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A Cancer and Leukemia Group B Phase II Study of Sunitinib Malate in Patients with Previously Treated Metastatic Pancreatic Adenocarcinoma (CALGB 80603)

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Sunitinib malate is not an approved drug for the treatment of pancreas adenocarcinoma.

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ABSTRACT

Background. **The Cancer and Leukemia Group B (CALGB) conducted a phase II study evaluating sunitinib in patients with progressive metastatic pancreas adenocarcinoma following prior gemcitabine-based therapy (trial CALGB 80603; ClinicalTrials.gov identifier, NCT00397787). The primary endpoint was to determine the disease control rate (DCR) as measured by the Response Evaluation Criteria in Solid Tumors (complete response, partial response [PR], and stable disease) at 6 weeks.**

Patients and Methods. **Patients aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 and with progressive pancreas adenocarcinoma following treatment with gemcitabine were eligible. Sunitinib was dosed at 50 mg orally days 1–28, every 42 days (1 cycle). The statistical plan called for a three-stage design. A DCR ≥15% was considered worthy of further study.**

Results. **In total, 77 patients were enrolled. Forty-two (54.6%) enrollees were male. The median age was 65 years. The ECOG performance status score distribution was: 0, 39%; 1, 50%; 2, 11%. The DCR was 21.6%; one patient (1.4%) had a PR and 15 patients (20.3%) had stable disease as their best response. The progres-**

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sion-free survival time was 1.31 months (95% confidence interval [CI] 1.25–1.38 months) and overall survival time was 3.68 months (95% CI, 3.06–4.24 months).

Conclusions. **The study met its primary endpoint; however sunitinib had minimal activity and moderate toxicity in a population of gemcitabine-refractory pancreas adenocarcinoma patients. For future studies, limiting enrollment to patients with an ECOG performance status score of 0–1 is recommended.** ***The Oncologist*** 2010;15: 1310–1319

Introduction

Pancreas adenocarcinoma is a very challenging malignancy because of its refractoriness to available treatments. About 42,000 people were estimated to have been diagnosed with this disease in the U.S. in 2009, the substantial majority of whom would have either locally advanced or metastatic pancreas adenocarcinoma. These patients received either gemcitabine or a gemcitabine-based combination as initial therapy for locally advanced or metastatic disease [1, 2]. Most patients derive modest benefit from frontline therapy, with a median time to progression of 2–4 months. About half of all patients who receive frontline therapy are well enough and eligible for second-line therapy [3, 4]. There is not a standard second-line therapy for pancreas adenocarcinoma, nor a set of well-defined prognostic factors for second-line therapy, and there is a relative dearth of trials conducted in this disease setting [5]. Data from the randomized Charité Onkologie (CONKO)-003 trial and single-institution data have suggested that a fluoropyrimidine combined with oxaliplatin may represent a reasonable second-line option [6–8]. Also, recent observations have demonstrated that only a tiny fraction, approximately 2%, of patients with pancreas adenocarcinoma who are potentially eligible for a second-line therapy actually receive such therapy in the context of a clinical trial [9]. This latter observation may be related to the limited availability of second-line trials in this disease setting.

Sunitinib malate (SU11248, NSC #736511) is an orally bioavailable, multitargeted small molecule inhibitor of several receptor tyrosine kinases that are involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor, and stem cell factor receptor (KIT) [10, 11]. VEGF and its receptors are over expressed in pancreas adenocarcinoma and have been associated with the development of metastases and a poor prognosis [12]. In part, the rationale for assessing sunitinib in pancreas adenocarcinoma in this study relates to the contribution of multiple signaling pathways to the pathogenesis of this disease and the potential to impact these pathways with a relatively broad-spectrum targeted therapy along with, at the time, promising data from other anti-VEGF inhibitors in this disease [13]. There is a precedent for the development of novel targeted agents in pancreatic cancer [14]. Treatment with erlotinib combined with gemcitabine has been shown to result in a longer time to tumor progression and higher median and 1-year survival rates than with gemcitabine alone in advanced pancreas cancer [15]. Pancreatic adenocarcinoma is also characterized by a profound desmoplastic and stromal reaction that has rarely been considered as a potential therapeutic target [16, 17]. Sunitinib, via its broad inhibition of receptor tyrosine kinases, offers the potential to target both the tumor directly and the stromal matrix. This paper reports a trial performed by a National Cancer Institute (NCI)-funded cooperative group evaluating the antitumor efficacy and safety of sunitinib malate in patients with previously treated pancreas adenocarcinoma.

Patients and Methods

Patients

This phase II study was conducted by the Cancer and Leukemia Group B (CALGB). Men and women aged ≥18 years with pancreas adenocarcinoma with histologic or cytologic proof of malignancy and with evidence of disease progression on a gemcitabine-containing frontline regimen were eligible. Patients had to fall into one of the following groups: (a) only one prior regimen of gemcitabine or a gemcitabine-containing combination was to have been administered; (b) one prior combined chemoradiotherapy regimen containing gemcitabine for inoperable locally advanced pancreas adenocarcinoma was permitted, as long as the patient had subsequently progressed with measurable disease outside the radiation port; (c) one prior adjuvant gemcitabine-containing regimen or combined chemoradiotherapy regimen containing gemcitabine could have been administered, if the patient subsequently experienced progression of disease within 3 months of completion of adjuvant therapy. Prior erlotinib was allowed. Measurable, metastatic disease was required (≥20 mm by conventional computerized tomography [CT] or ≥10 mm by spiral CT); locally advanced pancreatic cancer with the primary tumor as the sole site of disease was not allowed. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 was required. Required initial laboratory cri-

teria included the following: absolute neutrophil count ≥1,500/ul, platelet count ≥100,000/μl, bilirubin <1.5 mg/dl, prothrombin time and partial thromboplastin time <1.5× the upper limit of normal (ULN), serum creatinine ≤1.5 mg/dl, and aspartate aminotransferase ≤2.5× ULN if no liver metastases r ≤5× ULN if liver metastases were present. Written informed consent was required and the protocol was reviewed and approved by the local institutional review board at each participating site.

Exclusion criteria included the following. No prior therapy with any other antiangiogenic agent (e.g., bevacizumab, sorafenib, etc.) was permitted. No significant cardiac disease was permitted; specifically, the QTc interval had to be ≤500 msec. No prior myocardial infarction, cardiac arrhythmia, active angina, active congestive cardiac failure (New York Heart Association class III or class IV), or coronary artery bypass grafting or stenting in the previous 12 months prior to registration was allowed. No history of a cerebrovascular accident or transient ischemic attack within 12 months or pulmonary emboli within 6 months prior to registration was allowed. Patients with a nonhealing wound, ulcer, or bone fracture were not enrolled. No history of significant bleeding (within 6 months), abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess was permitted. Patients with duodenal invasion by tumor on CT were not enrolled. Inhibitors and inducers of cytochrome P450 3A4 had to be discontinued prior to and during treatment with sunitinib. Also, drugs with proarrhythmic potential were not allowed during the study. Use of warfarin anticoagulants was not allowed. No "currently active" second malignancy, other than nonmelanoma skin cancer, was permissible. Patients were not considered to have a "currently active" malignancy if they had completed therapy and were considered by their physician to have a <30% risk for relapse. Brain metastases excluded patients from enrollment.

Study Procedures

Prior to registration, patients underwent a history and physical examination including notation of height, weight, ECOG performance status score, vital signs (blood pressure, temperature, pulse, respiration), and a pregnancy test for all females of child-bearing potential. A baseline CT or magnetic resonance imaging scan documenting all sites of metastatic disease was required within 4 weeks of study enrollment. A baseline electrocardiogram and either echocardiogram (ECHO) or multigated acquisition (MUGA) scan were performed prior to the initiation of therapy. Patients were evaluated weekly for toxicity and blood pressure monitoring during the first cycle. Tumor restaging was performed every cycle (every 6 weeks) for each of the first four cycles and then every other cycle thereafter. A follow up ECHO or MUGA scan was performed after the second cycle of therapy (every 12 weeks). Treatment was continued indefinitely until either disease progression or unacceptable toxicity occurred.

As part of the quality assurance program of the CALGB, members of the audit committee visit all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 11 patients (14%) of the 77 patients under this study.

Treatment and Dose Adjustments

Sunitinib malate was provided by the Division of Cancer Treatment and Diagnosis (DCTD), NCI, under a collaborative agreement between Pfizer and the DCTD. The starting dose of sunitinib was 50 mg. Sunitinib was dosed at 50 mg orally daily irrespective of timing of food, for days 1–28 followed by 14 days of rest, constituting one treatment cycle (42 days, 6 weeks). Dose level −1 of sunitinib was 37.5 mg and level −2 was 25 mg. No dose re-escalation was permitted following dose adjustment for toxicity. Patients requiring dose reduction beyond the −2 level were to discontinue protocol therapy. A treatment break of up to 4 weeks was permitted for toxicity or other disease-related complications. Protocol-specific dose modifications were prescribed for grade 3 or 4 hematologic toxicity (neutropenia, thrombocytopenia), grade 3 or 4 fatigue, hypertension, QTc prolongation, decreases in left ventricular ejection fraction, and grade 3 or 4 skin toxicity or grade 3 or 4 bleeding. For all other grade 3 toxicities, sunitinib was held until toxicity improved to grade ≤2. For other grade 4 toxicities, protocol therapy was permanently discontinued.

Statistical Plan and Analysis

The study was designed as a single-arm, nonrandomized, multicenter cooperative group (CALGB) phase II trial of single-agent sunitinib for previously treated pancreas adenocarcinoma in patients with measurable metastatic disease. The primary endpoint of the study was disease the control rate (DCR), specified as either a complete response (CR), partial response (PR), or stable disease (SD) as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) 6 weeks following the initiation of protocol therapy [18, 19]. The null hypothesis that the DCR according to the RECIST was ≤5%, versus the alternative that the DCR was ≥15%, was tested using a three-stage design. If the

DCR was ≥15%, then single-agent sunitinib was to be considered worthy of further study in gemcitabine-refractory pancreas adenocarcinoma. Nineteen patients were to be entered in stage 1. If a DCR of 0% was observed during the first 19 patients studied, the trial was to be closed because of a lack of efficacy. If a DCR >5% was observed among the first 19 patients studied, 20 additional patients were to be enrolled in stage 2. If a DCR ≤2% was observed among the first 39 patients studied, the trial was to close at stage 2 because of a lack of efficacy. If two or more cases of a CR, PR, or SD (DCR >5%) were observed among the first 39 patients studied, 21 additional patients were to be enrolled in stage 3. Sunitinib was to be considered worthy of further investigation at stage 3 if six cases of CR, PR, or SD (DCR of 10%) were observed among 60 eligible patients treated. The simulated power and significance level under this design (10,000 simulations) are 0.9 and 0.08, respectively. The sample size was increased to 64 to allow for replacement of patients who did not initiate protocol therapy. All patients who met the eligibility criteria and received at least one dose of protocol therapy were included in the analysis of the primary endpoint.

The secondary endpoints of the study were: response duration, progression-free survival (PFS), toxicity, and overall survival. Duration of response was determined for the subset of patients who achieved a confirmed response (CR or PR). Duration of an objective response was defined as the time from the first tumor assessment indicating response to the time of disease progression or death from any cause. PFS and overall survival times were assessed using the Kaplan–Meier method. Toxicity data were graded using the NCI Common Toxicity Criteria for Adverse Events, version 3.0. Particular attention was paid to hypertension, cardiac events, bleeding, and thrombotic events. All adverse events were reported to the CALGB. All patients who received at least one dose of sunitinib were evaluable for toxicity.

RESULTS

Patient Characteristics

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson (E.O.'R.). Statistical analyses were performed by CALGB statisticians.

In total, 77 patients were enrolled from November 2006 through November 2007. The study met the criteria for proceeding to the third stage. Enrollment to the study was very brisk in the last several weeks and hence, in view of commitment to multiple study sites, the study recruitment exceeded the goal of 64 patients. Forty-two patients (54.5%) were male. The median age was 65 years (range, 42–87 years). The ECOG performance status score was 0 in 30 patients (38.9%), 1 in 38 patients (49.4%), and 2 in nine patients (11.7%). Eight-four percent of patients had liver metastases on entry to the study. Thirty-six percent of patients had had stable disease to prior gemcitabine and 10.4% had experienced a response to gemcitabine therapy. A detailed summary of patient characteristics is provided in Table 1.

Primary Endpoint

Seventy-four patients were eligible for analysis of the primary study endpoint. Three of the 77 patients enrolled never received treatment. The median follow-up time was 22.1 months. The median number of cycles delivered was one. The (CR, PR, or SD by the RECIST at 6 weeks) was 21.6%, with one patient (1.4%) with a PR and 15 patients (20.3%) with SD. Forty patients (54%) had progressive disease as their best response. Eighteen patients (24.3%) did not have a follow-up scan and were not evaluable for the primary endpoint. Those patients ended treatment prior to completing one cycle of therapy as a result of progressive disease ($n = 3$), death resulting from progressive disease ($n = 9$), and withdrawal of consent prior to receiving any treatment ($n = 3$). Only one of those patients was reported to have gone on to receive further treatment. For the patient with an observed PR, this was maintained for 16 weeks. For the 15 patients who had SD as their best response, the median SD duration was 11.3 weeks (range, 5.7–55 weeks). Response data are summarized in Table 2.

Secondary Endpoints

Seventy-four patients were eligible for the survival analysis. The median duration of protocol therapy was 28 days (range, 2–126 days). The median PFS interval for all 74 patients was 1.31 months (95% confidence interval [CI], 1.25–1.38 months) (Fig. 1). Seventy-three patients had died and one was alive at the time of the final study analysis. The overall median survival duration was 3.68 months (95% CI, 3.06–4.24 months) (Fig. 2).

Toxicity

All 74 patients who received any dose of study drug were eligible for toxicity assessment. Twenty-one (27.1%) patients required a dose modification during cycle 1. The principal grade 3–5 toxicities observed were hematologic ($n = 16$, 21.7%, and nonhematologic ($n = 32$, 43.2%). Specifically, relevant grade 3 toxicities included: hypertension in three patients (4%), fatigue in 13 patients (17.6%), bleeding

Table 1. Patient characteristics ($n = 77$)

Characteristic	*n* (%)
Gender	
Male	42 (54.6%)
Female	35 (45.4%)
Race	
White	66 (85.7%)
Black	9 (11.7%)
Asian	1 (1.3%)
Multiracial	1 (1.3%)
Median age (range), yrs	65 (42–87)
ECOG performance status score	
0	30 (39%)
1	38 (49.4%)
2	9 (11.7%)
Disease site	
Pancreas/primary bed	50 (64.9%)
Liver	65 (84.4%)
Lung	23 (29.9%)
Intra-abdominal (other)[a]	15 (19.5%)
Bone	1 (1.3%)
Prior surgery[b]	
No	40 (51.9%)
Yes	37 (48.1%)
Prior therapy	
Gemcitabine	47 (61%)
Gemcitabine-based cytotoxic combination	29 (38%)
Gemcitabine + tyrosine kinase inhibitor (erlotinib)	12 (15.6%)
(Chemo)radiation therapy	19 (24.7%)
Experimental therapy with or without gemcitabine	4 (5.2%)
Best response to prior gemcitabine therapy[c]	
Complete response	2 (2.6%)
Partial response	6 (7.8%)
Stable disease	28 (36.4%)
Progression of disease	38 (49.4%)
Unknown response	3 (3.9%)
Prior therapy context	
Adjuvant therapy	5 (6.5%)
Locally advanced disease	5 (6.5%)
Metastatic disease	67 (87%)
Months from initial diagnosis to start of protocol therapy, median (range)	8 (2.8–80)
Weeks from prior therapy to start of protocol therapy, median (range)	5 (2.9–31) wks

[a]Other sites include lymph nodes, ascites, retroperitoneum, spleen.
[b]Prior surgery included prior definitive resection, exploratory laparotomy, and surgical bypass.
[c]As reported by investigator.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Response data ($n = 74$)

Characteristic	*n* (%)
Primary endpoint: disease control rate at 6 wks (CR, PR, SD)	16 (21.6%)
Response 6 wks after starting therapy	
PR	1 (1.4%)
SD[a]	15 (20.3%)
Progressive disease	40 (54%)
Insufficient evaluation	18 (24.3%)

[a]One patient had an insufficient response evaluation at 6 weeks, but the best overall response was SD and the patient subsequently progressed after 1 year on study.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

in five patients (6.8%), thrombotic microangiopathy/renal failure in two patients (2.7%), and thrombosis in two patients (2.7%). There were two (2.7%) grade 5 events on study, a gastrointestinal perforation and respiratory distress. Both of these grade 5 toxicities were attributed to the study drug and related to progression of underlying pancreas adenocarcinoma. The commonest reasons for study discontinuation were progression of disease (POD) during therapy (61%), adverse event (9.1%), death during treatment/POD (14.3%), or declining further treatment (9.1%). Toxicity information is summarized in Table 3.

Discussion

Progressive metastatic pancreas adenocarcinoma following frontline gemcitabine-based therapy represents a very poor prognostic disease setting with median survival times measured in the several month range [20, 21]. However, this patient group represents a significant patient number in that about 40%–60% of patients who receive frontline therapy are well enough and eligible to receive further therapy [4]. New therapies are desperately needed for this patient population. This study assessed the single-agent utility of sunitinib, a broad-spectrum receptor tyrosine kinase inhibitor, in this patient population in the context of a large, cooperative group, single-arm, phase II clinical trial. Sunitinib represents an attractive drug to assess given its inhibition of multiple targets and the importance of the VEGF pathway in pancreas adenocarcinoma [12, 22] and, notwithstanding, potential activity against the desmoplastic stromal matrix, which appears to be fundamental to the development and maintenance of the pancreatic neoplastic phenotype [23]. This study technically met its primary endpoint of disease control in that 21.7% of patients had a CR, PR, or SD at 6 weeks (mostly SD). However, the very short time on study of less than one treatment cycle, reflected in

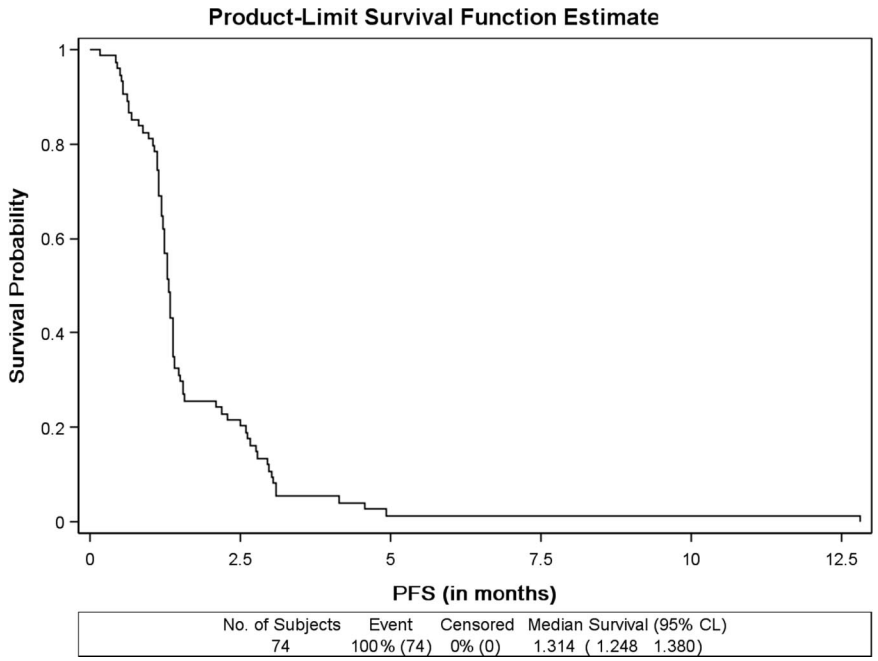

Figure 1. PFS in patients treated with sunitinib in the setting of prior gemcitabine treatment for metastatic pancreas adenocarcinoma.

Abbreviations: CI, confidence interval; PFS, progression-free survival.

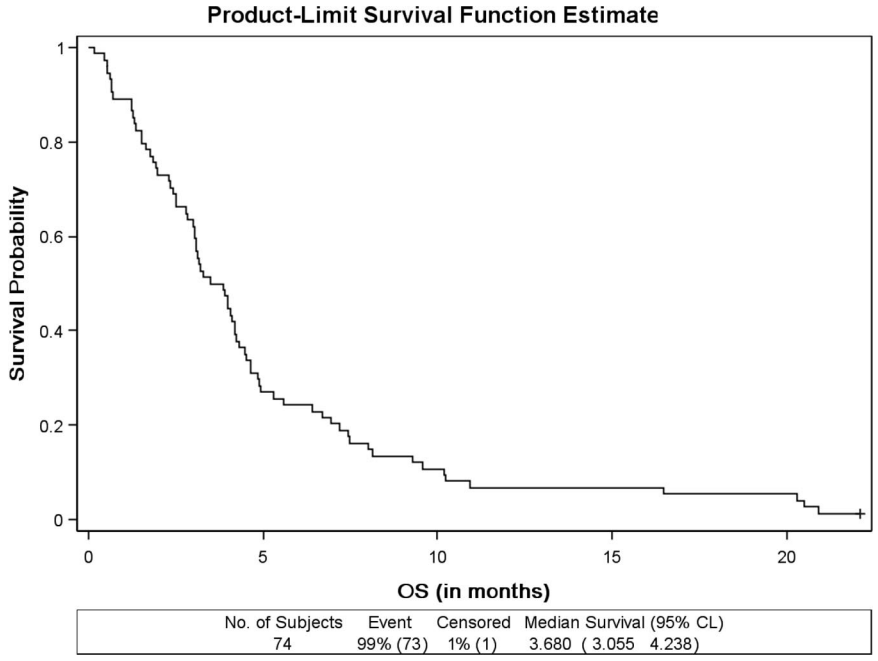

Figure 2. OS in patients treated with sunitinib in the setting of prior gemcitabine treatment for metastatic pancreas adenocarcinoma.

Abbreviations: CI, confidence interval; OS, overall survival.

the short PFS time of 1.31 months, the moderate toxicity, and the limited survival argue against any usefulness of sunitinib in this patient population. The experience and results observed in this study have been mirrored by other trials conducted with other targeted agents in a similar treatment population [20, 24–27]. One positive note was the interest in this trial evident in its very brisk recruitment, suggesting that a cooperative group can provide a good forum for conducting second-line clinical trials with novel agents in patients with previously treated pancreas adenocarcinoma.

Since the time of study conception, notwithstanding the

Table 3. Toxicity data ($n = 74$)

Adverse event	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)
Hematologic			
Hemoglobin	4 (5.4%)	–	–
Neutrophils	5 (6.8%)	–	–
Platelets	6 (8.1%)	1 (1.4%)	–
Cardiovascular			
Hypertension	3 (4%)	–	–
Constitutional			
Fatigue	13 (17.6%)	1 (1/4%)	–
GI			
Anorexia	1 (1.4%)	–	–
Dehydration	5 (6.8%)	–	–
Diarrhea	2 (2.7%)	–	–
Constipation	2 (2.7%)	–	–
Bloating	2 (2.7%)		
Stomatitis	1 (1.4%)	–	–
Nausea	7 (9.5%)	–	–
Vomiting	5 (6.8%)	–	–
GI obstruction	1 (1.4%)	–	–
GI perforation	–	–	1 (1.4%)
GI stricture	1 (1.4%)	–	–
Hemorrhage			
Respiratory	1 (1.4%)	–	–
GI	4 (5.4%)	–	–
Infection			
Febrile neutropenia	2 (2.7%)	–	–
Fever and grade 1–2 ANC	4 (5.4%)	–	–
Other	3(4.1 %)	–	–
Metabolic/laboratory			
AST/ALT	5 (6.8%)	–	–
Bilirubin	3 (4.1%)	1 (1.4%)	
Hypercalcemia	1 (1.4%)		
Hypocalcemia	2 (2.7%)	–	–
Hypoglycemia	1 (1.4%)	–	–
Hypokalemia	2 (2.7%)	–	–
Hyponatremia	3 (4.1%)	1 (1.4%)	–
Hypernatremia	1 (1.4%)	–	–
Prolonged PT	2 (2.7%)	–	–
Neurologic			
Confusion	2 (2.7%)	–	–
Dizziness	1 (1.4%	–	–
Muscle weakness	2 (2.7%)	–	–
Pain	9 (12.2%)	1 (1.4%)	–
Pulmonary			
Dyspnea	3 (4.1%)	–	1 (1.4%)
Renal			
Thrombotic microangiopathy	1 (1.4)	–	–
Renal failure	1 (1.4)	–	–
GU stricture	1 (1.4%)	–	–
Vascular			
Thrombosis/embolism	2 (2.7%)	1 (1.4%)	–

Toxicity information pertains to all causes.
Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; GI, gastrointestinal; GU, genitourinary; PT, prothrombin time.

Table 4. Selected phase II trials of second-line therapy for pancreas adenocarincoma using targeted agents

Therapy	*n*	RR	Median survival	Study
Bevacizumab + erlotinib	36	2.7%	102 days (3.4 mos)	Ko et al. [20]
Capecitabine + erlotinib	30	11%	6.7 mos	Kulke et al. [36]
Erlotinib	18	NR	3.1 mos	Iyer et al. [25]
Saracatinib	19	NR	2.5 mos	Messersmith et al. [24]
5-Fluorouracil + celecoxib	17	11.7%	15 weeks (3.5 mos)	Milella et al. [39]
Capecitabine + celecoxib[a]	35	9%	19 weeks (4.4 mos)	Pino et al. [40]
Nab-paclitaxel	20	5%	7.3 mos	Hosein et al. [41]
Gemcitabine + oxaliplatin + imatinib (phase I)	26	7.7%	5.7 mos	Starling et al. [42]
Everolimus (RAD001)	33	0%	4.5 mos	Wolpin et al. [26]
Sunitinib	77	1.4%	3.68 mos	O'Reilly et al. [present study]

[a]Included patients with pancreas and biliary malignancies.
Abbreviations: NR, not reported; RR, response rate.

strong preclinical rationale for antivascular therapy in pancreas adenocarcinoma [12, 22, 28], the accumulating clinical data speak against the utility of targeting VEGFR pathways as being a useful clinical approach. In the treatment of frontline advanced pancreas adenocarcinoma, there are now two fully reported randomized trials that have failed to meet a primary survival endpoint of demonstrating superiority for the addition of the antivascular agent [29–34], and two other studies evaluating the addition of axitinib to gemcitabine and the addition of aflibercept (VEGF-Trap) to gemcitabine have been preliminarily reported as not meeting a survival endpoint. The reasons for the failure of antivascular therapy remain relatively poorly understood and may relate to the hypoxic microenvironment of pancreas adenocarcinoma, along with drug delivery and distribution challenges [17, 35].

Targeted agents have been extensively assessed in both the first- and second-line setting in pancreas adenocarcinoma. Using single or combination targeted agents in a second-line setting has yielded rare responses, short PFS and overall survival times, and limited value to this strategy (Table 4). Drugs assessed include erlotinib [25], saracatinib [24], everolimus [26], bevacizumab plus erlotinib [20], and sunitinib. Somewhat more activity has been observed for combining a targeted agent with cytotoxic therapy in the refractory disease setting [36], although here the benefit may relate to the cytotoxic backbone alone because no randomized trials have evaluated the addition of a targeted agent in the second-line setting when combined with cytotoxic therapy.

Where do we go from here in the second-line treatment of pancreas adenocarcinoma? Treating patients with advanced pancreas cancer refractory to frontline therapy remains very challenging. Of fundamental importance is the patient's functional status at the time of second-line treatment initiation [5, 30]. Arguably, performance status may be one of the key predictors of outcome in the second-line setting of treatment for pancreas adenocarcinoma, along with whether or not patients responded to initial gemcitabine-based therapy. The latter characteristic was not formally assessed as part of this particular study, but was provided by the investigator. In the trial reported herein, response to prior therapy did not appear to correlate with outcome; however, other cytotoxic-based trials have stratified for response to frontline therapy [21]. In another retrospective analysis, the first-line PFS interval was identified to be the main prognostic factor for benefit from second-line therapy [3]. The current study permitted patients with an ECOG performance status score of 2. In reality, these patients probably never really had a chance to benefit from second-line therapy because their disease-related complications/comorbidities were always likely to overwhelm the potential benefit of the therapeutic agent under study. Restricting enrollment in this second-line setting to patients with an ECOG performance status score of 0–1 is recommended going forward, particularly in studies accrued from a broad base spanning academic centers through community practice settings.

Regardless, the fundamental challenge for making progress in the treatment of pancreas adenocarcinoma, irrespective of disease setting, does not relate to patient selection. It relates to the dearth of truly active drugs with meaningful impacts on pathways that are important for maintenance and progression of the malignant metastatic state and the natural history of the disease. In these authors' opinions, cytotoxic therapy remains entrenched as part of

the treatment of pancreas cancer either first- or second-line. Conroy et al. [37] recently reported preliminary results from the Partenariat de Recherche Oncologie Digestive (PRODIGE) 4/ACCORD 11 trial demonstrating clear superiority for 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (the FOLFIRINOX regimen) over gemcitabine in patients with untreated metastatic pancreas cancer. This signal deserves further evaluation, and indeed, variants of it (infusional 5-fluorouracil and oxaliplatin [6, 21, 38]) are already established as a second-line treatment. For now, the role of targeted agents in previously treated pancreas cancer patients appears to be with integration with cytotoxic therapy. Olive and colleagues elegantly demonstrated that inhibition of Hedgehog signaling in a pancreas cancer mouse model refractory to gemcitabine may enhance drug delivery and effect short-term disease stabilization in the presence of IPI-926, a hedgehog signaling inhibitor [35]. If the proof of principle of this strategy holds, the implications could be significant for the treatment of pancreas adenocarcinoma.

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