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Clinical Studies

Phase I study of axitinib combined with paclitaxel, docetaxel or capecitabine in patients with advanced solid tumours

LP Martin*[,1], MF Kozloff[2], RS Herbst[3], TA Samuel[4], S Kim[5], B Rosbrook[5], M Tortorici[5], Y Chen[5], J Tarazi[5], AJ Olszanski[5,7], T Rado[6], A Starr[2] and RB Cohen[1]

[1]Department of Medical Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA, USA; [2]Section of Oncology/Hematology, Ingalls Hospital, University of Chicago, Harvey, IL, USA; [3]Department of Thoracic/Head & Neck Medical Oncology, University of Texas MD Anderson Center, Houston, TX, USA; [4]Department of Medical Oncology, Georgia Health Sciences University Cancer Center, Medical College of Georgia, Augusta, GA, USA; [5]Pfizer Oncology, San Diego, CA, USA; [6]Clinical Research Department, Columbia Basin Hematology & Oncology, Kennewick, WA, USA

BACKGROUND: Axitinib, a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors, enhanced the efficacy of chemotherapy in human xenograft tumour models. This phase I study investigated the safety, tolerability, pharmacokinetics and antitumour activity of axitinib combined with chemotherapy.

METHODS: A total of 42 patients with advanced solid tumours received a continuous axitinib starting dose of 5 mg twice daily (b.i.d.) plus paclitaxel (90 mg m^{-2} weekly), docetaxel (100 mg m^{-2} every 3 weeks) or capecitabine (1000 or 1250 mg m^{-2} b.i.d., days 1–14).

RESULTS: Common treatment-related adverse events across all cohorts were nausea (45.2%), hypertension (45.2%), fatigue (42.9%), diarrhoea (38.1%), decreased appetite (33.3%) and hand–foot syndrome (31.0%). There was one complete response, nine partial responses and seven patients with stable disease. Ten patients (23.8%) remained on therapy for >8 months. Paclitaxel and capecitabine pharmacokinetics were similar in the absence or presence of axitinib, but docetaxel exposure was increased in the presence of axitinib. Axitinib pharmacokinetics were similar in the absence or presence of co-administered agents.

CONCLUSIONS: Axitinib combined with paclitaxel or capecitabine was well tolerated; no additive increase in toxicities was observed. Antitumour activity was observed for each treatment regimen and across multiple tumour types.

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It is clear that the efficacy of chemotherapy is limited by the development of drug resistance and the occurrence of significant toxicities associated with such agents. There remains an urgent need to enhance the activity of chemotherapy through combinations with biologically targeted drugs that may help overcome resistance and/or have non-overlapping mechanisms of action and side effects. Much of the current clinical research has focussed on targeting angiogenesis pathways as a means to enhance chemotherapy efficacy, as these pathways are critical to tumour growth and metastasis. Tumour angiogenesis is mediated largely by vascular endothelial growth factor (VEGF) and its tyrosine kinase receptor VEGFR (Folkman, 1990, 1992; Ferrara *et al*, 2003; Hicklin and Ellis, 2005). Several angiogenesis inhibitors that target VEGF/VEGFR are approved or in clinical development (Tugues *et al*, 2011).

The strategy of combining drugs that inhibit VEGF signalling with chemotherapy is supported by several phase III clinical trials that showed that regimens of bevacizumab, an anti-VEGF monoclonal antibody, plus chemotherapy improved outcomes compared with chemotherapy alone in patients with metastatic colorectal cancer (CRC), advanced non-squamous non-small cell lung cancer (NSCLC) and metastatic breast cancer (Hurwitz *et al*, 2004; Miller *et al*, 2005; Sandler *et al*, 2006; Miller *et al*, 2007). Although the beneficial results to date have been seen mainly with drugs that bind to receptor ligands (e.g., VEGF) involved in angiogenesis, further improvement in patient outcomes may be achieved using agents that target this pathway by other mechanisms (e.g., kinase inhibition).

Axitinib is a potent, oral and selective second-generation inhibitor of VEGFR 1, 2 and 3 (Hu-Lowe *et al*, 2008). In preclinical studies, axitinib demonstrated antiangiogenic and antitumour activity in human tumour models. Phase II or phase III studies have shown that axitinib has single-agent clinical activity in a range of tumour types, including renal cell carcinoma (Rixe *et al*, 2007; Rini *et al*, 2009, 2011), thyroid cancer (Cohen *et al*, 2008), NSCLC (Schiller *et al*, 2009) and melanoma (Fruehauf *et al*, 2011). Preclinical studies showed that axitinib enhanced the antitumour efficacy of a number of chemotherapeutic agents, including docetaxel, carboplatin and gemcitabine (Hu-Lowe *et al*, 2008). Axitinib is approved in the United States for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy (Pfizer Inc., 2012).

The phase I study presented here investigated the safety, tolerability, pharmacokinetics and antitumour activity of axitinib in combination with weekly paclitaxel, docetaxel or capecitabine in patients with advanced solid tumours, including breast cancer and CRC. Another component of this study, which investigated axitinib

*Correspondence: Dr L Martin; E-mail: L_Martin@fccc.edu
[7]Current address: Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA.
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plus chemotherapy doublet regimens commonly used in the treatment of advanced NSCLC, is reported in an accompanying article (Kozloff *et al*, 2012).

MATERIALS AND METHODS

Study design and end points

As part of an open-label, multicentre, phase I study, patients with advanced solid tumours were treated with axitinib in combination with standard doses and schedules of paclitaxel, docetaxel or capecitabine. The primary end point was maximum tolerated dose (MTD) of axitinib plus paclitaxel, docetaxel or capecitabine. Secondary end points were safety, tumour response rates and plasma pharmacokinetics.

The trial was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and applicable local regulatory requirements and laws. All patients provided written informed consent. This trial is registered on ClinicalTrials.gov (NCT00454649).

Patients

Adult patients ($\geqslant$18 years of age) with histologically or cytologically proven advanced solid tumours suitable for treatment with taxanes or capecitabine were eligible. Key inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; adequate liver, renal and bone marrow function; and no pre-existing uncontrolled hypertension (i.e., blood pressure (BP) $\geqslant$140/90 mm Hg). Patients whose hypertension was controlled with antihypertensive therapy were eligible. For patients receiving axitinib plus docetaxel, no prior cytotoxic chemotherapy was allowed, except adjuvant treatment completed $\geqslant$12 months before enrolment. Patients receiving axitinib plus weekly paclitaxel or capecitabine may have received any type of prior chemotherapy.

Key exclusion criteria included central nervous system metastases; clinically significant gastrointestinal abnormalities; myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident (including transient ischaemic attack) or pulmonary embolus $<$12 months before enrolment; haemoptysis ($>$0.5 teaspoon of blood per day) within 1 week of enrolment; and one or more lung lesions with cavitation or any lesion invading and/or supporting large blood vessels.

Study treatments

The schedules for the four treatment cohorts are shown in Figure 1. Patients in all cohorts received axitinib 5 mg twice daily (b.i.d.) administered orally with food. A lead-in period, during which patients received an axitinib starting dose of 5 mg b.i.d., was utilised in the axitinib/docetaxel cohort. After cycle 1, patients with no grade $>$2 adverse events (AEs) related to axitinib for consecutive 2-week periods could have their axitinib dose titrated to 7 mg b.i.d. and then to a maximum of 10 mg b.i.d., unless BP measured $>$150/100 mm Hg or the patient was receiving antihypertensive medication. In patients who developed systolic BP $>$150 mm Hg or diastolic BP $>$100 mm Hg, antihypertensive therapy was initiated or the dose of current medication increased. In patients with grade $\geqslant$3 nonhaematologic treatment-related AEs, axitinib was reduced to 3 mg b.i.d. and then, if needed, to 2 mg b.i.d. Axitinib was discontinued and a radiologic assessment was considered in patients who developed haemoptysis ($>$0.5 teaspoon of bright red blood per day).

Paclitaxel was administered in 4-week cycles as a 60-min intravenous (i.v.) infusion of 90 mg m^{-2} once weekly on days 1, 8 and 15 of each cycle, followed by a 1-week rest period. Docetaxel was administered in 3-week cycles as a 60-min i.v. infusion of 100 mg m^{-2} once every 3 weeks on day 1 of each treatment cycle. Two cohorts of patients received oral capecitabine in 3-week cycles as 1000 mg m^{-2} and 1250 mg m^{-2} b.i.d., respectively, within 30 min of a meal on days 1–14 of each treatment cycle, followed by a 1-week rest period. Chemotherapy doses were modified at the discretion of the investigator. Paclitaxel, docetaxel and capecitabine were delayed in patients with absolute granulocyte counts $<$1500 cells mm^{-3} or platelet counts $<$100 000 cells mm^{-3} and discontinued if recovery did not occur after 4 weeks. Patients with abnormal liver function tests had their dose of paclitaxel or docetaxel reduced. The dose of paclitaxel and docetaxel was withheld in patients with grade $\geqslant$3 haematologic or nonhaematologic toxicities and resumed at one lower dose level when the toxicity was grade $\leqslant$1. Paclitaxel and docetaxel were reduced in patients with grade 2 neurotoxicity or withheld until neurotoxicity was grade $\leqslant$1. Capecitabine was interrupted in patients with grade $\geqslant$2 toxicities and resumed when the toxicity was grade $\leqslant$1, with capecitabine administered at a lower dose level if the toxicity was grade 2 and previously reported or grade 3. In patients with grade 4 toxicities, capecitabine was discontinued or interrupted and resumed when the toxicity was grade $\leqslant$1. Treatment with chemotherapy and axitinib continued until disease progression or unacceptable toxicity. Patients who discontinued chemotherapy because of toxicity or who reached a maximum number of cycles according to institutional guidelines were allowed to continue treatment with axitinib monotherapy. Patients who permanently discontinued axitinib because of toxicity could continue to receive chemotherapy as long as such treatment was considered beneficial, at the discretion of the treating physician.

Assessments

The MTD for axitinib plus paclitaxel, docetaxel or capecitabine was defined as the highest dose level at which no more than one of the first six patients enrolled in each cohort experienced a dose-limiting toxicity (DLT) during the first cycle of therapy with two or more of the six patients experiencing a DLT at the next highest dose level. If the MTD was not exceeded within the planned dose levels, the MTD was defined as the maximum dose tested. The DLTs were defined as grade 4 neutropenia or thrombocytopenia for $\geqslant$14 days or grade 4 febrile neutropenia; proteinuria $\geqslant$2 g per 24 h; haemoptysis ($\geqslant$0.5 teaspoon per day) for $\geqslant$7 days; uncontrolled grade $\geqslant$3 nonhaematologic toxicity for $\geqslant$7 days; or inability to resume study treatment within 14 days after stopping because of axitinib-related toxicity.

Severity of AEs was graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (Trotti *et al*, 2003). Physical examinations, assessment of ECOG PS, chest X-rays and laboratory tests were conducted at baseline, day 1 of each cycle and at follow-up (28 days after the last dose). Additional physical examinations and haematology tests were performed at days 8 and 15 of each cycle. Measurements of BP were recorded at clinic visits and b.i.d. using a BP monitoring cuff and measurement diary by patients, who were instructed to contact their physicians immediately for systolic BP $>$150 mm Hg, diastolic BP $>$100 mm Hg or symptoms related to elevated BP. Home BP measurements were not used to assess DLTs. Objective tumour responses were radiologically assessed every two cycles according to Response Evaluation Criteria in Solid Tumours (RECIST version 1.0) (Therasse *et al*, 2000).

Pharmacokinetic analysis

Pharmacokinetics of axitinib alone were determined using blood samples collected on cycle 1 day 22 for patients receiving axitinib/paclitaxel, on cycle 1 day –1 for those receiving axitinib/docetaxel and on cycle 1 day 18 for those receiving axitinib/capecitabine.

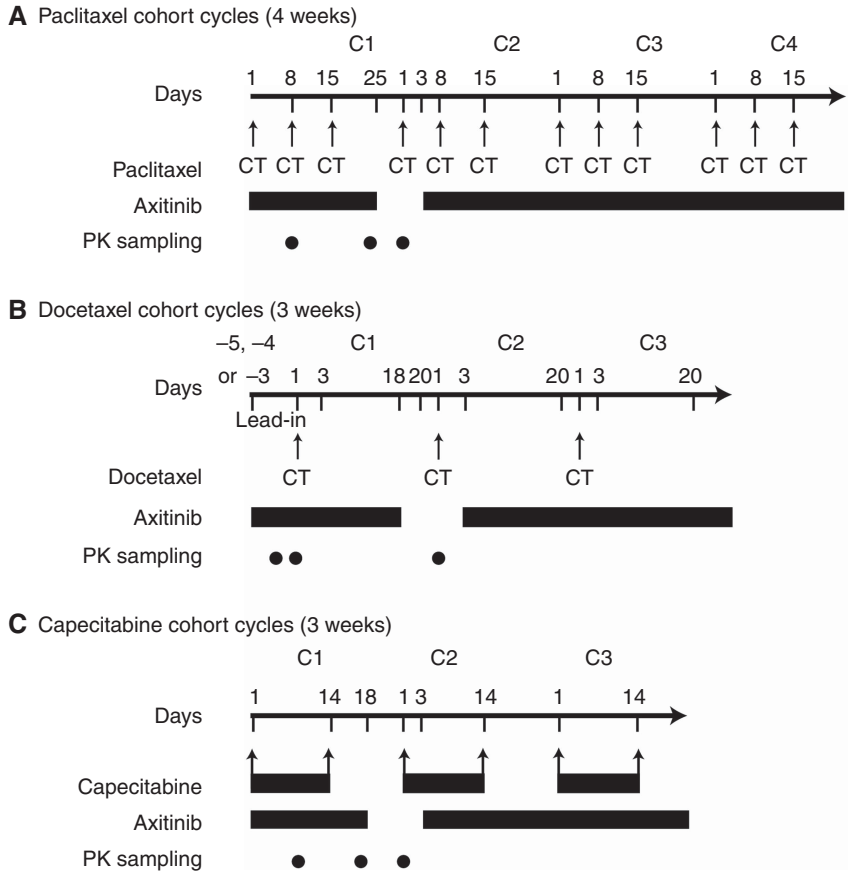

Figure 1 Treatment schedule. C = cycle; CT = chemotherapy; PK = pharmacokinetic.

Pharmacokinetics of chemotherapy alone were determined using blood samples collected on cycle 2 day 1 for all treatment regimens. Pharmacokinetics of axitinib plus chemotherapy were determined using blood samples collected on cycle 1 day 1 for patients receiving axitinib/docetaxel and on cycle 1 day 8 for patients receiving axitinib/paclitaxel or axitinib/capecitabine. Samples for axitinib analysis were collected before dose and 1, 2, 3, 4, 6 and 8 h post dose. Samples for paclitaxel analysis were collected before dose and 0.5, 1, 2, 3, 4, 6, 8, 24 and 30 h after the start of paclitaxel infusion. Samples for docetaxel analysis were collected before dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 and 30 h after the start of docetaxel infusion. Samples for capecitabine analysis were collected before dose and 0.25, 0.5, 1, 2, 3, 4, 6 and 8 h post dose. Plasma concentrations of axitinib were measured using a validated high-performance liquid chromatography with tandem mass spectrometric detection method (LC/MS/MS; Charles River Discovery and Development Services, Shrewsbury, MA, USA) (Rugo *et al*, 2005). Concentrations of paclitaxel and docetaxel (Covance Bioanalytical Services, Indianapolis, IN, USA) and capecitabine and metabolites (BASi, McMinnville, OR, USA) were measured using a validated LC/MS/MS assay. Pharmacokinetic parameter estimates were conducted using WinNonlin Professional (version 4.1; Pharsight Corp., Mountain View, CA, USA).

Statistical methods

All patients who received at least one dose of study medication were included in the safety analysis. Patients with one or more target lesions according to RECIST, who received at least one dose of study medication and who had a baseline assessment of disease were included in the analysis of best objective response. Descriptive statistics (including mean, median, standard error, ranges for continuous data and frequencies and percentages for categorical data) were reported for safety and pharmacokinetic analyses.

RESULTS

Patient characteristics

A total of 42 patients were enrolled in the four treatment cohorts (Table 1). The axitinib/capecitabine 1250 mg m^{-2} b.i.d. group was expanded in August 2007 to include an additional 12 patients. Median chemotherapy exposure was two cycles of paclitaxel (range 2–6), four cycles of docetaxel (range 1–17), two cycles of 1000 mg m^{-2} capecitabine (range 1–11) and four cycles of 1250 mg m^{-2} capecitabine (range 1–24). Median axitinib exposure was 136 days (range 43–1085), with a median daily dose of 6.4 mg (range 3.9–12.1), in the axitinib/paclitaxel group; 74 days (range 10–599), with a median daily dose of 8.7 mg (range 2.6–10.0), in the axitinib/docetaxel group; 42 days (range 2–290), with a median daily dose of 10.0 mg (range 5.2–10.0), in the axitinib/capecitabine 1000 mg m^{-2} b.i.d. group; and 75 days (range 18–593), with a median daily dose of 7.5 mg (range 4.4–10.0), in the axitinib/capecitabine 1250 mg m^{-2} b.i.d. group. Ten (23.8%) patients remained on therapy for >8 months in the axitinib/paclitaxel ($n = 3$), axitinib/docetaxel ($n = 2$) and axitinib/capecitabine ($n = 5$) cohorts.

In all, 20 patients required an axitinib dose reduction because of any causality AEs: axitinib/paclitaxel cohort ($n = 5$; 71.4%),

Table 1 Patient baseline characteristics

	Axitinib +			
	Paclitaxel ($n=7$)	**Docetaxel ($n=7$)**	**Capecitabine 1000 mg m^{-2} ($n=9$)**	**Capecitabine 1250 mg m^{-2} ($n=19$)**
Male/female, *n*	4/3	2/5	4/5	8/11
Age, median (range), years	66 (45–70)	66 (44–76)	57 (45–81)	54 (22–70)
ECOG PS, 0/1/NR, *n*	2/4/1	3/4/0	4/5/0	8/11/0
Primary tumour type, n *(%)*				
Colorectal	1 (14.3)	0	1 (11.1)	11 (57.9)
Breast	0	1 (14.3)	1 (11.1)	4 (21.1)
Pancreatic	0	0	4 (44.4)	0
Thyroid	3 (42.9)	0	0	0
Melanoma	1 (14.3)	1 (14.3)	0	0
Oesophageal	0	2 (28.6)	0	0
Other	2 (28.6)[a]	3 (42.9)[b]	3 (33.3)[c]	4 (21.1)[d]
Prior therapy, n *(%)*				
Surgery	7 (100)	6 (85.7)	9 (100)	19 (100)
Radiation therapy	3 (42.9)	1 (14.3)	5 (55.6)	7 (36.8)
Drug therapy[e]	5 (71.4)	2 (28.6)	9 (100)	18 (94.7)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; NR = not reported. [a]Ovarian, unknown primary tumour. [b]Carcinoid, squamous cell carcinoma of skin, gastric. [c]Pancreatic islet cell carcinoma, urinary tract, gastrointestinal. [d]Head and neck, cervical, hepatocellular, bladder. [e]Includes cytotoxic chemotherapy and targeted agents.

axitinib/docetaxel cohort ($n=4$; 57.1%), axitinib/capecitabine 1000 mg m^{-2} b.i.d. cohort ($n=2$; 22.2%) and axitinib/capecitabine 1250 mg m^{-2} b.i.d. cohort ($n=9$; 47.4%). Twenty-nine patients required axitinib dose interruptions for any causality AEs: axitinib/paclitaxel cohort ($n=4$; 57.1%), axitinib/docetaxel cohort ($n=5$; 71.4%), axitinib/capecitabine 1000 mg m^{-2} b.i.d. cohort ($n=6$; 66.7%) and axitinib/capecitabine 1250 mg m^{-2} b.i.d. cohort ($n=14$; 73.7%).

In the axitinib/paclitaxel cohort, six patients discontinued study because of insufficient clinical response ($n=3$) or for other reasons ($n=3$). All patients receiving axitinib/docetaxel discontinued the study because of AEs ($n=2$), insufficient clinical response ($n=4$) or for other reasons ($n=1$). All patients receiving axitinib/capecitabine discontinued the study because of AEs ($n=7$), insufficient clinical response ($n=18$) or for other reasons ($n=3$).

DLTs and MTD

None of the first six patients receiving axitinib/paclitaxel experienced a DLT during the first cycle, and the MTD was determined to be axitinib 5 mg b.i.d. continuously in combination with weekly paclitaxel 90 mg m^{-2}. In the axitinib/docetaxel cohort, three of the first six patients experienced DLTs during the first cycle: stomatitis and hand–foot syndrome ($n=1$), mucositis ($n=1$) and colitis ($n=1$). Axitinib 5 mg b.i.d. continuously in combination with docetaxel 100 mg m^{-2} was determined to exceed the MTD. One of the first six patients receiving axitinib/capecitabine 1000 mg m^{-2} had a DLT of hypertension and seizure, and one of the first six patients receiving axitinib/capecitabine 1250 mg m^{-2} experienced a DLT comprising diarrhoea, urinary tract infection and dyspnoea during the first cycle. The MTD was determined to be axitinib 5 mg b.i.d. continuously in combination with capecitabine 1250 mg m^{-2}. Dose escalation to 10 mg b.i.d. was achieved in one patient receiving axitinib/paclitaxel; this patient required a subsequent axitinib dose reduction.

Adverse events

Serious treatment-related AEs occurred in 12 patients: 1 receiving axitinib/paclitaxel, 4 receiving axitinib/docetaxel and 7 receiving axitinib/capecitabine. Commonly reported treatment-related AEs were nausea ($n=19$; 45.2%), hypertension ($n=19$; 45.2%), fatigue ($n=18$; 42.9%) and diarrhoea ($n=16$; 38.1%; Table 2). Grade 4 treatment-related AEs were neutropenia and colitis ($n=1$ each) in the axitinib/docetaxel cohort and hypertension and dyspnoea ($n=1$ each) in the axitinib/capecitabine cohorts. No grade 5 treatment-related AEs were reported. Common haematologic laboratory abnormalities were anaemia and lymphopenia, reported in 79.5% and 71.8% of evaluable patients, respectively (Table 2); all cases of anaemia were grade $\leqslant 2$. Grade 4 haematologic laboratory abnormalities were one case of thrombocytopenia in the axitinib/paclitaxel cohort and five cases of neutropenia in the axitinib/docetaxel ($n=4$) and axitinib/capecitabine ($n=1$) cohorts. Treatment-related haematologic laboratory abnormalities reported as AEs were anaemia and neutropenia ($n=3$ each) and thrombocytopenia ($n=1$). Nine patients discontinued the study because of AEs, including two patients receiving axitinib/docetaxel and seven patients receiving axitinib/capecitabine; three of the nine were treatment related.

Antitumour activity

A total of 10 patients achieved objective responses (Table 3), including one complete response in a patient with squamous cell skin cancer who received axitinib/docetaxel; this patient had metastatic disease with lesions in lymph nodes ($n=2$) and neck ($n=1$). Nine partial responses were recorded in patients with thyroid cancer ($n=3$) or with CRC, melanoma or breast, hepatocellular, ovarian or pancreatic cancers ($n=1$ each). Seven patients had stable disease for >8 weeks.

Pharmacokinetics

Overall, the pharmacokinetic parameters for paclitaxel and capecitabine were similar in the absence or presence of axitinib (Table 4 and Figure 2). Docetaxel pharmacokinetic parameters in the small cohort of patients appeared to indicate higher exposure in the presence of axitinib. Axitinib drug concentrations and pharmacokinetic parameters were largely unchanged when co-administered with any of the chemotherapeutic agents studied compared with axitinib alone (Table 4 and Figure 2).

Table 2 Safety and tolerability findings

(A) Treatment-related, nonhaematologic AEs,[a] *n* (%)

		Axitinib +							
	Total, $N=42$	Paclitaxel, $n=7$		Docetaxel, $n=7$		Capecitabine 1000 mg m^{-2}, $n=9$		Capecitabine 1250 mg m^{-2}, $n=19$	
	All grades	All grades	Grade 3/4[b]	All grades	Grade 3/4[b]	All grades	Grade 3/4[b]	All grades	Grade 3/4[b]
Nausea	19 (45.2)	4 (57.1)	0	3 (42.9)	1 (14.3)	3 (33.3)	2 (22.2)	9 (47.4)	1 (5.3)
Hypertension	19 (45.2)	3 (42.9)	2 (28.6)	2 (28.6)	0	2 (22.2)	1 (11.1)	12 (63.2)	1 (5.3)
Fatigue	18 (42.9)	4 (57.1)	1 (14.3)	5 (71.4)	2 (28.6)	3 (33.3)	1 (11.1)	6 (31.6)	5 (26.3)
Diarrhoea	16 (38.1)	4 (57.1)	0	3 (42.9)	3 (42.9)	3 (33.3)	1 (11.1)	6 (31.6)	1 (5.3)
Decreased appetite	14 (33.3)	2 (28.6)	0	2 (28.6)	1 (14.3)	2 (22.2)	0	8 (42.1)	1 (5.3)
Hand–foot syndrome	13 (31.0)	5 (71.4)	0	2 (28.6)	2 (28.6)	1 (11.1)	0	5 (26.3)	1 (5.3)
Vomiting	10 (23.8)	3 (42.9)	0	0	0	2 (22.2)	0	5 (26.3)	1 (5.3)
Headache	10 (23.8)	1 (14.3)	0	1 (14.3)	0	2 (22.2)	0	6 (31.6)	1 (5.3)
Dysgeusia	7 (16.7)	4 (57.1)	0	2 (28.6)	0	0	0	1 (5.3)	0
Dyspepsia	7 (16.7)	4 (57.1)	0	3 (42.9)	1 (14.3)	0	0	0	0
Weight decreased	7 (16.7)	4 (57.1)	0	0	0	1 (11.1)	0	2 (10.5)	0
Stomatitis	6 (14.3)	2 (28.6)	0	2 (28.6)	2 (28.6)	1 (11.1)	0	1 (5.3)	0
Mucosal inflammation	6 (14.3)	0	0	2 (28.6)	2 (28.6)	0	0	4 (21.1)	1 (5.3)
Proteinuria	6 (14.3)	1 (14.3)	0	2 (28.6)	0	0	0	3 (15.8)	0
Rash	6 (14.3)	5 (71.4)	0	0	0	0	0	1 (5.3)	0

(B) Haematologic laboratory abnormalities, *n* (%)

		Axitinib +							
	Total, $N=39$	Paclitaxel, $n=7$		Docetaxel, $n=6$		Capecitabine 1000 mg m^{-2}, $n=8$		Capecitabine 1250 mg m^{-2}, $n=18$	
	All grades	All grades	Grade 3/4[b]	All grades	Grade 3/4[a]	All grades	Grade 3/4[b]	All grades	Grade 3/4[b]
Anaemia	31 (79.5)	5 (71.4)	0	4 (66.7)	0	7 (87.5)	0	15 (83.3)	0
Lymphopenia	28 (71.8)	5 (71.4)	2 (28.6)	5 (83.3)	4 (66.7)	6 (75.0)	1 (12.5)	12 (66.7)	7 (38.9)
Leukopenia	21 (53.8)	5 (71.4)	0	5 (83.3)	4 (66.7)	4 (50.0)	0	7 (38.9)	0
Neutropenia	14 (35.9)	3 (42.9)	1 (14.3)	5 (83.3)	4 (66.7)	3 (37.5)	1 (12.5)	3 (16.7)	1 (5.6)
Thrombocytopenia	10 (25.6)	2 (28.6)	1 (14.3)	3 (50.0)	0	2 (25.0)	0	3 (16.7)	0

Abbreviation: AE = adverse event. [a]Reported in $\geqslant 10\%$ of patients. [b]No grade 5 adverse events were reported.

DISCUSSION

Paclitaxel or capecitabine was well tolerated when administered in combination with axitinib in patients with advanced solid tumours. Based on the DLTs observed in this study, the recommended phase II doses of axitinib combined with chemotherapy are 5 mg axitinib b.i.d. plus standard-dose paclitaxel (90 mg m^{-2}) or capecitabine (1000 mg m^{-2} or 1250 mg m^{-2} b.i.d.). The combination of axitinib 5 mg b.i.d. plus docetaxel 100 mg m^{-2} was found to be above the MTD. In addition, two patients in this cohort experienced febrile neutropenia and subsequent reductions in docetaxel doses were often required. These results are consistent with findings from a randomised phase II study that reported a numerically higher incidence of febrile neutropenia among patients with metastatic breast cancer receiving continuous axitinib 5 mg b.i.d. plus docetaxel 80 mg m^{-2} compared with docetaxel alone (Rugo *et al*, 2011).

Most AEs reported in patients receiving either axitinib/paclitaxel or axitinib/capecitabine were grade $\leqslant 2$ in severity (Table 2), which were manageable and similar to those previously seen with the respective chemotherapeutic agents (Crown and O'Leary, 2000; Eniu *et al*, 2005; Walko and Lindley, 2005) or single-agent axitinib (Rixe *et al*, 2007; Cohen *et al*, 2008; Rini *et al*, 2009; Schiller *et al*, 2009; Fruehauf *et al*, 2011). No apparent additive increases in toxicities were observed when axitinib was combined with paclitaxel or capecitabine. Dose reductions or treatment interruptions for axitinib, paclitaxel or capecitabine due to AEs were common, although discontinuation due to AEs was only required in a small proportion of patients.

Although paclitaxel and axitinib are primarily metabolised through distinct primary pathways – paclitaxel primarily via cytochrome P450 2C8 (CYP2C8) (Steed and Sawyer, 2007) and axitinib primarily via CYP3A4/5 (Pithavala *et al*, 2010) – results from *in vitro* analyses demonstrated that axitinib inhibits CYP2C8 with an inhibition coefficient of 0.5 μmol l^{-1} (Pfizer Inc., data on file), which suggests that axitinib has the potential to increase plasma concentrations of paclitaxel when administered in combination. In this study, paclitaxel exposure was similar when administered alone or in combination with axitinib. Moreover, the maximum plasma concentration of axitinib observed when the drug was co-administered with paclitaxel was 35.4 ng ml^{-1}, which is substantially lower than 193.23 ng ml^{-1} (0.5 μmol l^{-1}) required for CYP2C8 inhibition. Together, these results suggest that at clinical concentrations, axitinib does not inhibit CYP2C8.

Similarly, no change in capecitabine exposure was observed in the absence or presence of axitinib. However, 5-fluorouracil exposure was higher when capecitabine was co-administered with axitinib. Similar results were observed in a phase I study of the experimental epidermal growth factor receptor tyrosine kinase inhibitor EKB-569, in which 5-fluorouracil exposure was increased approximately two-fold when capecitabine was given in combination with EKB-569 compared with single-agent

administration (Laheru *et al*, 2008). In contrast, results of a ongoing clinical study have shown that axitinib may be co-administered with 5-fluorouracil (as part of the folinic acid and 5-fluorouracil plus oxaliplatin (FOLFOX) or folinic acid and 5-fluorouracil plus irinotecan (FOLFIRI) regimens) without affecting the plasma concentration of either drug (Sharma *et al*, 2010). The observed differences in 5-fluorouracil exposure during co-administration with targeted agents may reflect the variability associated with the three-step metabolic process required for conversion of the capecitabine pro-drug to its active metabolite (Walko and Lindley, 2005). Overall, in the current study, the observed pharmacokinetic parameters and plasma profiles for axitinib, paclitaxel and capecitabine/5-fluorouracil were consistent with previously reported data (Kondo *et al*, 2005; Rugo *et al*, 2005; Albanell *et al*, 2008; Laheru *et al*, 2008).

Table 3 Best response to therapy, by RECIST[a]

	Axitinib +			
	Paclitaxel, *n* = 6, *n* (%)	**Docetaxel, *n* = 6, *n* (%)**	**Capecitabine 1000 mg m^{-2}, *n* = 9, *n* (%)**	**Capecitabine 1250 mg m^{-2}, *n* = 17, *n* (%)**
Objective response rate[b]	4 (66.7)	3 (50.0)	1 (11.1)	2 (11.8)
Complete response	0	1 (16.7)	0	0
Partial response	4 (66.7)	2 (33.3)	1 (11.1)	2 (11.8)
Stable disease	1 (16.7)	0	2 (22.2)	4 (23.5)
Disease progression	1 (16.7)	1 (16.7)	2 (22.2)	7 (41.2)
Indeterminate/missing	0	2 (33.3)	4 (44.4)	4 (23.5)

Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumours. [a]Includes treated patients with ⩾1 target lesion according to RECIST and a baseline assessment of disease. [b]Complete responses + partial responses.

Table 4 Plasma pharmacokinetic parameters of (A) paclitaxel, docetaxel and capecitabine (and metabolites) in the absence or presence of axitinib and (B) axitinib in the absence or presence of paclitaxel, docetaxel and capecitabine

Treatment cohort		**Mean (%CV)**				
(A) CT treatment with/without axitinib		**C_{max}(ng ml^{-1})**	**$AUC_{0-\infty}$[a] (ng·h ml^{-1})**	**CL[b] (l h^{-1})**	**V_z[c] (l)**	**$t_{½}$ (h)**
Paclitaxel	Alone	3821 (27)	5942 (24)	30.5 (20)	555 (26)	12.5 (8)
(*n* = 6)[d]	+ axitinib	4053 (27)	6157 (29)	28.8 (26)	521 (41)	12.4 (26)
Docetaxel[e]	Alone	3882 (11)	4417 (16)	43 (14)	718 (22)	11.5 (8)
(*n* = 5)	+ axitinib	5170 (12)	6852 (28)	28.9 (27)	482 (29)	11.6 (15)
Capecitabine[f,g]	Alone	10015 (84)	19980 (67)	294 (77)	520 (219)	1.33 (207)
(*n* = 21)	+ axitinib	7324 (84)	17214 (51)	288 (58)	278 (147)	0.60 (61)
	5′-DFCR	5435 (59)	19926 (32)	—	—	1.04 (58)
	5′-DFCR + axitinib	5058 (56)	19861 (38)	—	—	1.14 (73)
	5′- DFUR	6512 (63)	20629 (30)	—	—	0.93 (68)
	5′- DFUR + axitinib	7193 (62)	21510 (46)	—	—	0.84 (49)
	5-FU	246 (80)	698 (32)	—	—	0.87 (61)
	5-FU + axitinib	419 (80)	1160 (68)	—	—	0.84 (63)
(B) Axitinib treatment with/without CT		**C_{max}(ng ml^{-1})**	**$AUC_{0\text{-}24}$(ng·h ml^{-1})**	**CL/F (l h^{-1})**	**V_z/F (l)**	**$t_{½}$ (h)**
Axitinib[h]	Alone	44.6 (101)	154 (19)	65.7 (18)	140 (37)	1.45 (19)
(*n* = 5)	+ Paclitaxel	35.4 (74)	113 (15)	88.6 (14)	197 (30)	1.52 (18)
Axitinib[i]	Alone	68.0 (58)	781 (69)	14.4 (53)	74.8 (64)	4.07 (64)
(*n* = 7)	+ Docetaxel	73.2 (91)	754 (72)	17.1 (92)	103 (75)	7.1 (137)
Axitinib[j,k]	Alone	41.9 (60)	416 (63)	60.7 (219)	162 (128)	3.7 (52)
(*n* = 22)	+ Capecitabine	44.4 (54)	410 (63)	44.4 (151)	150 (87)	3.5 (49)

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time 0 to infinity; AUC_{0-24} = AUC from time 0 to 24 h; CL = plasma clearance; CL/F = apparent oral plasma clearance; C_{max} = maximum plasma concentration; CT = chemotherapy; CV = coefficient of variation; DFCR = deoxy-5-fluorocytidine; DFUR = deoxy-5-fluorouridine; FU = fluorouracil; PK = pharmacokinetics; $t_{½}$ = plasma terminal elimination half-life; V_z = volume of distribution of the drug during the elimination phase; V_z/F = apparent oral volume of distribution during the elimination phase. [a]AUC for capecitabine and its metabolites = AUC_{0-24}. [b]For capecitabine CL/F is reported. [c]For capecitabine V_z/F is reported. [d]One patient excluded because matching cycle 1 and cycle 2 PK evaluations were not completed. [e]Two patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed. C_{max} and $AUC_{0-\infty}$ on cycle 2 dose-normalised for patients who underwent docetaxel dose reduction. One patient excluded from summary statistics for $AUC_{0-\infty}$, CL,V_z and $t_{1/2}$ because of nonestimable half-life on cycle 1 day 1. [f]Data were pooled from patients receiving 1000 mg m^{-2} and 1250 mg m^{-2} capecitabine. C_{max} and AUC_{0-24} from patients receiving 1250 mg m^{-2} were dose normalised to 1000 mg m^{-2}. [g]Five patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed; one patient excluded because of positive pre-dose on day 1 of cycle 2. For capecitabine, 5-DFCR, 5-DFUR and 5-FU, five, two, three and four additional patients excluded for AUC_{0-24}, CL/F, V_z/F and $t_{1/2}$, respectively, because of nonestimable half-life. [h]Two patients excluded because matching PK evaluations were not completed. Two additional patients excluded from calculation of AUC_{0-24}, V_z/F and CL/F parameters because of nonestimable half-life. [i]One patient excluded from calculation of AUC_{0-24}, V_z/F and CL/F parameters because of nonestimable half-life. [j]Data were pooled from patients receiving 1000 mg m^{-2} and 1250 mg m^{-2} capecitabine. [k]Five patients excluded because matching cycle 1 day 8 and cycle 1 day 18 PK evaluations were not completed; seven additional patients excluded for AUC_{0-24}, CL/F, V_z/F and $t_{1/2}$ because of nonestimable half-life.

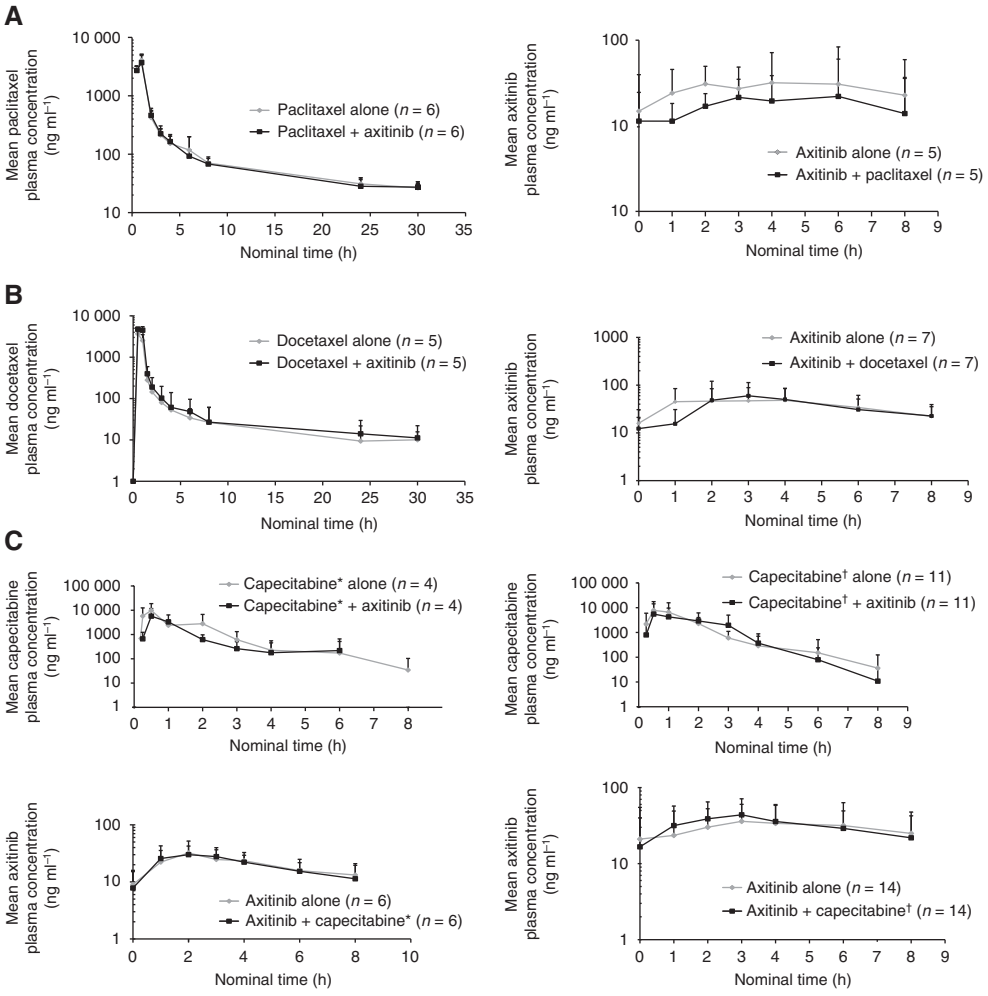

Figure 2 Plasma concentration–time curves. (**A**) Axitinib/paclitaxel: Left panel, one patient excluded because cycle 2 day 1 pharmacokinetic (PK) samples were not collected. Right panel, two patients excluded because cycle 1 day 1 pharmacokinetics samples were not collected. (**B**) Axitinib/docetaxel: Left panel, two patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed. (**C**) Axitinib/capecitabine: Upper left panel, three patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed. Upper right panel, two patients excluded because matching cycle 1 and cycle 2 PK evaluations not completed and six patients excluded because of dose change from cycle 1 to cycle 2. Lower left panel, one patient excluded because matching cycle 1 and cycle 2 PK evaluations were not completed and one patient excluded because of dose reduction. Lower right panel, three patients excluded because matching cycle 1 and cycle 2 PK evaluations were not completed and two patients excluded because of dose reduction. *1000 mg m^{-2}; †1250 mg m^{-2}.

In contrast, co-administration of axitinib and docetaxel appeared to change the pharmacokinetics of docetaxel. Although the sample size was small ($n = 5$ for assessment of area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) in the axitinib/docetaxel cohort), mean docetaxel exposure was ~55% higher in the presence of continuous b.i.d. dosing with axitinib. Docetaxel exposure, when administered alone as observed in this study (4417 ng · h ml^{-1}) was similar to what has been previously reported (Brunsvig *et al*, 2007). Our study was not statistically powered to enable a rigorous assessment of the quantitative change in exposure of each drug; however, an alteration in docetaxel pharmacokinetics in the presence of axitinib could not be excluded. Both drugs are primarily metabolised by the CYP3A4 pathway and are highly bound to plasma proteins (Clarke and Rivory, 1999; Tortorici *et al*, 2011). Changes in hepatic clearance and protein binding of axitinib and docetaxel may affect the disposition of these drugs, as both are characterised by a low hepatic extraction ratio (Crommentuyn *et al*, 1998). To avoid this potential increase in docetaxel exposure, an investigation of temporary interruption of axitinib dosing around the time of docetaxel administration is warranted.

To date, randomised clinical trials have not shown improved outcomes for tyrosine kinase inhibitors combined with chemotherapy compared with chemotherapy alone in the treatment of various cancers. Although this study was a phase I trial enrolling patients with diverse malignancies and treatment histories, preliminary evidence of antitumour activity was observed, with responses reported in each treatment cohort and across multiple tumour types. Co-administration of axitinib with chemotherapeutic agents was not associated with overlapping toxicities, making this an attractive strategy for cancer therapy. Larger studies are needed to document increases in efficacy with combination regimens of axitinib plus chemotherapy compared with chemotherapy alone. In a phase II study in metastatic breast cancer, higher objective response rates were seen with axitinib/docetaxel compared with docetaxel/placebo (41.1% *vs* 23.6%, respectively; $P = 0.011$) (Rugo *et al*, 2011). Ongoing and recently completed studies of axitinib in combination with chemotherapy include a phase II study of axitinib compared with bevacizumab plus FOLFOX or FOLFIRI for metastatic CRC (NCT00615056), a phase II study of axitinib plus FOLFOX and bevacizumab as first-line treatment for metastatic CRC (NCT00460603) and a phase I study

of axitinib plus cisplatin/capecitabine for advanced gastric cancer (NCT00842244).

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