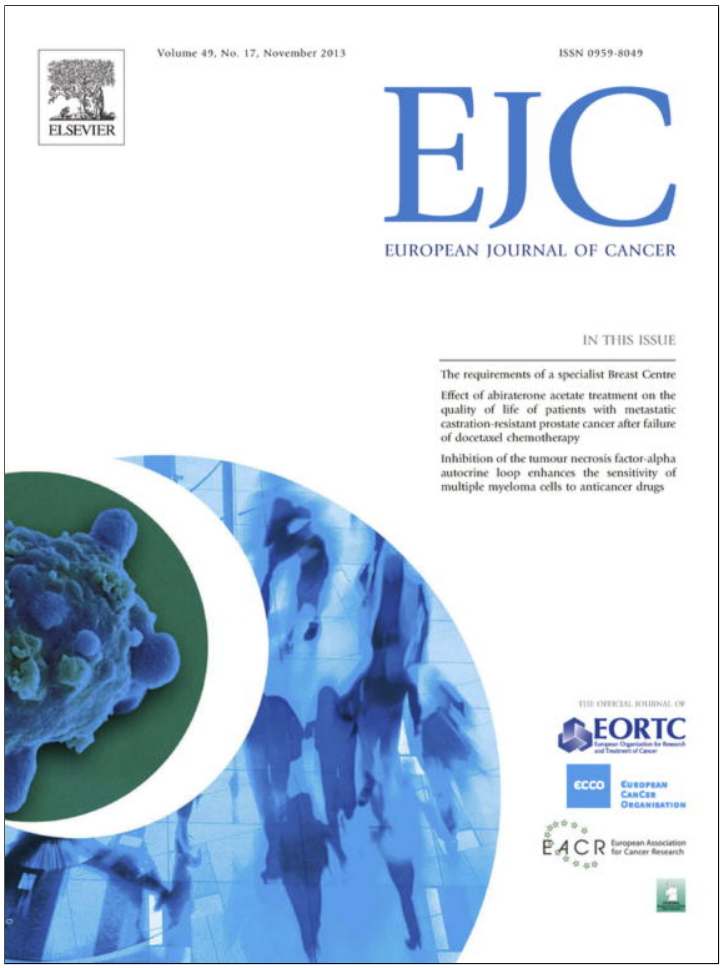

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Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: A phase II randomised trial

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Abstract ***Background:*** New strategies to prolong disease control warrant investigation in patients with metastatic pancreatic adenocarcinoma. This open-label, randomised, multicentre phase II trial explored the role of maintenance sunitinib after first-line chemotherapy in this setting.

Methods: Patients with pathologic diagnosis of metastatic pancreatic adenocarcinoma, performance status >50%, no progression after 6 months of chemotherapy were centrally randomised by an independent contract research organisation, which was also responsible for data collection and monitoring, to observation (arm A) or sunitinib at 37.5 mg daily until progression or a maximum of 6 months (arm B). The primary outcome measure was the probability of being progression-free at 6 months (PFS-6) from randomisation. Assuming P0 = 10%; P1 = 30%, α .10; β .10, the target accrual was 26 patients per arm.

Results: 28 per arm were randomised. One arm B patient had kidney cancer and was excluded. Sunitinib was given for a median of 91 days (7–186). Main grade 3–4 toxicity was

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thrombocytopenia, neutropenia and hand–foot syndrome (12%), diarrhoea 8%. In arm A versus B, PFS-6 was 3.6% (95% confidence interval (CI): 0–10.6%) and 22.2% (95% CI: 6.2–38.2%; $P < 0.01$); 2y overall survival was 7.1% (95% CI: 0–16.8%) and 22.9% (95% CI: 5.8–40.0%; $P = 0.11$), stable disease 21.4% and 51.9% ($P = 0.02$).

Conclusion: This is the first randomised trial on maintenance therapy in metastatic pancreatic adenocarcinoma. The primary end-point was fulfilled and 2y overall survival was remarkably high, suggesting that maintenance sunitinib is promising and should be further explored in this patient population.

1. Introduction

More than half of patients with pancreatic adenocarcinoma present with metastatic disease at diagnosis and over 70% of them receive single agent gemcitabine as upfront therapy.[1] The most relevant therapeutic progress came from the combination of gemcitabine with nab-paclitaxel[2] or of multiple cytotoxic agents.[3,4]

Despite the outcome improvement, patients continue to fail and die of their disease and chemotherapy still remains a palliative approach whose efficacy has to be balanced with its toxicity. The optimal duration of chemotherapy is controversial because evidence of any additional benefit by continuing treatment until progression of disease (PD) is lacking. Conversely, the risk of cumulative toxicity is not negligible and a negative impact of relentless chemotherapy on patients' quality-of-life cannot be ruled out. Therefore, new strategies, such as maintenance therapy, aimed to prolong disease control warrant investigation.

Angiogenesis is a distinct and crucial step in the development and progression of cancer and vascular endothelial growth factor (VEGF) plays a pivotal role in the growth and metastasis of many tumours, being associated with prognosis.[5] Furthermore, inhibition of platelet-derived growth factor receptor (PDGFR) signalling, which is also implicated in the autocrine growth of tumour cells and in the recruitment and regulation of tumour fibroblasts, augments the antitumour and anti-angiogenic effects of VEGF receptor (VEGFR) inhibitors.[6] According to the Folkman's induced dormancy theory, angiogenesis inhibitors should prevent disease progression and maintain stable disease.[7] Consistently, maintenance therapy with sunitinib after radiotherapy, significantly prolonged tumour control in murine models.[8] Sunitinib (sunitinib malate; Sutent®; Pfizer Pharmaceuticals Group, New York, NY) is an orally bioavailable, multitargeted small molecule that inhibits several receptor tyrosine kinases, including VEGFR, PDGFR, kit and Flt-3 receptors[9–11] that are over-expressed in pancreatic cancer[12,13] and appears a suitable candidate for maintenance therapy in this disease.

The PACT-12 (Pancreatic AdenoCarcinoma Trials-12; ClinicalTrials.gov ID: NCT00967603) trial was undertaken to explore the hypothesis that sunitinib maintenance therapy is able to increase the rate of patients with metastatic pancreatic adenocarcinoma who are progression-free at 6 months from the end of first-line treatment.

2. Patients and methods

The PACT-12 was a multicenter, open-label, randomised, phase II trial. Patients were required to have pathologically confirmed metastatic pancreatic adenocarcinoma; absence of progressive disease after 6 months of first-line chemotherapy demonstrated with: (a) two consecutive computed tomography or magnetic resonance scans separated by at least 6 weeks and (b) normal or no carbohydrate antigen 19-9 (CA19-9) increase >20% during the last month; interval >3 and <8 weeks from last chemotherapy administration (>1 week in the case of 5-fluoruracil as continuous infusion or capecitabine); age >18 years; Karnofsky performance status (KPS) >50%; adequate bone marrow (granulocytes > 1500/μL, platelets > 100,000/μL, haemoglobin > 10 g/dL), hepatic (total bilirubin < 1.5 mg/dL, transaminases < 3 × upper limit of normal (ULN)), renal (creatinine < 1.5 mg/dL), coagulation (prothrombin time and partial thromboplastin time <1.5 ULN) and thyroid function. Measurable disease was not required. Patients who received prior adjuvant therapy; more than one line of chemotherapy for metastatic disease; or prior treatment with anti-angiogenic drugs were excluded. Patients could not have previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma in-site of the cervix and basal or squamous cell carcinoma of the skin, and of other neoplasms without evidence of disease at least from 5 years. Other exclusion criteria included inability to take oral medications; tumour invasion of stomach, duodenum or intestine; major surgery within the preceding 30 days; clinically significant cardiovascular disease; pre-existing uncontrolled hypertension; QTc interval prolongation; pregnancy or lactation; current use of drugs with potential anti-arrhythmic activity or thrombolytic agents at therapeutic dose; current use or <7 days interval from withdrawal of drugs that are known CYP3A4 inhibitors; current use or <12 day interval from withdrawal of drugs that are known CYP3A4 inducers; concurrent treatment with other experimental drugs.

All patients provided written informed consent. The trial protocol was approved by the institutional ethics committee at each site and was conducted in accordance with the principles of good clinical practice, the ethical principles stated in the current revision of the Declaration of Helsinki, and local ethical, legal and regulatory requirements.

Patients were enrolled by the attending oncologist who registered them at an independent contract research organisation (CRO) that randomly assigned patients with equal probability to either arm A (observation) or B (sunitinib) by a randomisation list which was previously generated using the nQuery Advisor statistical software version seven with a block of four. Patients were stratified according to previous chemotherapy regimen (single agent versus combination chemotherapy) and KPS (>80 versus <90). Arm A patients were submitted to observation alone. Arm B patients received oral sunitinib, which was provided by Pfizer, Italy, at 37.5 mg/day for 28 days of a 4-week cycle. Treatment was discontinued for progressive disease, unacceptable adverse events, medical decision, patient withdrawal of consent or after a maximum of 6 months. Data were collected by the CRO, which was responsible for monitoring accuracy, completeness and reliability of the acquired data. After the end of the trial the database was consigned at the coordinating institution.

Dose modifications were based on toxicities within 1 day of treatment. Adverse effects were graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. In case of grade >2 toxicity sunitinib was withheld until toxicity resolved to grade <2 and was discontinued if recovery was not evident within 3 weeks. In case of grade 4 or recurrent grade 3 toxicity, the patient upon recovery was re-challenged with study drug at 25 mg/day.

Pre-treatment evaluation included a complete medical history and physical examination, KPS assessment, contrast enhanced computed tomography scan or magnetic resonance of the abdomen, computed tomography scan or chest X-ray of the chest, complete blood count and differential, chemistry panel, CA19-9, prothrombin time and partial thromboplastin time, electrocardiography.

All these examinations were performed monthly apart from imaging scans for tumour assessments, which were repeated every 2 months.

In patients with measurable disease, tumour assessment was made by the treating physician/local investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 guidelines.[14] Patients were followed for survival and subsequent disease treatment until death, loss to follow-up or trial termination.

The primary outcome measure was the probability of being progression-free at 6 months (PFS-6) from trial enrolment. The Fleming design was used for sample size calculation. Assuming a PFS-6 probability of 10% in untreated patients (P0 = 10%) and an improvement by 20% (P1 = 30%) in the experimental arm, with alpha .10 and beta .10, the target accrual was 26 patients per arm. With six or more PFS-6 patients, the experimental drug had to be considered of interest for further study.

The primary efficacy analysis population was the intention-to-treat population, defined as all eligible patients randomly assigned, irrespective of whether the assigned treatment was actually received. Secondary end-points included overall survival (OS), PFS, response rate and safety. OS was defined as the time between the date of randomisation and the date of death from any cause. Patients without an event (death) were censored on the date they were last known to be alive. PFS was defined as the time between the date of randomisation and the date of documented radiological PD or death from any cause, whichever occurred first. Patients without an event were censored on the date of last follow-up for PD or last available tumour assessment if no further follow-up for disease progression was performed.

Safety analyses were performed on the safety population, which included all randomly assigned to arm B patients who received at least one dose of trial treatment.

Survival distribution was estimated by the Kaplan–Meier method. Comparisons of significant differences in probability of surviving between the arms were evaluated by log-rank test. Binomial exact 95% confidence interval (CI) was calculated for percentages. All probability values were calculated from two-sided tests and P values of 0.05 were considered to indicate a statistical significance.

3. Results

Between March 2008 and June 2011, 56 patients were recruited at 10 institutions and randomly assigned to arm A ($N = 28$) or B ($N = 28$). All patients were managed according to the assigned arm. Material for pathological examination was yielded by fine needle biopsy in 47 cases and by laparotomy in eight cases (five arm A; three arm B). At pathology review, one patient in arm B resulted to have pancreatic metastases from kidney cancer and was therefore ineligible. Patient flow is summarised in the CONSORT diagram (Fig. 1), and patient characteristics are listed in Table 1.

There were no statistically significant differences between treatment arms with respect to age, gender, KPS, basal CA19-9 value or prior chemotherapy regimen (Table 1).

The median duration of sunitinib treatment was 91 days (range: 7–186); the median relative dose intensity was 85%. Dose reductions occurred in three (11%) of 27 patients. Three patients discontinued therapy after one to 4 months because of transitory acute renal insufficiency, consent withdrawal and second tumour diagnosis (breast ductal adenocarcinoma).

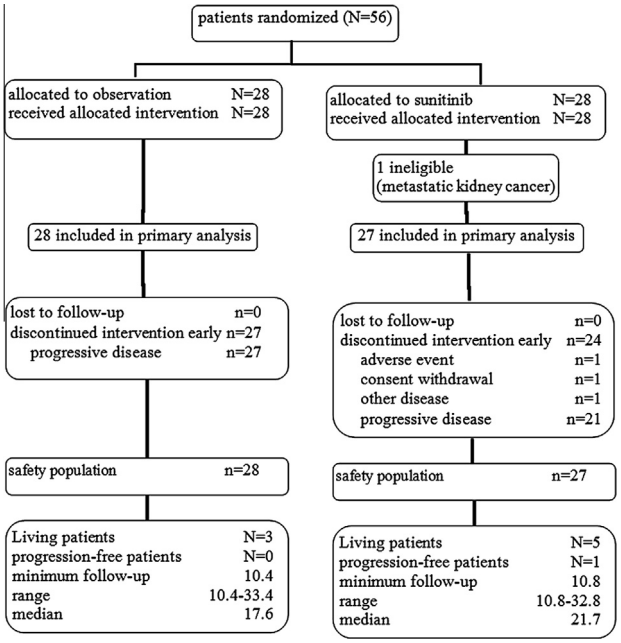

Fig. 1. CONSORT diagram.

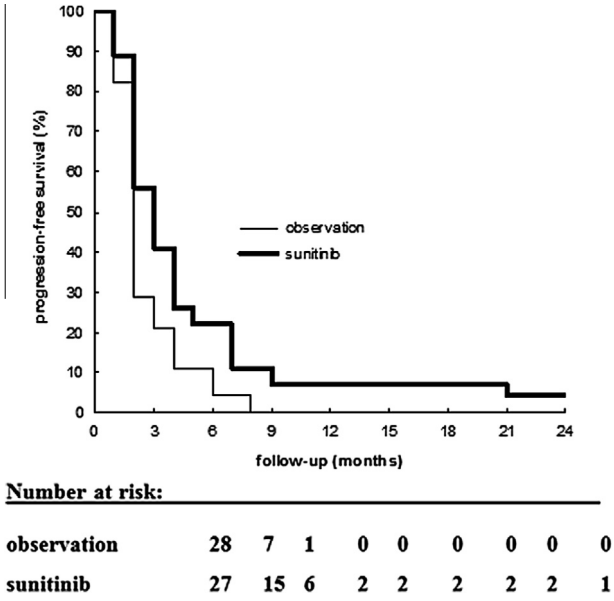

Fig. 2a. Kaplan–Meier curves for progression-free survival in patients with metastatic pancreatic adenocarcinoma randomised to either maintenance sunitinib or observation.

The final analysis for the primary outcome measure was conducted when all patients had PD. PFS-6 was 3.6% (1 of 28; 95% CI: 0–10.6) in arm A and 22.2% (6 of 27; 95% CI: 6.2–38.2) in arm B. Median progression-free survival was 2.0 (interquartile range 1.8–3.2) and 3.2 (interquartile range 2.1–5.1) months, respectively ($P < 0.01$; hazard ratio (HR) 0.51; 95% CI 0.29–0.89; Fig. 2a).

The analysis of OS was based on 47 events. Median, 1- and 2-year OS was 9.2 months (interquartile range 5.9–16.3), 35.7% (95% CI: 17.5–53.9) and 7.1% (95% CI: 0–16.8) for patients allocated to observation and 10.6 months (interquartile range: 6.2–18.9), 40.7% (95% CI: 20.8–60.5) and 22.9% (95% CI: 5.8–40.0) for those allocated to maintenance sunitinib (log-rank test for overall survival: $P = 0.11$; HR 0.71; 95% CI 0.40–1.26; Fig. 2b).

Table 1
Summary of clinical features and baseline characteristics of the tumour.

Characteristic		Observation (%)	Sunitinib (%)	*P*-Value
Eligible patients		28	27	
Age, median (range) years		65 (32–73)	61 (42–75)	0.59
Gender	Male	15 (54)	13 (48)	0.69
	Female	13 (46)	14 (52)	
Karnofsky PS	90–100	26 (93)	26 (96)	0.57
	70–80	2 (7)	1 (4)	
CA19-9 median, (range)	U/ML	45 (1–8683)	34 (1–1496)	0.29
	>ULN	15 (54)	14 (52)	0.90
Prior surgery	DCP	4 (14)	1 (4)	0.17
	L	1 (4)	2 (7)	0.53
Prior chemotherapy	Gemcitabine	3 (11)	2 (7)	0.67
	Combination	25 (89)	25 (93)	
	G + O/P	3	5	
	PEXG	17	16	
	PDXG	4	2	
	Others	1	2	
Prior response	Stable disease	16 (58)	16 (59)	0.87
	Partial response	12 (42)	11 (41)	

PS: performance status; CA19-9: carbohydrate antigen 19-9; ULN: upper limit of normal; DCP: duodenocephalopancreasectomy; L: laparotomy; G: gemcitabine; O: oxaliplatin; P: cisplatin; E: epirubicin; X: capecitabine; D: docetaxel.

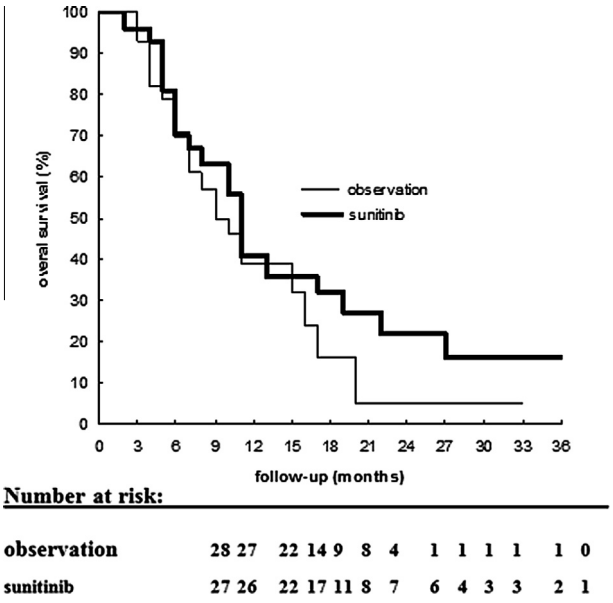

Fig. 2b. Kaplan–Meier curves for overall survival in patients with metastatic pancreatic adenocarcinoma randomised to either maintenance sunitinib or observation.

Table 2
Treatment-related toxicity (worst ever by patient).

Toxicity	Arm A		Arm B	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Granulocytes	–	–	5 [19%]	3 [12%]
Platelets	1 [3%]	–	7 [27%]	3 [12%]
Haemoglobin	–	–	1 [4%]	1 [4%]
Stomatitis	–	–	7 [27%]	1 [4%]
Nausea	1 [3%]	–	3 [12%]	–
Vomiting	–	–	4 [15%]	1 [4%]
Diarrhoea	1 [3%]	–	7 [27%]	2 [8%]
Fatigue	2 [7%]	–	7 [27%]	1 [4%]
Hand–foot syndrome	–	–	6 [23%]	3 [12%]
Hypertension	–	–	3 [12%]	–
Fever	1 [3%]	–	3 [12%]	–
Rash	–	–	1 [4%]	–
Headache	–	–	1 [4%]	–
Renal failure	–	–	1 [4%]	–

All patients, except two in arm A, had measurable disease. No objective response was observed. Stable disease was achieved in six (21.4%) arm A patients and in 14 (51.9%; $P = 0.02$) arm B patients.

Table 2 summarises the most common adverse events by maximum NCI-CTCAE grade. No grade 5 event, gastrointestinal haemorrhage, deep-vein thrombosis or pulmonary embolism occurred.

Neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhoea, hypertension, fatigue, fever hand–foot syndrome and stomatitis occurred more frequently in arm B.

Overall, 86% of patients in arm A and 81% in arm B received second-line therapy, consisting of combination chemotherapy in 66.7% and 50.0% of patients, respectively.

4. Discussion

The present randomised trial is the first to address the role of maintenance therapy in metastatic pancreatic adenocarcinoma. The trial met its primary end-point showing a PFS-6 of 22.2% in patients receiving sunitinib after induction chemotherapy. This figure is remarkable because PFS-6 was only 3.6% in the calibration arm.

While the small sample size of this phase II trial, producing wide CI's, does not allow to draw final conclusions on the role of maintenance therapy, the observed results appear credible because PFS data were paralleled by equally promising OS results (2-year OS 22.9% and 7.1% in the sunitinib and observation arm, respectively). These figures are in favour of further exploring this therapeutic strategy.

Prior clinical data stood out against the utility of targeting VEGFR pathway in pancreatic adenocarcinoma; indeed, anti-angiogenetic therapy was largely explored as upfront treatment in combination with chemotherapy with disappointing results.[15–18] Although sunitinib, a multi-target tyrosine-kinase inhibitor with other potential mechanisms of action besides inhibition of neo-angiogenesis, proved inactive in second-line therapy of pancreatic adenocarcinoma,[19] our data suggest that it may impact on disease course, when given as maintenance treatment in patients achieving disease control with first-line chemotherapy. This raises the interesting hypothesis that targeting of the VEGFR pathway, which may be of marginal relevance and insufficient to alter the natural history of the disease against a bulky and rapidly growing tumour, could still be effective against progression under conditions of maximum cytoreduction and chemotherapy-induced tumour damage. Alternatively, one could speculate that as more active agents against pancreatic cancer become available the maintenance setting may potentially achieve even more exciting results.

Our study population was highly selected because PFS-6 is rarely achieved in metastatic pancreatic adenocarcinoma. In fact, enrolled patients represented about 11% of those treated in the participating institutions during the study period (data not shown). Larger studies should involve correlative studies to better appreciate the favourable biology of these cancers. However, the likelihood of being PFS-6 was also related to the induction chemotherapy regimen ranging from 12% with gemcitabine, to 20% with gemcitabine-oxaliplatin, to 49% with either PEFG,[4] PEXG[20] (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG[20] (cisplatin, docetaxel, capecitabine, gemcitabine) regimens. Accordingly, the growing use of more effective chemotherapy regimens, such as gemcitabine plus nab-paclitaxel, PEXG or FOLFIRINOX, may allow to expand the candidate population for maintenance therapy.

The rate of 2-year survivors observed in our experimental arm also suggests that a better selection of the population that is likely to particularly benefit from treatment may allow to optimise the outcome. Apart from the clinical criterion of chemotherapy response, ancillary exploratory biomarker analyses, which were planned in this trial and will be reported separately, may allow to further define the optimal target population for this approach.

A potential topic for criticism to our trial design is that the control arm consisted of observation only instead of continuation of induction chemotherapy. However, there is no scientific evidence for an additional outcome benefit by carrying on the entire chemotherapy regimen or a part of the drugs used in the initial treatment until progression in pancreatic adenocarcinoma. Conversely, in other more chemo-sensitive tumour types, studies comparing a defined duration of therapy versus the same therapy until progression demonstrated that prolonged chemotherapy can lead to cumulative toxicity, with no proven advantage in efficacy.[21–23] In fact, the majority of patients failed to have a major response, or became intolerant of chemotherapy. Furthermore, quality-of-life parameters were the same or improved for patients randomised to receive a predefined number of chemotherapy cycles.[21,22] The results of this trial hold interest as a proof of concept of the potential usefulness of maintenance therapy after maximal response to induction chemotherapy, regardless of chemotherapy duration.

Another area of debate, may be the continuous sunitinib once-daily dosing regimen at 37.5 mg, which was adopted in this study based on the prior observations in kidney cancer showing that this schedule was a feasible alternative to 50 mg intermittent dosing.[24–26] Whether a different dosing regimen may obtain a better outcome as maintenance therapy for pancreatic adenocarcinoma may be object of speculation.

In conclusion, the results observed with the pioneering use of sunitinib as maintenance therapy after induction chemotherapy in metastatic pancreatic adenocarcinoma are encouraging and warrant further investigation.

Conflict of interest statement

Dr. Reni received consulting fees from Helsinn, served on an advisory board for Abraxis, Merck, Clovis, and Celgene, and received lecture fees from Celgene. All remaining authors have declared no conflicts of interest.

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