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ORIGINAL ARTICLE

# Dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma

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**Abstract**
*Background* PEFG regimen (cisplatin and epirubicin 40 mg/m$^2$ day 1, gemcitabine 600 mg/m$^2$ days 1 and 8, 5-fluorouracil (FU) 200 mg/m$^2$/day continuous infusion) significantly improved the outcome of patients with advanced pancreatic adenocarcinoma (PA) with respect to standard gemcitabine in a previous phase III trial. This regimen was subsequently modified in a dose-finding study by increasing dose intensity of cisplatin and epirubicin (both at 30 mg/m$^2$ every 14 days) and of gemcitabine (at 800 mg/m$^2$ every 14 days). Results of a consecutive series treated by dose-intense PEFG regimen are herewith reported.
*Material and methods* Dose-intense PEFG was administered to chemotherapy-naive patients with stages III–IV PA, < 75 years, performance status (PS) > 50, till progressive disease or for a maximum of 6 months.
*Results* Between January 2004 and June 2005, 49 (31 or 63% metastatic) patients, median age 62 years, median PS 80, were treated with dose-intense PEFG. Partial response and stable disease was observed in 24 (49%) and 16 (33%) patients, respectively; 31 patients were progression-free at 6 months (PFS-6 = 63%). Median survival was 10.5 months and 1-year overall survival (OS) was 48% (95% confidence interval: 33–61%). Main grade 3–4 toxicity was: neutropenia in 26% of patients, stomatitis and fatigue in 8%, anaemia, diarrhoea, nausea/vomit in 6%, febrile neutropenia and thrombocytopaenia in 4%, hand-foot syndrome in 2%.
*Conclusion* When compared with 84 patients treated by classical PEFG at the same institution, dose-intense PEFG was not inferior in terms of PFS-6 (63 versus 57%), 1-year OS (48 versus 42%) and response rate (49 versus 49%); it allowed to increase dose intensity for gemcitabine by 32%, for cisplatin and epirubicin by 36% (FU reduced by 3%), to significantly reduce grade 3–4 hematological toxicity (neutropenia: 26 versus 86%; $P < 0.00001$; thrombocytopaenia: 4 versus 58%; $P < 0.00001$) and to reduce by one-third the number of outpatient accesses. The new PEFG schedule appears more suitable for clinical use and should be preferred as a basis for further development of therapeutic strategies against pancreatic cancer.

**Keywords** Pancreatic cancer · Chemotherapy · PEFG regimen · Dose-intense PEFG

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## Introduction

Gemcitabine has long been considered as a standard treatment in advanced pancreatic adenocarcinoma (PA). After a decade of unfruitful attempts, in 2005, three gemcitabine-based combinations yielded a statistically significant outcome improvement over single-agent in phase III trials [1–3]. However, in two of these trials, the advantage in overall survival (OS) was of

marginal clinical significance, consisting of an absolute 7% improvement at 1 year (from 17–19% with gemcitabine alone to 24–26% with combined therapy) [1, 2]. The OS impact of PEFG regimen (cisplatin and epirubicin 40 mg/m$^2$ on day 1, gemcitabine 600 mg/m$^2$ on days 1 and 8, 5-fluorouracil 200 mg/m$^2$/day continuous infusion) was greater (1-year OS from 21% with gemcitabine alone to 38% with combined therapy) and long lasting, as survival curves remained separate for over 2 years [3]. However, this trial had a small sample size and used OS as a secondary endpoint. Thus, a larger confirmatory trial should be completed to support the use of PEFG regimen as a standard treatment in clinical practice. Because of the empirical bases that lead to this four-drug combination, to the complex schedule and to the absence of novel drugs, such a trial is unlikely to be performed. On the other hand, results of the phase III trial comparing PEFG with gemcitabine alone [3] fully confirmed the encouraging results in terms of OS, progression-free survival (PFS), objective response rate (ORR), response duration and clinical benefit observed in a previous phase II trial [4], and the control single-agent arm was reliable as it duplicated the results reported in other phase III trials [5–16]. Accordingly, we continued to investigate this four-drug combination in the attempt to further improve activity and efficacy, to reduce toxicity and to yield a schedule more suitable to the patient. In a previous dose-finding study, the administration schedule was modified, leading to the construction of a dose-intense PEFG regimen in which cisplatin and epirubicin were administered every 14 days at 30 mg/m$^2$ together with gemcitabine at 800 mg/m$^2$, while 5-fluorouracil (5-FU) remained unmodified [17]. While classical PEFG required three monthly outpatient accesses on days 1, 8 and 15 (due to portable pump reservoir refill), the dose-intense regimen foresaw only two monthly accesses, on days 1 and 15. On the other hand, this pilot experience did not suggest the possibility of significantly improving the activity and efficacy of the regimen. Based on these results, the prescription of single-agent gemcitabine at our institute was deemed inappropriate by an internal review board, which selected the modified four-drug combination for ordinary clinical practice administration. The present report describes the outcome of 49 consecutive patients treated in ordinary clinical practice by dose-intense PEFG regimen.

## Materials and methods

Dose-intense PEFG was administered to chemotherapy-naive patients ≤ 75 years, Karnofsky performance status (PS) > 50, with cytologically or histologically proven stages III–IV PA, until progressive disease or for a maximum of 6 months. Patients had to have adequate bone marrow [absolute neutrophil count (ANC) ≥ 1,500 cells/mm$^3$; platelet count ≥ 100,000 cells/mm$^3$ and haemoglobin ≥ 10 g/dl]; kidney (serum creatinine ≤ 1.5 mg/dL) and liver function (serum total bilirubin ≤ 1.5 mg/dL and serum transaminases ≤ 3 upper limit of laboratory normal). Patients with ampullary tumors or other histologic variants of pancreatic carcinoma were not considered for this analysis. Patients with at least one measurable indicator lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [18] were assessable for response evaluation. All participating patients were required to give written informed consent. Toxicity was graded according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC) [19]. Anti-tumour treatment effects were registered using the RECIST response criteria. PFS was calculated as the interval between the initiation of treatment and the occurrence of progressive disease (PD) or death, and survival was measured from initiation of treatment to date of death or to the last follow-up assessment.

### Treatment plan

Hydration, anti-emetic treatment and drug dilution were previously described [3, 4, 17, 20]. The dose of 5-FU was 200 mg/m$^2$ a day as protracted infusion for the duration of chemotherapy by use of an indwelling, implanted central venous catheter. All other drugs were administered on days 1 and 15: epirubicin and cisplatin at 30 mg/m$^2$ and gemcitabine at 800 mg/m$^2$. Cycles were repeated every 28 days for a maximum of six cycles or until there was evidence of either unacceptable side effects or PD. At the end of the treatment, patients with operable stage III disease were recommended for surgery and were allowed to receive concomitant chemoradiation, which was also indicated for patients with inoperable stage III disease. Guidelines for dose reduction and treatment delay have been previously reported [3, 4, 17, 20]. Briefly, dose adjustments, which were made according to the greatest degree of toxicity, consisted of reduction of gemcitabine dose by 25% in case of grade 2 neutropenia (ANC: 1,000–1,500 cells/mm$^3$) and/or grade 1 thrombocytopenia (platelets: 75,000–130,000 cells/mm$^3$). Treatment was delayed for a maximum of 2 weeks in case of grade ≥ 3 neutropenia (ANC < 1,000 cells/mm$^3$), anaemia (Hb < 8.0 g/dL) or non-haematological toxicity, or of grade > 1 thrombocytopenia (platelets < 75,000 cells/mm$^3$). If recovery was not evident within 2 weeks, the patient was discontinued

from the study. If the patient had grade 4 neutropenia or thrombocytopenia, 5-FU infusion was withheld until recovery to grade 3 level. In case of grade 4 neutropenia or grade ≥ 3 thrombocytopenia, gemcitabine dose was reduced by 25% in the subsequent cycles. If the patient had ≥ grade 3 non-haematological toxicity, the treatment was withheld until recovery to grade 1 level and the dose of the drug responsible for toxicity was subsequently reduced by 25%.

### Study evaluations

Assessment of disease, including CA19.9 measure and spiral computed tomography of the abdomen and chest was made at baseline, every 8 weeks during chemotherapy and then every 3 months or when PD was clinically suspected. Complete blood, platelet and differential counts were carried out every 2 weeks, while biochemistry profile was done on a monthly basis.

### Statistical analysis

As this was an observational study of our ordinary clinical practice, no statistical design was performed. Main analyses were by intention to treat. At univariate analyses, survival curves were estimated with the Kaplan-Meier method and compared by means of the log-rank test. Multivariate analysis by the Cox proportional hazard model was carried out to estimate independent risk factors that could affect PFS and OS. Clinical characteristics, toxic effects, and response were assessed with the $\chi^2$ test or Fisher's exact test for categorical variables. Clinical benefit response was used to demonstrate improvement in patients treated with gemcitabine [5]. However, this measure is not a validated endpoint and has numerous questionable aspects [4]. In our previous experience, it was assessable in only 43–65% of patients [3, 4]. Accordingly, this variable was not analysed in the current study. All probability values were from two-sided tests. Analyses were done with the Statistica 4.0 statistical package for Microsoft Windows.

## Results

### Treatment summary

Final analysis was performed on March 17, 2006 when all living patients had completed at least 9 months of follow-up (median follow-up 13 months, range 9–24 months). No patient was lost to follow-up. Table 1 shows baseline characteristics of patient groups. Between January 2004 and June 2005, 49 consecutive patients at a single institution were registered. Two-hundred-and-thirteen courses (range 1–6, median 5) of dose-intense PEFG regimen were administered. Dose intensity was 12.9 mg/m$^2$/week (86% of the intended dose) for both epirubicin and cisplatin, 1,106 mg/m$^2$/week (79% of the intended dose) for 5-FU, and 338 mg/m$^2$/week (84% of the intended dose) for gemcitabine. The median duration of chemotherapy was 17 weeks (interquartile range 9–25). Therapy was discontinued prior to completion in 27 patients: 15 patients had radiological PD;1 had clinical PD; 3 patients refused to continue chemotherapy; 2 patients discontinued treatment because of toxicity and 6 stage III patients were recommended for chemoradiation after four cycles. Total number of cycles administered is reported in Table 2. At the end of chemotherapy, 3 of 18 (17%) stage III patients became operable and were submitted to curative surgery. Chemoradiation with 5-FU at 250 mg/m$^2$ a day as protracted infusion for the duration of radiotherapy (48–60 Gy; median 60 Gy) was delivered to 14 of 18 (78%) stage III patients, including the three patients submitted to curative surgery.

**Table 1** Patient characteristics at baseline

| Characteristic | Dose-intense PEFG *n* (%) | Classical PEFG |
|---|---|---|
| Patients enrolled | 49 | 84 |
| Median age | 62 (range 36–73) | 60 (range 30–70) |
| Sex | | |
| Male | 31 (63) | 48 (57) |
| Female | 18 (37) | 36 (43) |
| Karnofsky ECOG | | |
| 0 | 14 (29) | 29 (35) |
| 1 | 32 (67) | 49 (58) |
| 2 | 2 (4) | 6 (7) |
| Stage | | |
| III | 18 (37) | 28 (33) |
| IV | 31 (63) | 56 (67) |
| Prior therapy | | |
| Prior pancreatic surgery | 4 (8) | 9(11) |
| Prior radiotherapy or chemotherapy | 0 (0) | 0 (0) |
| Site of metastases | | |
| Liver | 29 (94) | 48 (86) |
| Lung | 4 (8) | 8 (14) |
| Median CA19.9 (UI) | 586 (range 4–160,000) | 835 (range 1–204,100) |
| > ULN | 38 (78) | 67 (80) |
| < ULN | 10 (20) | 14 (17) |
| Unknown | 1 (2) | 3 (4) |

*PS* performance status, *n* number, *ULN* upper limit of laboratory normal, *PEFG* cisplatin, epirubicin, 5-fluorouracil, gemcitabine, *ECOG* Eastern Cooperative Oncology Group

**Table 2** Total number of cycles received

| Number of cycles | *n* = 49 |
|---|---|
| 1 | 7 |
| 2 | 6 |
| 3 | 0 |
| 4 | 10 |
| 5 | 4 |
| 6 | 22 |

n number of patients

**Table 3** Treatment-related toxicity per cycle (and worst ever by patient)

| Toxicity | Grade 0 | Grade 1/2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Granulocytes | 53 (29) | 38 (45) | 6 (14) | 3 (12) |
| Platelets | 70 (57) | 29 (39) | 1 (4) | 0 (0) |
| Haemoglobin | 15 (4) | 82 (90) | 3 (6) | 0 (0) |
| Stomatitis | 90 (76) | 8 (16) | 2 (8) | 0 (0) |
| Nausea/vomiting | 62 (55) | 36 (39) | 2 (6) | 0 (0) |
| Diarrhoea | 86 (67) | 13 (27) | 1 (6) | 0 (0) |
| Fatigue | 77 (49) | 20 (43) | 3 (8) | 0 (0) |
| Hand-foot syndrome | 93 (86) | 6 (12) | 1 (2) | 0 (0) |
| Febrile neutropenia | 99 (96) | 0 (0) | 1 (4) | 0 (0) |

Numbers are expressed as percentages

## Safety and toxicity

Table 3 summarizes the main haematological and non-haematological toxicities observed. Growth factors were utilized for 1–3 days in six cycles (3%). Red cell transfusion was used in three cycles. Erythropoietin was administered to six patients. No treatment-related deaths were observed.

## Efficacy and activity analyses

A summary of efficacy and activity analyses is reported in Table 4. Forty-six patients had PD and three were progression free (PF) at 8–11 months. Thirty-seven patients died of PD. Twelve patients were alive at 9–26 months (median 14 months). Median duration of partial response (PR) was 7.3 months (interquartile range, 5.9–13.6 months). Median duration of stable disease (SD) was 7.2 months (interquartile range 5.5–8.6 months).

## Salvage therapy

At time of PD, 18 patients (39%) received salvage therapy with eight different regimens: PEFG regimen was resumed in five patients; gemcitabine alone or the combination raltitrexed–oxaliplatin was administered to three patients each; the combination ifosfamide–mitomycin or paclitaxel-CCI-779 to two patients each; the combination gemcitabine–5-FU, gemcitabine–cisplatin–epirubicin or single-agent docetaxel to one patient each.

## Exploratory analyses

Eighty-four patients were previously treated by classical PEFG at the same institution in a phase II trial (*n* = 49) [4] or as a subset of a phase III trial (*n* = 35) [3]. Table 1 shows baseline characteristics of this population.

**Table 4** Activity and efficacy analyses summary

| Outcome measure | Dose-intense PEFG | | Classical PEFG | |
|---|---|---|---|---|
| | *n* | 95% CI | *n* | 95% CI |
| Best response during the treatment | | | | |
| Partial response | 24 (49%) | 35–63% | 41 (49%) | 38–60% |
| Stable disease | 16 (33%) | 20–46% | 25 (30%) | 20–40% |
| Progressive disease | 9 (18%) | 5–31% | 18 (21%) | 11–32% |
| *P* value | 0.98 | | | |
| CA19.9 response | | | | |
| Elevated basal value | 38 (78%) | 64–87% | 66 (79%) | 69–86% |
| Reduction > 50% basal value | 24 (63%) | 47–77% | 41 (62%) | 50–73% |
| *P* value | 0.30 | | | |
| Progression-free survival (PFS) | | | | |
| Median PFS | 6.9 months | 5.5–10.3months[a] | 7.0 months | 4.6–10.7 months[a] |
| 6-month PFS | 63% | 49–77% | 57% | 46–68% |
| *P* value | 0.40 | | | |
| Overall survival (OS) | | | | |
| 1-year OS | 48% | 33–61% | 42% | 31–53% |
| 2-year OS | 11% | 2–21% | 12% | 5–19% |
| *P* value | 0.42 | | | |

n number; CI confidence interval; PEFG cisplatin, epirubicin, 5-fluorouracil, gemcitabine

[a] Interquartile range

A summary of efficacy and activity analyses of classical PEFG is reported in Table 4. No difference in PFS or in OS was observed between patients receiving classical PEFG and patients receiving dose-intense PEFG. Among patients receiving classical PEFG at our institution, the median survival was 9.5 months (interquartile range 7.5–18.2 months), while median survival of patients receiving dose-intense PEFG was 10.5 months (interquartile range 6.4–19.0 months) (Fig. 1). A multivariate analysis confirmed that only stage (hazard ratio 2.38; 95% confidence interval 1.53–3.71; $P = 0.0002$) and CA19.9 value (hazard ratio 1.00002; 95% confidence interval 1.00001–1.00003; $P = 0.00003$) were significantly predictive of survival, while regimen, age, PS and gender were not independently correlated to survival. A PR was observed in 41 of 84 patients (49%; 95% confidence interval: 38–60%) and an SD in 25 patients (30%; 95% confidence interval: 20–40%). Median duration of PR and SD was 8.6 months (interquartile range, 6.4–12.3 months) and 6.8 months (interquartile range 5.1–10.6 months), respectively. Among 28 stage III patients, 4 (14%) became operable at the end of chemotherapy and were submitted to curative surgery.

With regard to toxicity, the risk of grades 3–4 neutropenia ($P < 0.00001$) and thrombocytopenia ($P < 0.00001$) was significantly reduced among patients receiving dose-intense PEFG as compared with classical PEFG, while no significant difference was observed in terms of anaemia, stomatitis, fatigue, nausea/vomiting and diarrhoea (Table 3).

## Discussion

The present study shows dose-intense PEFG to be an active and feasible regimen. Objective response rate, CA19.9 reduction, PFS-6, and 1-year OS in this series of 49 consecutive patients were at least as good as those observed in 84 patients treated by classical PEFG at the same institution (Table 4) [3, 4]. While the comparison among different series is troublesome, and analyses can have only exploratory relevance, the characteristics of the two populations appeared to be similar (Table 1) and the proportion of patients receiving second-line therapy was comparable between studies (39% for dose-intense PEFG and 49% for classical PEFG). No significant difference in terms of survival between the two regimens at both univariate and multivariate analyses was observed. When compared with classical PEFG, dose-intense PEFG allowed an increase of the dose intensity for gemcitabine by 32%, and for cisplatin and epirubicin by 36% (FU reduced by 3%). Worthy of mention is the fact that this improvement in dose intensity was not achieved at the cost of impaired toxicity. Conversely, while non-haematological toxicity was comparable between the two regimens, grades 3–4 neutropenia and thrombocytopenia were consistently and significantly reduced amongst patients receiving dose-intense PEFG regimen. The detection of haematological toxicity may have been influenced by the blood count schedule, that is, performed weekly in classical PEFG and every other week in dose-intense PEFG. However, only 17 and 11% of patients treated by classical PEFG had day 8 grades 3–4 neutropenia and thrombocytopenia, respectively. This bias cannot, therefore, account for the total difference observed. It is likely that the delay of the second gemcitabine administration from day 8 (classical PEFG) to day 15 (dose-intense PEFG) allowed a reduction of per cycle cumulative toxicity. Another important advantage, possibly not a negligible one in a group of patients receiving a purely palliative treatment, was the reduction by one-third of the number of outpatient accesses associated with dose-intense PEFG regimen administration.

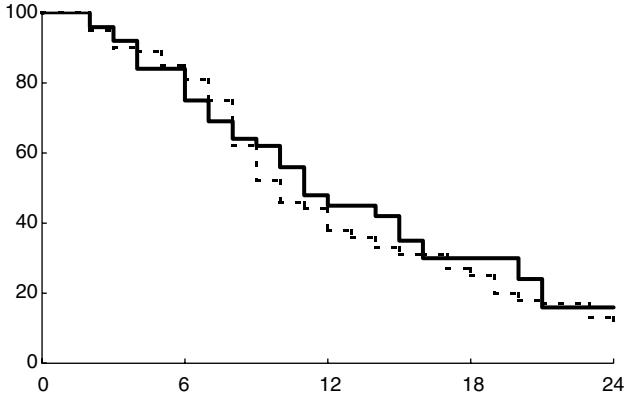


**Fig. 1** Survival curves for classical cisplatin, epirubicin, 5-fluorouracil, gemcitabine (*PEFG*; *dashed line*) and dose-intense PEFG (*solid line*)

The PEFG regimen was based on the combination of four amongst the most active and most largely studied agents against pancreatic cancer. These drugs were tested both as a single-agent [5, 21–24] and as double-agent therapies [25–31] in phase II trials that showed promising activity and suggested synergism for gemcitabine–FU [25], FU–cisplatin [26–28], gemcitabine–epirubicin [29] and gemcitabine–cisplatin [30] combinations. However, when assessed in a phase III setting, gemcitabine- [6, 11] and 5-FU-based [31] doublets did not perform any better than a single-agent. Altogether, the addition of a second agent to gemcitabine did not improve outcome over single-agent standard gemcitabine [8, 9, 12–15]. An absolute 7% 1-year OS improvement over gemcitabine alone was achieved by

**Table 5** Grades 3–4 treatment-related toxicity (worst ever by patient)

| References | Regimen | Neutrophils (%) | Platelets (%) | Haemoglobin (%) | Nausea/ vomiting (%) | Diarrhoea (%) | Fatigue (%) | Stomatitis (%) | Neurological (%) |
|---|---|---|---|---|---|---|---|---|---|
| a | G | 5–39 | 2–14 | 2–16 | 2–14 | 0–6 | 4–15% | 0–4 | 0–3 |
| [2] | GC | 17 | 3 | 1 | 1 | 1 | nr | nr | nr |
| [6] | GF | 7 | 19 | 10 | 8 | 10 | nr | 1 | 5 |
| [8] | GI | 38 | 20 | 16 | 17 | 19 | 17 | nr | nr |
| [9] | GM | 3 | nr | 3 | 7 | nr | nr | nr | nr |
| [11] | GP | 9 | 6 | 2 | 21 | 3 | nr | nr | nr |
| [15] | GA | 45 | 18 | 14 | 3 | 3 | 15 | 3 | nr |
| [12] | GT | 40 | 15 | 20 | 7 | 4 | 11 | nr | 2 |
| [13] | GO | 20 | 14 | 6 | 10 | 6 | nr | nr | 19 |
| [3, 4] | PEFG 1, 8 | 86 | 58 | 13 | 8 | 5 | 6 | 13 | 0 |
| cs | PEFG 1,15 | 26 | 4 | 6 | 6 | 6 | 8 | 8 | 0 |

[a] Range of values reported in Refs. [2, 3, 5–13, 15]; *G* gemcitabine; *F* fluorouracil; *I* irinotecan; *M* marimastat; *P* cisplatin; *A* pemetrexed; *C* capecitabine; *T* tipifarnib; *O* oxaliplatin; *E* epirubicin; *cs* current series; *nr* not reported; *PEFG* cisplatin, epirubicin, 5-fluorouracil, gemcitabine

combining gemcitabine with oxaliplatin [13], erlotinib [1] and capecitabine [2]. Despite the identical numerical value, the difference in survival observed in the smaller series was not statistically significant [13], while the two larger series achieved statistical significance [1, 2]. Overall, from a clinical perspective, these trials confirmed the lack of a significant impact of double-agent combination therapy on the clinical course of pancreatic cancer and endorsed the need for development of more effective systemic therapies against this disease. A more favourable activity profile as compared with single- and double-agent combinations was suggested for triple-agent 5-FU, cisplatin and either gemcitabine or epirubicin combination therapy [32, 33], but no confirmatory phase III trial has been performed. Conversely, the promising results observed with this four-agent combination [4] were subsequently confirmed in a phase III trial [3], which showed a significant improvement in PFS, OS, response rate and clinical benefit for patients receiving the PEFG regimen when compared with those treated with single-agent gemcitabine. Furthermore, clinically significant improvement in quality of life from baseline was observed more often after PEFG than after gemcitabine, suggesting that PEFG regimen did not impair quality of life [3, 34].

The results described in the present report assessing feasibility and activity of a modified schedule of PEFG regimen and in a previous dose-finding study [17] duplicated the overall outcome observed with the original schedule [3, 4]. Altogether, these findings compared very favourably in terms of both activity and efficacy with those achieved with gemcitabine alone or with other gemcitabine-containing regimens [1, 2, 5–16]. Worthy of mention is the fact that the PEFG combination was not less manageable because of toxicity compared with gemcitabine alone or other regimens (Table 5). While the increase of dose intensity did not achieve any remarkable improvement of OS, PFS or response rate when compared with the original schedule, the new schedule seems to be more suitable for clinical use both in terms of toxicity and of the number of outpatient accesses and should be preferred as a basis for further development of therapeutic strategies against pancreatic cancer.

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