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Sunitinib in combination with gemcitabine for advanced solid tumours: a phase I dose-finding study

M D Michaelson^{*,1}, A X Zhu¹, D P Ryan¹, D F McDermott², G I Shapiro³, L Tye⁴, I Chen^{4,6}, P Stephenson⁵, S Patyna⁴, A Ruiz-Garcia⁴ and A B Schwarzberg¹

¹Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey 7, Boston, MA 02114, USA; ²Beth Israel Deaconess Medical Center, 375 Longwood Avenue, Boston, MA 02215, USA; ³Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA; ⁴Pfizer Oncology, 10777 Science Center Drive La Jolla, CA 92121, USA and ⁵Rho, Inc., 6330 Quadrangle Drive, Suite 500, Chapel Hill, NC 27517, USA

Background: This phase I, dose-finding study determined the maximum tolerated dose (MTD), safety, and pharmacokinetics of sunitinib plus gemcitabine in patients with advanced solid tumours.

Methods: Two schedules with sunitinib (25–50 mg per day) and IV gemcitabine (750–1250 mg m⁻²) in escalating doses were studied. First, patients received sunitinib on a 4-weeks-on-2-weeks-off schedule (Schedule 4/2) plus gemcitabine on days 1, 8, 22, and 29. Second, patients received sunitinib on a 2-weeks-on-1-week-off schedule (Schedule 2/1) plus gemcitabine on days 1 and 8. The primary endpoint was determination of MTD and tolerability.

Results: Forty-four patients received the combination (Schedule 4/2, *n* = 8; Schedule 2/1, *n* = 36). With no dose-limiting toxicities (DLTs) at maximum dose levels on Schedule 2/1, MTD was not reached. Grade 4 treatment-related AEs and laboratory abnormalities included cerebrovascular accident, hypertension, and pulmonary embolism (*n* = 1 each), and neutropenia (*n* = 3), thrombocytopenia and increased uric acid (both *n* = 2), and lymphopenia (*n* = 1). There were no clinically significant drug–drug interactions. Antitumor activity occurred across dose levels and tumour types. In poor-risk and/or high-grade renal cell carcinoma patients (*n* = 12), 5 had partial responses and 7 stable disease \geq 6 weeks.

Conclusion: Sunitinib plus gemcitabine on Schedule 2/1 with growth factor support was well tolerated and safely administered at maximum doses of each drug, without significant drug–drug interactions.

Therapeutic inhibition of tumour angiogenesis and multiple signalling pathways associated with tumour development (e.g., pathways controlled by vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs)) results in clinically meaningful antitumor activity, as demonstrated across multiple tumour types, including colon cancer, pancreatic carcinoma, renal cell carcinoma (RCC), breast cancer (BC) and non-small-cell lung cancer (NSCLC) (Hurwitz *et al*, 2005; Sandler *et al*, 2006; Miller *et al*, 2007; Burstein *et al*, 2008; Manegold *et al*, 2008;

Escudier *et al*, 2009). When combined with chemotherapy, antiangiogenic therapies may provide effective treatment of historically treatment-resistant solid tumours (Hurwitz *et al*, 2005; Sandler *et al*, 2006; Miller *et al*, 2007; Manegold *et al*, 2008). Thus, treatment that specifically interrupts tumour vasculature through inhibition of various important receptor tyrosine kinase (RTK) signalling pathways, combined with a chemotherapy, may be of interest.

Sunitinib malate, an oral multitargeted inhibitor of VEGFRs, PDGFRs, stem cell factor receptor (KIT), and other RTKs (Abrams

*Correspondence: Dr MD Michaelson; Email: dmichaelson1@partners.org

⁶Current address: Aragon Pharmaceuticals, San Diego, CA, USA.

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et al, 2003; Mendel *et al*, 2003; O'Farrell *et al*, 2003a,b; Faivre *et al*, 2006), is approved for treatment of advanced RCC, imatinib-resistant gastrointestinal stromal tumour, and progressive, well-differentiated pancreatic neuroendocrine tumours (Demetri *et al*, 2006; Motzer *et al*, 2006; Motzer *et al*, 2007; Kulke *et al*, 2008; Raymond *et al*, 2011; SUTENT (sunitinib malate) prescribing information (2012)). In phase I and II trials, sunitinib has also shown antitumor activity in patients with other advanced solid tumours, including BC, NSCLC, neuroendocrine tumour, sarcoma, thyroid cancer and melanoma (Rosen *et al*, 2003; Faivre *et al*, 2006; Burstein *et al*, 2008; Socinski *et al*, 2008).

Gemcitabine is a nucleoside analogue that primarily targets cells undergoing DNA synthesis (S-phase) and also blocks progression of cells through the G1/S-phase boundary. Gemcitabine is used (alone or in combination with other chemotherapies, such as cisplatin or carboplatin) across a broad spectrum of solid tumours, including locally advanced or metastatic adenocarcinoma of the pancreas, metastatic BC, advanced NSCLC, ovarian cancer, bladder cancer, and others (Gemzar (gemcitabine HCl) prescribing information (2010); Gemzar (gemcitabine HCl) product monograph (2006)).

A multitargeted approach for treatment-resistant solid tumours is an attractive strategy. Targeting PDGF and VEGF signalling pathways with sunitinib plus gemcitabine may enhance antitumor activity compared with either agent alone. Extensive preclinical evidence suggests additive and/or synergistic effects in solid tumour models when a variety of chemotherapies, including gemcitabine, are combined with targeted agents, including sunitinib (Yee *et al*, 2004; Carter *et al*, 2007; Christensen *et al*, 2008), as demonstrated in a recently reported phase I trial of sunitinib on a continuous daily dosing schedule plus gemcitabine in patients with advanced solid tumours (Brell *et al*, 2012). The phase I dose-finding study reported here was also conducted to investigate the safety, pharmacokinetics (PK) and antitumor activity of sunitinib (on an intermittent dosing schedule) in combination with gemcitabine in patients with advanced solid tumours for whom curative therapy was not available. Our study focused on patients with RCC and pancreatic cancer (adenocarcinoma), for whom sunitinib and gemcitabine are standard treatments, respectively.

PATIENTS AND METHODS

Patients. The population comprised patients aged ≥ 18 years with life expectancy ≥ 12 weeks and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. All patients had histologically proven advanced solid tumours for which curative therapy was not available, had received ≤ 1 prior chemotherapy regimen, and were considered eligible for treatment with standard doses of single-agent gemcitabine. Other inclusion criteria included adequate organ function and haematological parameters without transfusion requirement (erythropoietin or darbepoietin permitted).

Patients were excluded if previously treated with gemcitabine or sunitinib; had severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, cerebrovascular accident, or transient ischaemic attack within the previous 12 months; National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0) grade 3 haemorrhage within 4 weeks of study entry; uncontrolled hypertension; uncontrolled brain metastases; and a second malignancy diagnosis within the last 5 years.

Study design and treatment. The study (registered with ClinicalTrials.gov, NCT00615446) was conducted at institutions within Dana-Farber/Harvard Cancer Centre (DFHCC) including Massachusetts General Hospital, Dana-Farber Cancer Institute, and Beth

Israel Deaconess Medical Centre. In this phase I, open-label, non-randomized, dose-finding study, successive cohorts of three patients each received escalating doses of oral sunitinib in combination with escalating doses of intravenous gemcitabine, at starting doses of 37.5 mg and 750 mg m⁻², respectively, using a standard 3 + 3 design. Sunitinib was administered using one of two once-daily dosing schedules: repeated 6-week cycles consisting of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2), or 3-week cycles consisting of 2 weeks on treatment followed by 1-week off (Schedule 2/1). Gemcitabine was administered on days 1, 8, 22, and 29 on Schedule 4/2 and on days 1 and 8 on Schedule 2/1 (Figure 1). Planned dose-escalation schemes for sunitinib (both schedules) and gemcitabine are shown in Table 1.

The initial cohorts were expanded to six patients if 1/3 patients experienced a DLT (as defined below) during cycle 1. In addition, up to six additional patients could be included at specific dose levels on either schedule to further define the observed toxicity profile.

Patients were treated until disease progression, unacceptable toxicity, or consent withdrawal. Provision was made for dose reduction if patients experienced drug-related toxicities. The study was performed with approval from the DFHCC institutional review board and in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable local regulatory requirements and laws. All patients provided written informed consent.

Dose-limiting toxicity and determination of maximum tolerated dose (MLT). Haematological DLTs were defined as grade 4 neutropenia for ≥ 7 days; febrile neutropenia (fever $> 38.5^{\circ}\text{C}$ for ≥ 24 h); neutropenic infection (\geq grade 3 neutropenia with grade ≥ 3 infection); grade ≥ 4 thrombocytopenia, with bleeding or lasting ≥ 7 days; or lymphopenia accompanied by related infection. Non-haematological DLTs were any drug-related grade 3 or 4 toxicities lasting ≥ 7 days (except for grade 3/4 hyperamylasemia or hyperlipasemia without signs of pancreatitis, grade 4 hyperuricemia or grade 3/4 hypophosphatemia without clinical symptoms, or grade 3 asymptomatic hypertension), and nausea, vomiting, or diarrhoea persisting at grade 3 or 4 despite treatment.

The MTD was defined as the highest dose at which 0/6 or 1/6 patients experienced a DLT during the first 36 or 21 days of cycle 1 (Schedule 4/2 or 2/1, respectively), with the next higher dose having at least 2/3 or 2/6 patients experiencing a DLT. Additional patients could be enrolled at the MTD to further characterise safety and tolerability at that dose level.

Changes to study design and treatment. Schedule 4/2 was not evaluated past the initial combination dose level (sunitinib 37.5 mg and gemcitabine 750 mg m⁻²) as it proved to be an awkward scheduling regimen in practice because of missed or delayed doses of gemcitabine (see Determination of MTD). After moving to the Schedule 2/1 dose-escalation phase, the original protocol was amended to allow use of growth factor support. On day 8, if absolute neutrophil count (ANC) was > 1000 cells per mm³, gemcitabine was given as scheduled. If ANC was between 500 and 1000 cells per mm³ with no signs and symptoms of infection, gemcitabine was given as scheduled and growth factor administration (Neulasta; pegfilgrastim) occurred 1 day later. If ANC was < 500 cells per mm³, then the gemcitabine dose was held. Missed doses of day 8 gemcitabine were not made up.

Study endpoints. The primary objective was to assess the MTD and overall safety and tolerability of sunitinib administered in combination with gemcitabine in patients with advanced solid tumours. Secondary objectives included evaluation of the antitumor activity and determination of the PK profiles of sunitinib, its active metabolite (SU12662), total drug (sunitinib + SU12662), and

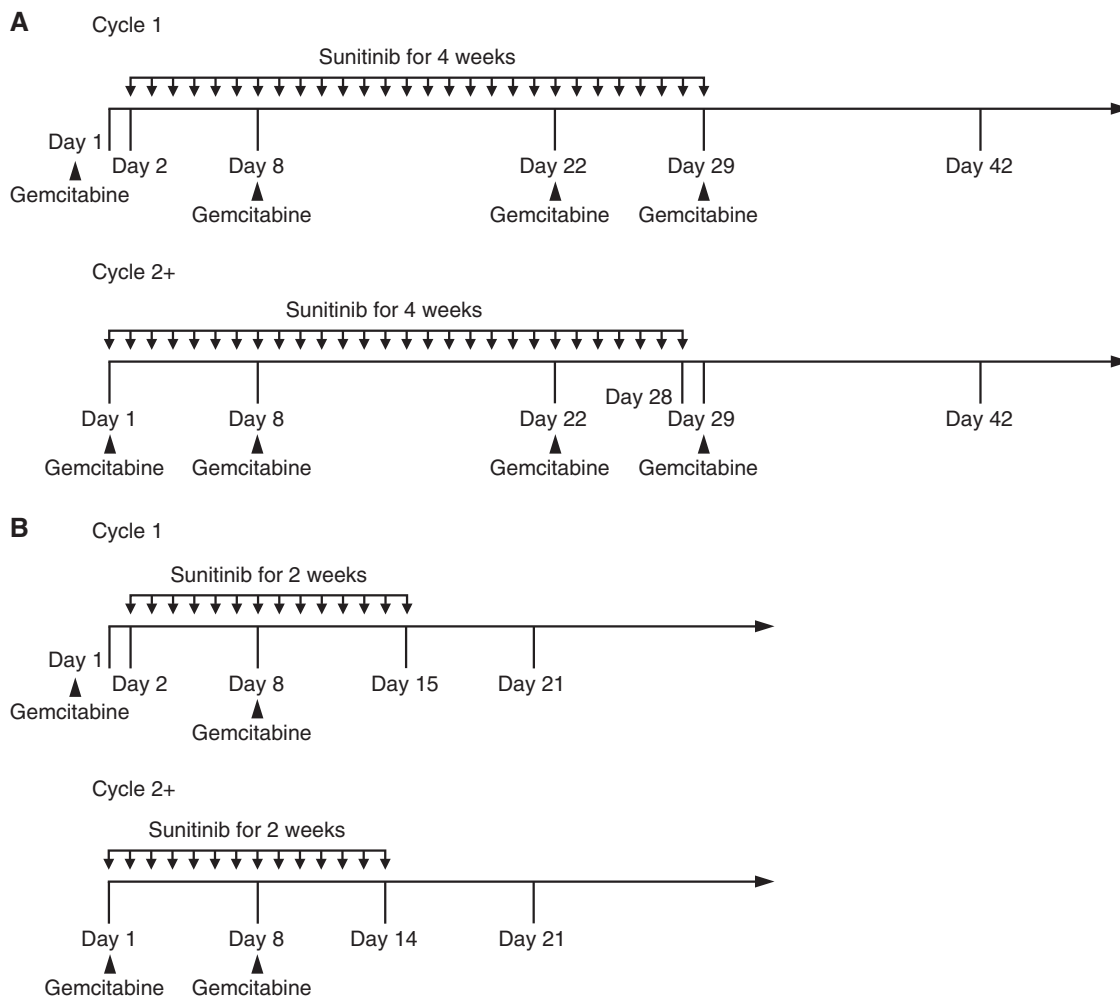


Figure 1. Study schema for (A) Schedule 4/2 and (B) Schedule 2/1.

gemcitabine and its main metabolite (2'-deoxy- 2', 2'-difluorouridine; dFdU), when given in combination.

Study assessments. Safety assessment included AE monitoring with severity graded according to NCI CTCAE, Version 3.0, and urinalysis, clinical laboratory tests (haematology and blood chemistry), physical examinations, and 12-lead electrocardiogram, all scheduled at regular intervals. Objective tumour response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.0) (Therasse *et al*, 2000). Radiological tumour assessments were performed at screening and on day 29 of cycle 1 and even cycles thereafter (Schedule 4/2), week 3 of cycles 2, 4, and every 4 cycles thereafter (Schedule 2/1), whenever disease progression was suspected, and to confirm response.

Blood samples for determination of full PK profiles for sunitinib and SU12662 were collected for patients receiving Schedule 4/2 on cycle 1, day 15 (sunitinib alone) and day 22 (sunitinib and gemcitabine), and for patients receiving Schedule 2/1 on cycle 1, day 8 (sunitinib and gemcitabine) and day 15 (sunitinib alone) at pre-dose and up to 25 h post-dose. In addition, blood samples for determination of trough levels of sunitinib and SU12662 were taken for Schedule 4/2 pre-dose on day 1 (cycles 1–3) and 24 h after the last dose (cycles 1–3 and 5), and for Schedule 2/1 were obtained before dosing on day 1 (cycles 1, 4, and 6), days 8 and 15 (cycle 1) and day 14 (cycles 4, 6, and 10). For gemcitabine and dFdU PK profiles, blood samples were drawn pre-dose and up to 9 h after the start of infusion on cycle 1, days 1 and 22 (with

Table 1. Dose escalation scheme		
	Dose level	
	Gemcitabine (mg m ⁻²)	Sunitinib (mg)
Schedule 4/2		
- 2	600	25
- 1	600	37.5
1 (Starting dose)	750	37.5
2	750	50
3a	850	37.5
3	850	50
4a	1000	37.5
4	1000	50
Schedule 2/1		
- 2	600	25
- 1	600	37.5
1 (Starting dose)	750	37.5
2	850	37.5
3	1000	37.5
4	1000	50
5	1250	37.5
6	1250	50

sunitinib on Schedule 4/2) or on cycle 1, days 1 and 8 (with sunitinib on Schedule 2/1).

Statistical methods. The population for all analyses included enrolled patients who received ≥ 1 dose of study medication. Owing to the exploratory nature of the study, no confirmatory inferential analyses were planned and descriptive statistics were used to summarise patient characteristics, treatment administration/compliance, efficacy, and safety. Pharmacokinetics parameters were calculated for each subject by noncompartmental analysis of concentration–time data using WinNonlin version 4.1.

RESULTS

Baseline patient characteristics and treatment. In total, 44 patients were enrolled: 8 on Schedule 4/2 and 36 on Schedule 2/1. Of the 36 patients on Schedule 2/1, 11 were enrolled before the protocol amendment that allowed the use of growth factor support and 25 were enrolled post-amendment. Eleven patients total (all on Schedule 2/1) received growth factor support, including one patient before the amendment. Baseline patient characteristics (all patients and patients treated on Schedule 2/1, post-amendment) are summarised in Table 2. The most common primary tumour types were RCC (52%) and pancreatic cancer (30%).

Patients treated on Schedule 4/2 and Schedule 2/1, pre- and post-amendment, began a median of 3 cycles (range 1–8), 4 cycles (range 1–9), and 9 cycles (range 2–17), respectively. Median days on sunitinib treatment were 92, 84, and 83–254 (depending on the dose level), respectively, and the median relative dose intensity for sunitinib was 58.4, 72.9, and 77.4–100% (67.8, 75.0, and 87.6–100% for gemcitabine). Sunitinib dose interruptions occurred in 62.5, 63.6, and 33.3–100%, and sunitinib dose reductions occurred in 12.5, 18.2, and 0–75.0%.

Fifty per cent or more of patients were on treatment for more than 6 months at all dose levels, except the lowest (sunitinib 37.5 mg plus 750 mg m⁻²).

Determination of MTD. One of eight patients on Schedule 4/2 experienced a DLT (grade 3 neutropenia) at the initial dose level of sunitinib 37.5 mg + gemcitabine 750 mg m⁻², warranting further dose escalation. However, several patients treated on this regimen either missed or had delayed doses of gemcitabine because of slow recovery from neutropenia, and it was decided not to pursue this regimen further. Two of eleven patients (18%) on Schedule 2/1, pre-amendment, had DLTs at the dose level of sunitinib 37.5 mg + gemcitabine 750 mg m⁻² (appendicitis/abscess and QTc prolongation). Following the amendment allowing growth factor support, no further protocol-defined DLTs were observed. Dose escalation proceeded to the maximum planned dose level of sunitinib 50 mg and gemcitabine 1,250 mg m⁻²; further dose escalation was not tested as these are the highest approved doses for each agent individually.

Adverse events. The most common treatment-emergent (all causality) non-haematological AEs (all schedules, all doses) were fatigue (75.0%), gastrointestinal disorders (nausea, vomiting, diarrhoea, constipation (each 45.5%)), and pyrexia (45.5%), the majority grade 1 or 2 in severity. The most common haematological toxicities were neutropenia (54.6%), thrombocytopenia (50.0%), leucopenia (34.1%), and anaemia (38.6%). The sunitinib dose was interrupted in 25 patients and reduced in 12 patients across all cohorts. The gemcitabine dose was not modified in any patients. Seven patients died on study, six related to disease progression and one to liver failure (hepatotoxicity has been observed with sunitinib; SUTENT (sunitinib malate) prescribing information (2012)). All deaths were considered unrelated to study treatment as assessed by investigators.

Table 2. Patient characteristics at baseline

Characteristic	No. of patients (%)	
	All patients ^a (N = 44)	Schedule 2/1 post-amendment ^b (N = 25)
Median age (range), years	55.5 (27–77)	58 (41–77)
Male/female	33/11 (75/25)	20/5 (80/20)
Race		
White	37 (84)	22 (88)
Black	2 (5)	0
Asian	4 (9)	2 (8)
Not listed	1 (2)	1 (4)
ECOG performance status		
0	15 (34)	9 (36)
1	29 (66)	16 (64)
Primary tumour types		
RCC	23 (52)	14 (56)
Clear cell	10 (23)	6 (24)
Non-clear cell	13 (30)	8 (32)
Pancreatic cancer	13 (30)	5 (20)
Adenocarcinoma	10 (23)	5 (20)
Ductal adenocarcinoma	3 (7)	0
Other tumour type	8 (18)	6 (24)
Adenocarcinoma	3 (7)	1 (4)
Carcinoma	1 (2)	1 (4)
Dedifferentiated	1 (2)	1 (4)
Soft tissue and lung	1 (2)	1 (4)
Mesothelioma	1 (2)	1 (4)
Unknown	1 (2)	1 (4)
Previous treatment		
Surgery ^f	43 (98)	25 (100)
Radiotherapy	9 (20)	6 (24)
Prior systemic therapy	15 (34)	7 (28)
1 treatment	14 (32)	7 (28)
≥ 2 treatments	1 (2)	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RCC = renal cell carcinoma.
^aIncludes patients on Schedule 4/2 (n=8), Schedule 2/1 pre-amendment (n=11), and Schedule 2/1 post-amendment (n=25).
^bSchedule 2/1 study design was amended in order to allow use of growth factor support during cycle 1, if necessary.
^cSurgery includes diagnostic procedures.

Among the eight patients treated on Schedule 4/2, the only treatment-related non-haematological grade ≥ 3 AEs were grade 3 fatigue (n = 1) and increased lipase (n = 1). Laboratory abnormalities included grade 3 neutropenia (n = 4), anaemia (n = 1), and thrombocytopenia (n = 1).

On Schedule 2/1, pre-amendment, treatment-related non-haematological grade ≥ 3 AEs for sunitinib 37.5 mg plus gemcitabine 750 mg m⁻² were nausea, diarrhoea, vomiting, abscess, appendicitis, electrocardiogram QT-prolongation, hyperamylasemia (each n = 1), and hyperlipasemia (n = 2). For the patient with grade 3 QT-prolongation, which began on cycle 1, day 8, the AE resolved after sunitinib dose interruption for 3 days and dose reduction. Haematological AEs were neutropenia (grade 3 (n = 1) and grade 4 (n = 2)) and leucopenia (grade 3 (n = 2)). No grade 5 events occurred.

Table 3. Grade 3 and 4 treatment-related adverse events by dose level on schedule 2/1, post-amendment (n = 25)^a

Dose level (sunitinib/ gemcitabine)	No. of patients																	
	37.5 mg/ 750 mg m ⁻² (n = 3)			37.5 mg/ 850 mg m ⁻² (n = 3)			37.5 mg/ 1000 mg m ⁻² (n = 3)			37.5 mg/ 1250 mg m ⁻² (n = 3)			50 mg/ 1000 mg m ⁻² (n = 4)			50 mg/ 1250 mg m ⁻² (n = 9)		
Adverse event	G 3	G 4	Any G	G 3	G 4	Any G	G 3	G 4	Any G	G 3	G 4	Any G	G 3	G 4	Any G	G 3	G 4	Any G
Neutropenia	2	0	2	1	1	3	1	1	2	1	0	2	2	1	3	3	0	3
Lymphopenia	2	0	2	0	1	2	0	0	0	1	0	1	2	0	3	1	0	1
Thrombocytopenia	0	0	2	1	1	3	1	0	3	0	0	2	2	0	3	1	1	4
Leucopenia	1	0	2	2	0	3	1	0	2	1	0	1	2	0	3	1	0	2
Cerebrovascular accident	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Hypertension	0	0	0	0	0	1	0	0	0	1	1	2	0	0	0	0	0	0
Leukoencephalopathy	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0
Mucosal inflammation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2
Nausea	0	0	1	0	0	2	0	0	1	0	0	1	1	0	4	0	0	7
Pericardial effusion	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0
Pulmonary embolism	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amylase increase	0	0	0	0	0	0	0	0	2	1	0	1	1	0	1	0	0	0
Hypomagnesemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Hypophosphatemia	0	0	0	0	0	2	0	0	1	0	0	0	0	0	1	1	0	1
Lipase increase	0	0	0	0	0	0	0	0	0	1	0	1	0	0	1	0	0	0
Uric acid increase	0	0	0	0	1	1	0	0	2	0	0	0	0	1	1	0	0	0

Abbreviation: G = grade.

^aNo grade 5 adverse events occurred.

Treatment-related AEs (grade ≥ 3) occurring among the 25 patients on Schedule 2/1, post-amendment, are detailed in Table 3. The most common grade 3 or 4 haematological toxicities related to sunitinib plus gemcitabine treatment in patients on Schedule 2/1, post-amendment, were neutropenia ($n = 13$), leucopenia ($n = 8$), and lymphopenia and thrombocytopenia (both $n = 7$). Non-haematological treatment-related AEs included: grade 4 uric acid elevation ($n = 2$), hypertension, pulmonary embolism, and cerebrovascular accident ($n = 1$ each), grade 3 elevation of amylase ($n = 2$) or lipase ($n = 1$), hypertension, pericardial effusion, leukoencephalopathy, nausea, mucosal inflammation, hypophosphatemia, and hypomagnesemia (each $n = 1$).

Pharmacokinetics. Pharmacokinetics data were evaluated for dose levels 1–6 of Schedule 2/1 (Table 1). Plasma PK parameters and geometric mean ratios for subjects with paired observations for sunitinib, SU12662, total drug, gemcitabine and dFdU, as a single agent or in combination, are summarised for all dose levels combined in Table 4 (plasma concentration time curves for patients on Schedule 2/1 are shown in Supplementary Figure 1). The slightly lower sunitinib and total drug C_{max} and AUC_{24} values for sunitinib plus gemcitabine (i.e., on day 8) as compared with sunitinib alone (i.e., on day 15) is likely because of sunitinib and its metabolite not achieving complete steady-state levels by day 8 (sunitinib half-life is 40–86 h) (Faivre *et al*, 2006). This would explain the lower sunitinib exposure at day 8 compared with day 15 when steady state concentrations were achieved. However, overall, there was no evidence of clinically relevant drug–drug interaction between sunitinib and gemcitabine based on drug exposure at any dose level.

Efficacy. Overall, of the total population ($n = 44$), 8 patients (18%) had an objective response, including 7 of 25 patients (28%) on

Schedule 2/1, post-amendment (Table 5). A further 18 patients (41%), including 12 (48%) on schedule 2/1, post-amendment, had stable disease (s.d.) ranging from 10.3 to 47.9 weeks, yielding clinical benefit rates of 59% (total population) and 76% (Schedule 2/1 post-amendment), respectively.

Among 25 patients on Schedule 2/1, post amendment, PRs were observed in 7 patients across the full range of doses: two with pancreatic carcinoma and five with RCC. s.d. of median 29.1 weeks (range 11.1–47.9) was experienced by an additional 12/25 patients.

Efficacy in RCC. Across all schedules and cohorts, 6/23 patients (26%) with RCC achieved a PR and 13 patients (57%) exhibited s.d. lasting 6 weeks or longer, including 4 patients with s.d. > 6 months. The majority who failed to achieve any clinical benefit had either papillary or chromophobe histology. Twelve of the RCC patients were either poor risk based on the Memorial Sloan-Kettering Cancer Centre (MSKCC) criteria (Motzer *et al*, 2002) or had disease that was characterised histologically by sarcomatoid differentiation or Fuhrman grade 4/4 features. Among these twelve patients, five achieved a PR and seven had SD.

DISCUSSION

We conducted a phase I dose-escalation study of sunitinib combined with gemcitabine in patients with advanced solid tumours. Our results indicate that oral sunitinib given on Schedule 2/1 combined with IV gemcitabine given on days 1 and 8, with each agent at the maximum individual approved dose, has a favourable safety profile. Schedule 4/2 was not pursued beyond the initial dose level of sunitinib 37.5 mg plus gemcitabine 750 mg m⁻²

Table 4. Pharmacokinetic parameters for sunitinib, its active metabolite (SU12662), and total drug (sunitinib plus SU12662), and gemcitabine and its main metabolite (dFdU) in patients treated on Schedule 2/1 (subjects with paired observations only)

Analyte	Parameter	Mean (CV%) sunitinib alone, C1D15 (median)	Mean (CV%) gemcitabine alone, C1D1 (median)	Mean (CV%) sunitinib plus gemcitabine, C1D8 (Median)	Geometric mean ratio (combination vs sunitinib alone)
All dose cohorts combined (n = 32)^a					
Sunitinib	C_{max} , ng ml ⁻¹	63.6 (43) (56.6)	—	71.5 (58) (60.0)	0.92
	AUC_{24} , ng h ml ⁻¹	1241 (46) (1113)	—	1445 (52) (1282)	0.87
	T_{max} , h ^b	4.0 (0.0–9.0)	—	7.0 (3.0–24.0)	N/A
	CL/F, l h ⁻¹	47.0 (37) (44.9)	—	41.4 (37) (39.0)	1.14
SU12662	C_{max} , ng ml ⁻¹	19.4 (51) (15.7)	—	27.5 (68) (20.6)	0.74
	AUC_{24} , ng h ml ⁻¹	411 (51) (333)	—	596 (71) (453)	0.73
	T_{max} , h ^b	4.0 (0.0–24.0)	—	4.0 (0.0–24.0)	NA
Total drug (sunitinib + SU12662)	C_{max} , ng ml ⁻¹	82.4 (38) (71.0)	—	98.3 (53) (82.2)	0.87
	AUC_{24} , ng h ml ⁻¹	1653 (40) (1485)	—	2043 (49) (1736)	0.83
	T_{max} , h ^b	4.0 (0.0–24.0)	—	7.0 (3.0–24.0)	NA
All dose cohorts combined (n = 30)^a					
Gemcitabine	C_{max} , µg ml ⁻¹	—	20.9 (25) (20.7)	25.0 (36) (24.4)	1.16
	$AUC_{∞}$, µg h ml ⁻¹	—	10.5 (30) (10.5)	12.6 (36) (12.8)	1.18
	T_{max} , h ^b	—	0.25 (0.3–0.5)	0.25 (0.3–0.5)	NA
	CL, l h ⁻¹	—	262 (38) (240)	225 (44) (203)	0.84
	$t_{1/2}$, h	—	0.26 (20) (0.26)	0.29 (23) (0.27)	NA
dFdU	C_{max} , µg ml ⁻¹	—	45.3 (17) (44.9)	50.8 (22) (49.7)	1.11
	AUC_{24} , µg h ml ⁻¹	—	268 (29) (248)	272 (31) (254)	1.01
	T_{max} , h ^b	—	0.5 (0.3–1.5)	0.5 (0.5–1.5)	NA

Abbreviations: $AUC_{24/∞}$ = area under the plasma concentration versus time curve from time zero to 24h/infinity; C = cycle; CL = clearance; CL/F = clearance at steady state after oral administration; C_{max} = maximum plasma concentration; CV% = coefficient of variation percentage; D = day; NA = not available; T_{max} = time to maximum plasma concentration, $t_{1/2}$ = terminal phase half life.

^aFor the combined cohorts (Schedule 2/1, dose levels 1–6; Table 1), dose correction to sunitinib 50 mg and gemcitabine 1250 mg m⁻² was performed.

^b T_{max} : median (t_{min} , max).

for practical reasons (i.e., because of missed or delayed doses of gemcitabine because of slow recovery from neutropenia). The study design was modified on Schedule 2/1 to allow growth factor support during cycle 1. No DLTs occurred at the maximum doses on Schedule 2/1, post-amendment, and most AEs were grade 1 or 2.

This safety profile is similar to that reported in phase I trials of sunitinib in combination with other chemotherapy regimens, including docetaxel, capecitabine, pemetrexed, carboplatin plus paclitaxel, and gemcitabine (with and without cisplatin), in which most AEs were mild to moderate in studies including patients with all solid tumours or those restricted to NSCLC (Sweeney *et al*, 2007; Chow *et al*, 2008; Heath *et al*, 2008; Traynor *et al*, 2008; Reck *et al*, 2010; Brell *et al*, 2012; Okamoto *et al*, 2012). In the earlier phase I trial with gemcitabine, growth factor support was excluded and the recommended phase II dose was gemcitabine 675 mg m⁻² on days 1 and 8 and sunitinib 25 mg on continuous daily dosing (Brell *et al*, 2012). However, the most common challenge in drug tolerability, as expected with this combination and also reported previously (Reck *et al*, 2010), was haematological toxicity, particularly with regard to day 8 administration of gemcitabine, but was manageable with growth factor support. For example, the incidences of the most common grade 3 or 4 haematological toxicities associated with this combination (Schedule 2/1, post-amendment) were substantially higher than that with sunitinib monotherapy (in treatment-naïve patients with metastatic RCC; SUTENT (sunitinib malate) prescribing information (2012)): neutropenia (52% vs 17%, respectively), leucopenia (32% vs 8%), lymphopenia (28% vs 18%) and thrombocytopenia (28% vs 9%). Clinically significant non-haematological AEs were rare and no treatment-related deaths were observed despite the advanced

nature of the patient population. In contrast, increases in grade 3 or higher non-haematological toxicity were reported for the combination of sunitinib plus erlotinib in a phase III trial of NSCLC (Scagliotti *et al*, 2012).

There appeared to be no clinically relevant changes in the PK of sunitinib and total drug when sunitinib was administered with gemcitabine, which is consistent with the literature in which gemcitabine has not been reported to be a substrate or inhibitor/inductor of CYP3A4, the main CYP450 isoenzyme involved in the metabolism of sunitinib and its metabolite. In addition, co-administration of sunitinib with gemcitabine did not appear to affect the PK of gemcitabine.

This treatment regimen has promising antitumor activity, surpassing that shown in the earlier gemcitabine phase I combination trial, in which 4 of 33 patients had a PR (Brell *et al*, 2012). Our results suggest that the combination merits further investigation in pancreatic cancer and RCC. In addition, although it is difficult to ascertain efficacy differences in a relatively small study such as this, efficacy with Schedule 2/1 appeared superior to that with Schedule 4/2. This may be related to better tolerability with Schedule 2/1, allowing patients to continue on therapy longer, with fewer interruptions, particularly after the introduction of growth factor use. Furthermore, it has been hypothesised that a shorter off-treatment period (i.e., 1 week vs 2 weeks) may prevent tumour rebound; however, evidence for this phenomenon is limited.

The antitumor activity observed in patients with poor-risk, high grade, or sarcomatoid RCC is noteworthy. Sarcomatoid differentiation, found across all RCC histological subtypes (de Peraltaventurina *et al*, 2001), is thought to represent transformation of RCC to a higher grade (Cheville *et al*, 2004; Golshayan *et al*, 2009),

Table 5. Best tumour response in all patients (on all dosing schedules) and in patients on Schedule 2/1 post-amendment

	No. of patients (%)	
	All patients (N = 44)	Schedule 2/1 post-amendment (N = 25)
Complete response (CR)	0	0
Partial response (PR) ^a	8 (18)	7 (28)
Stable disease (SD) ^b	18 (41)	12 (48)
Progressive disease	10 (23)	5 (20)
Not evaluable	3 (7)	0
Missing	5 (11)	1 (4)
ORR (CR + PR)	8 (18)	7 (28)
Clinical benefit rate (CR + PR + SD)	26 (59)	19 (76)

Abbreviations: ORR = objective response rate; RCC = renal cell carcinoma.

^aPRS: Schedule 2/1 post-amendment: 2 patients with pancreatic carcinoma (sunitinib 37.5 mg per day and gemcitabine 850 mg m⁻², sunitinib 50 mg per day and gemcitabine 1,250 mg m⁻²), 5 patients with RCC (sunitinib 37.5 mg per day and gemcitabine 750 mg m⁻² (n = 1), sunitinib 37.5 mg per day and gemcitabine 850 mg m⁻² (n = 1), sunitinib 37.5 mg per day and gemcitabine 1000 mg m⁻² (n = 2), sunitinib 50 mg per day and gemcitabine 1250 mg m⁻² (n = 1)); Schedule 4/2: 1 patient with RCC (sunitinib 37.5 mg per day and gemcitabine 750 mg m⁻²).

^bSD: As per RECIST, SD is defined as stable disease of at least 6 weeks duration. Schedule 2/1 post-amendment: 9 RCC patients (sunitinib 37.5 mg per day and gemcitabine 850 mg m⁻² (n = 1), sunitinib 37.5 mg per day and gemcitabine 1000 mg m⁻² (n = 1), sunitinib 37.5 mg per day and gemcitabine 1250 mg m⁻² (n = 3), sunitinib 50 mg per day and gemcitabine 1000 mg m⁻² (n = 3), sunitinib 50 mg per day and gemcitabine 1250 mg m⁻² (n = 1)) and 3 patients with other tumours (sunitinib 50 mg per day and gemcitabine 1250 mg m⁻²); Schedule 2/1, pre-amendment: 1 patient with pancreatic carcinoma (sunitinib 37.5 mg per day and gemcitabine 750 mg m⁻²), 3 patients with RCC (sunitinib 37.5 mg per day and gemcitabine 750 mg m⁻²); Schedule 4/2: 1 patient with RCC and 1 patient with hepatocellular carcinoma (both sunitinib 37.5 mg per day and gemcitabine 750 mg m⁻²).

and is associated with a relatively poor prognosis and median overall survival of only ~3–10 months with non-targeted agents (e.g., immunotherapy; de Peralta-Venturina *et al*, 2001; Escudier *et al*, 2002; Mian *et al*, 2002; Kwak *et al*, 2007). Similarly, among clinical poor-risk patients, overall survival remains short (median 4–11 months) despite the proven benefit of temsirolimus (Motzer *et al*, 1999, 2002; Hudes *et al*, 2007). There is no standard treatment for sarcomatoid RCC patients, and new treatment options for both of these particularly challenging RCC subgroups are urgently needed. In our study, all of the RCC patients who were poor risk and/or had high grade or sarcomatoid disease achieved a PR or SD with sunitinib plus gemcitabine. Although patient numbers are small, our results compare favourably with a recent retrospective analysis of patients with RCC and sarcomatoid differentiation treated with VEGF- or VEGFR-targeted therapy (Golshayan *et al*, 2009). In that study, 6/21 patients (29%) treated with sunitinib achieved a PR and a further nine patients treated with sunitinib (43%) had s.d. Our results also suggest that sunitinib combined with gemcitabine may be a more active regimen than gemcitabine-based chemotherapy, which has also shown limited activity in sarcomatoid RCC (Stadler *et al*, 2003; Nanus *et al*, 2004). A phase II trial investigating sunitinib plus gemcitabine in sarcomatoid and/or poor-risk patients with RCC (NCT00556049) is underway, and a randomized phase II study of sunitinib with/without gemcitabine in advanced RCC with sarcomatoid features (ECOG-E1808; NCT01164228) has been initiated.

Although targeted therapies have yet to deliver significant advances in pancreatic cancer treatment (O'Reilly 2009), there are indications that combining EGFR-directed and/or antiangiogenic

agents with gemcitabine may be beneficial (Moore *et al*, 2007; Van Cutsem *et al*, 2009). The two PRs reported in pancreatic cancer patients in our study offer encouragement, and a randomized phase II trial comparing gemcitabine with/without sunitinib is ongoing in this indication (NCT00673504). Improved patient selection based on identification of predictive biomarkers may be critical for determining patient subsets likely to derive meaningful clinical benefit from combinations of cytotoxic and targeted therapy.

In conclusion, patients with advanced solid malignancies for whom curative therapy was not available tolerated sunitinib and gemcitabine at the maximum approved doses of each agent on Schedule 2/1 with growth factor support. Preliminary antitumor data suggest clinical benefit in patients with particular malignancies, including poor-risk RCC. Phase II studies of this combination in patients with RCC or pancreatic cancer are underway.

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CONFLICT OF INTEREST

AXZ and McD have reported receiving consultant or advisory fees from Pfizer. LT, SP, and AR-G are full-time employees of Pfizer and hold Pfizer stock. The remaining authors declare no conflict of interest.

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