of surgery. *Cancer* 1987;**60**:2284—303.
2. **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 pancreas cancer: a randomized trial. *J Clin Oncol* 1997;**15**:2403—13.
3. **Louvet C,** Labianca R, Hammel P, *et al*. 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. *J Clin Oncol* 2005;**23**:3509—16.
4. **Abou Alfa GK,** Letourneau R, Harker WG, *et al*. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 2006;**24**:4441—7.
5. **Rocha Lima CM,** 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* 2004;**22**:3776—83.
6. **Heinemann V,** Quietzsch D, Gieseler F, *et al*. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;**24**:3946—52.
7. **Oettle H,** Richards DA, Ramanathan RK, *et al*. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol* 2005;**16**:1639—45.
8. **Philip PA,** Benedetti J, Fenoglio-Preiser C, *et al*. Phase III study of gemcitabine plus cetuximab versus gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma: SWOG S0205 study. *Proc Am Soc Clin Oncol* 2007;**25**:4509.
9. **Kindler HL,** Niedzwiecki D, Hollis D, *et al*. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in patients with advanced pancreatic cancer: a preliminary analysis of cancer and leukemia group B (CALGB). *Proc Am Soc Clin Oncol* 2007;**25**:4508.
10. **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.
11. **Rougier P,** Zarba JJ, Ducreux M, *et al*. Phase II study of cisplatin and 120-hour continuous infusion of 5-fluorouracil in patients with advanced pancreatic adenocarcinoma. *Ann Oncol* 1993;**4**:333—6.
12. **Ducreux M,** Rougier P, Pignon JP, *et al*. A randomised trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma. *Ann Oncol* 2002;**13**:1185—91.
13. **Taieb J,** Lecomte T, Ezenfis J, *et al*. 5-FU, folinic acid and cisplatin (LV5FU2-P) for unresectable pancreatic cancer. *Gastroenterol Clin Biol* 2002;**26**:605—9.
14. **Colucci G,** Labianca R, Di Costanzo F, *et al*. Gruppo Oncologico Italia Meridionale (GOIM); Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD); Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010;**28**:1645—51.
15. **Rothenberg ML,** Moore MJ, Cripps MC, *et al*. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol* 1996;**7**:347—53.
16. **Mitry E,** Ducreux M, Ould-Kaci M, *et al*. Oxaliplatin combined with 5-FU in second line treatment of advanced pancreatic adenocarcinoma. Results of a phase II trial. *Gastroenterol Clin Biol* 2006;**30**:357—63.
17. **Oettle H,** Arnold D, Esser M, *et al*. Paclitaxel as weekly second-line therapy in patients with advanced pancreatic carcinoma. *Anticancer Drugs* 2000;**11**:635—8.
18. **Kozuch P,** Grossbard ML, Barzdins A, *et al*. Irinotecan combined with gemcitabine, 5-fluorouracil, leucovorin, and cisplatin (G-FLIP) is an effective and noncrossresistant treatment for chemotherapy refractory metastatic pancreatic cancer. *Oncologist* 2001;**6**:488—95.
19. **Ulrich-Pur H,** Raderer M, Verena Kornek G, *et al*. Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. *Br J Cancer* 2003;**88**:1180—4.
20. **Cantore M,** Rabbi C, Fiorentini G, *et al*. Combined irinotecan and oxaliplatin in patients with advanced pre-treated pancreatic cancer. *Oncology* 2004;**67**:93—7.
21. **Milella M,** Gelibter A, Di Cosimo S, *et al*. Pilot study of celecoxib and infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma. *Cancer* 2004;**101**:133—8.
22. **Tsavaris N,** Kosmas C, Skopelitis H, *et al*. Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: a phase II study. *Invest New Drugs* 2005;**23**:369—75.
23. **Reni M,** Pasetto L, Aprile G, *et al*. Raltitrexed—eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer. *Br J Cancer* 2006;**94**:785—91.
24. **Reni M,** Cereda S, Mazza E, *et al*. PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) regimen as second-line therapy in patients with progressive or recurrent pancreatic cancer after gemcitabine-containing chemotherapy. *Am J Clin Oncol* 2008;**31**:145—50.
25. **Demols A,** Peeters M, Polus M, *et al*. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer* 2006;**94**:481—5.
26. **Ignatiadis M,** Polyzos A, Stathopoulos GP, *et al*. A multicenter phase II study of docetaxel in combination with gefitinib in gemcitabine-pretreated patients with advanced/metastatic pancreatic cancer. *Oncology* 2006;**71**:159—63.
27. **Gebbia V,** Maiello E, Giuliani F, *et al*. Second-line chemotherapy in advanced pancreatic carcinoma: a multicenter survey of the Gruppo Oncologico Italia Meridionale on the activity and safety of the FOLFOX4 regimen in clinical practice. *Ann Oncol* 2007;**18**:vi124—7.

28. **Togawa A,** Yoshitomi H, Ito H, *et al*. Treatment with an oral fluoropyrimidine, S-1, plus cisplatin in patients who failed postoperative gemcitabine treatment for pancreatic cancer: a pilot study. *Int J Clin Oncol* 2007;**12**:268—73.
29. **Wolpin BM,** Hezel AF, Abrams T, *et al*. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol* 2009;**27**:193—8.
30. **Ko AH,** Dito E, Schillinger B, *et al*. A phase II study evaluating bevacizumab in combination with fixed-dose rate gemcitabine and low-dose cisplatin for metastatic pancreatic cancer: is an anti-VEGF strategy still applicable? *Invest New Drugs* 2008;**26**:463—71.
31. **Boeck S,** Weigang-Köhler K, Fuchs M, *et al*. Second-line chemotherapy with pemetrexed after gemcitabine failure in patients with advanced pancreatic cancer: a multicenter phase II trial. *Ann Oncol* 2007;**18**:745—51.
32. **Oettle H,** Pelzer U, Stieler J, *et al*. Oxaliplatin/folinic acid/5-fluorouracil (OFF) in second line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). *Proc Am Soc Clin Oncol* 2005;**23**:4031.
33. **Pelzer U,** Kubica K, Stieler J, *et al*. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. *Proc Am Soc Clin Oncol* 2008;**26**:4508.