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Phase I trial to investigate the safety, pharmacokinetics and efficacy of sorafenib combined with docetaxel in patients with advanced refractory solid tumours

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Abstract *Aim:* The safety, pharmacokinetics and efficacy of sorafenib plus docetaxel in patients with advanced refractory cancer were investigated in a Phase I, dose-escalation trial.
Methods: Twenty-seven patients in four Cohorts received docetaxel on Day 1 (Cohorts 1 and 4: 75 mg/m^2; Cohorts 2 and 3: 100 mg/m^2) plus sorafenib on Days 2–19 (Cohorts 1 and 2: 200 mg twice-daily (bid); Cohorts 3 and 4: 400 mg bid) in 21-day cycles.
Results: Most common adverse events (AEs) (Grade 3–5) included neutropenia (89%), leucopaenia (81%), hand–foot skin reaction (30%) and fatigue (30%). The most common drug-related AEs leading to dose reduction/interruption or permanent discontinuation were dermatologic (41%), gastrointestinal (26%) and constitutional (22%). Coadministration of sorafenib altered the pharmacokinetics of docetaxel. On average, docetaxel area under the concentration–time curve $(AUC)_{0-24}$ increased by 5% (Cohort 1), 54% (Cohort 2), 36% (Cohort 3) and 80% (Cohort 4) with docetaxel plus sorafenib, while C_{max} increased by 16–32%, independent of sorafenib/docetaxel doses. Three of 25 evaluable patients (11%) had partial responses; 14 (52%) had stable disease.
Conclusion: Dose-limiting dermatologic AEs were more common than expected for either therapy alone. A starting dose of docetaxel 75 mg/m^2 plus sorafenib 400 mg bid (with dose reductions for dermatological toxicities) is proposed for Phase II.

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1. Introduction

Docetaxel (Taxotere®; Sanofi-Aventis) is an effective chemotherapeutic agent in patients with solid tumours.[1,2] However, single-agent docetaxel is limited by the development of tumour resistance, and by unpredictable inter-individual variability in efficacy and toxicity.[3,4] Overexpression of the P-glycoprotein is commonly associated with the development of multidrug resistance in cancer cells that are refractory to taxane therapy.[4] Combining taxanes with anticancer agents that have a different mechanism of action may improve anti-tumour activity over monotherapy and may overcome tumour resistance mechanisms.[5]

Several signalling pathways activated by receptor tyrosine kinases (RTKs) mediate tumour growth, progression, angiogenesis and metastasis.[6] One such pathway is the mitogen-activated protein kinase (MAPK or Raf/MEK/ERK) signalling pathway.[6] Sorafenib (Nexavar®; Bayer Pharmaceuticals and Onyx Pharmaceuticals) is an oral multikinase inhibitor that inhibits Raf-1. It also inhibits RTKs, including vascular endothelial growth factor receptors (VEGFR)-1/-2/-3, platelet-derived growth factor receptor-β and the c-Kit, Flt-3 and Ret RTKs that have a role in tumour progression.[6–8] In preclinical models, the tumour growth inhibitory effects of sorafenib were associated with the inhibition of signalling through Raf-1 and the V599E B-Raf oncogene[6,9] and/or anti-angiogenic effect via inhibition of VEGFR-1/-2/-3.[6,9–11] Sorafenib also promotes apoptosis of tumour and endothelial cells by inhibiting the anti-apoptotic effects of Raf.[6,9,12,13] The pro-apoptotic effects of sorafenib may contribute to improved efficacy of chemotherapies by overcoming drug-resistance mechanisms and enhancing cytotoxicity.[14] Furthermore, sorafenib inhibits Raf-1, which has been implicated in taxane resistance and upregulation of the P-glycoprotein multidrug resistance pump (i.e. mdr-1).[15]

Single-agent sorafenib has demonstrated good tolerability and anti-tumour efficacy in patients with a variety of solid tumours.[6,16–22] It also showed improvements in progression-free survival and overall survival (OS) compared with placebo in the renal cell carcinoma TARGET trial.[14] After censoring patients who crossed over from placebo to sorafenib, the OS was 17.8 months in sorafenib patients versus 14.3 months in placebo patients (hazard ratio (HR) = 0.78, $P = 0.029$).

Frequently reported adverse events (AEs) were mostly Grade 1–2 and included dermatologic (rash and hand–foot skin reaction [HFSR]), gastrointestinal (diarrhoea) and constitutional (fatigue) toxicities.[14] In the SHARP trial, sorafenib was the first agent to demonstrate an improvement in OS for patients with advanced hepatocellular carcinoma (HCC).[23] In addition, sorafenib-treated patients with metastatic renal cell carcinoma (RCC) experienced greater rates of tumour size reduction, better quality of life and improved tolerability compared with interferon alfa-2a.[24]

Due to its manageable AE profile, sorafenib has the potential to be combined with cytotoxic drugs that are generally associated with greater toxicity. In Phase I/II combination trials, sorafenib demonstrated good tolerability and preliminary anti-tumour activity against a variety of solid tumours when combined with other anticancer drugs, including oxaliplatin,[25] gemcitabine,[26] interferon-alpha 2a,[27] carboplatin/paclitaxel[28] and doxorubicin.[22] Docetaxel is subject to oxidative metabolic pathways catalysed primarily by cytochrome P450 isozyme 3A4 (CYP3A4).[29,30] CYP3A4 activity is the most significant predictor of docetaxel clearance; lower docetaxel clearance and greater toxicity is observed in patients with the lowest CYP3A4 activity.[31–33] Sorafenib is also metabolised by CYP3A4. However, *in vivo* data from patients with advanced metastatic melanoma, using midolazam as a CYP3A4 probe substrate, suggest that sorafenib 400 mg twice daily (bid) at steady state concentration is not a clinically relevant inhibitor of CYP3A4, as no changes in midolazam exposure or plasma levels of 1-hydroxy midolazam were observed.[34,35]

The aim of this Phase I study was to determine the safety, maximum tolerated dose (MTD), pharmacokinetics (PK) and preliminary tumour response of sorafenib in combination with docetaxel in patients with advanced, refractory solid tumours.

2. Methods

2.1. Patient selection

Patients with histologically confirmed solid tumours who were refractory to standard treatment were eligible for inclusion. Additional inclusion criteria included age $\geqslant$18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 12 weeks; adequate organ function of the liver and kidneys; and signed informed consent. All patients provided written informed consent.

The study was approved by the Jules Bordet Institute Ethics Committee and complied with the recommendations of the Declaration of Helsinki, Good Clinical Practice guidelines and local laws and regulations. Patients were excluded if they had one of the following: congestive heart failure, cardiac arrhythmias or symptoms of coronary heart disease, cerebral disease or brain tumours; known HIV or other serious active infections; other medical conditions that may interfere with participation in the study or evaluation of the results; history of organ transplant or allograft; immunotherapy or chemotherapy within 4 weeks of study entry; radiotherapy or major surgery within 3 weeks of study entry; previous exposure to a Ras pathway inhibitor; and previous exposure to docetaxel within 6 months prior to enrolment.

2.2. Study design

This was a single-centre, open-label, non-controlled, dose-escalation, Phase I trial. Patients were enrolled into four Cohorts and received docetaxel (intravenous infusion for 1 h) on Day 1 and sorafenib for 18 consecutive days on Days 2–19 of each 21-day treatment cycle, with a 3-day break in dosing around the administration of docetaxel, according to a standard, Phase I, dose-escalation design. Three patients were initially enrolled per cohort, and if a dose-limiting toxicity (DLT) occurred, then the cohort would be expanded to six patients. Dose-escalation proceeded if the rate of DLTs was $\leqslant$33%. Otherwise MTD was considered to be reached. Specifically, the regimen in each cohort was as follows: Cohort 1, sorafenib 200 mg twice-daily (bid) with docetaxel 75 mg/m^2; Cohort 2, sorafenib 200 mg bid with docetaxel 100 mg/m^2; Cohort 3, sorafenib 400 mg bid with docetaxel 100 mg/m^2. Because of significant toxicity observed in Cohort 3, the dose level for docetaxel was reduced in Cohort 4–75 mg/m^2, while the sorafenib dose level was kept at 400 mg bid. The dose selection and escalation to the next cohort were dependent on patients receiving at least two full cycles and one the occurrence of DLTs during the first two cycles of treatment (i.e. 42 days) of the previous cohort, as possible clinical or PK interaction between sorafenib and docetaxel was expected after the first cycle. AEs were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0. The following AEs were defined as DLTs: Grade 3/4 thrombocytopenia, $\geqslant$Grade 4 neutropenia for $\geqslant$7 days, febrile neutropenia (any grade), $\geqslant$Grade 4 anaemia, $\geqslant$Grade 3 non-haematologic toxicity (except alopecia, nausea, vomiting or diarrhoea controlled by anti-emetic medication or loperamide) or any other toxicity considered by the investigator to be related to the combination treatment with sorafenib and docetaxel. Any clinically significant event (Grade $\geqslant$3 AE) that was not expected to occur with docetaxel, or that worsened with coadministration with sorafenib, requiring withholding of sorafenib and/or docetaxel treatment for 14 days, was also considered a DLT.

2.2.1. Dose modifications

If a DLT occurred during the first treatment cycle, the patient was allowed to continue sorafenib monotherapy at the investigator's discretion. If a DLT first occurred during the second or subsequent cycles, the treatment was discontinued and only restarted at one dose level below the patient's previous dose of sorafenib at the time of the next cycle if the toxicity resolved to <Grade 2. If the toxicity failed to resolve to <Grade 2 within 14 days after discontinuation of treatment, the patient was removed from the study. Treatment continued until unacceptable toxicity or disease progression. Patients who discontinued docetaxel treatment for an unresolved toxicity were permitted to continue on sorafenib monotherapy. Patients who had to stop sorafenib treatment were removed from the study.

2.3. Study outcomes

The primary objectives were to determine the safety profile and tolerability of sorafenib in combination with docetaxel. The secondary objectives were to characterise the PK and tumour response with the combination of sorafenib and docetaxel.

2.3.1. Safety

All patients who had received at least one dose of docetaxel or sorafenib were evaluated for safety, which included toxicity, haematology and biochemical parameters at baseline and throughout the study. AEs were graded according to the NCI-CTC v2.0.

2.3.2. Plasma pharmacokinetics

Patients who completed at least one treatment cycle and had no missing PK measurements were included in the PK analyses. The following docetaxel PK parameters were calculated applying non-compartmental methods (Kincalc, Bayer HealthCare AG, Wuppertal, Germany): maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC_{0-24}), time to maximum plasma concentration (t_{max}) and apparent terminal half-life ($t_{½}$).

The PK profile of docetaxel in Cohorts 1–4 was determined on Day 1 of Cycle 1 (docetaxel alone) and Cycle 2 (i.e. docetaxel given after an interruption of sorafenib given from Days 2–19). Samples were taken at 0 (predose), 0.5, 1 (at the end of infusion), 1.5, 2, 3, 4, 6, 12 and 24 h. Plasma concentrations of docetaxel were quantified using a validated high-performance liquid chromatographic assay with UV detection with a lower limit of quantification of 5 μg/L. Mean inter-assay precision and accuracy ranged from 4.9% to 6.6% and from 99% to 101%, respectively.

2.3.3. Efficacy

All patients who received at least one treatment cycle and who had their disease re-evaluated after study entry were evaluable for efficacy. Baseline radiologic tumour assessments were performed 4 weeks prior to study treatment. Tumour response was evaluated every 8 weeks during the treatment period, using the Response Evaluation Criteria In Solid Tumours (RECIST).

2.3.4. Statistical analysis

Summary statistics were used to assess baseline characteristics, demographic variables, AEs, haematology, biochemistry and PK parameters. PK variables were compared using analysis of variance; mean values and the corresponding 90% confidence intervals of docetaxel with versus without sorafenib pre-treatment are

presented. Efficacy was summarised by cohort for the best response, RECIST measurement and duration of response. The objective tumour response was calculated as the percentage of patients with a complete or partial response based on the whole population. The response duration, defined as the time elapsing from the first measurement of a complete or partial response to the first objective documentation of recurrent or progressive disease (PD), was also measured. Stable disease (SD) duration was measured from the start of treatment until criteria for progression were met. The time to progression (TTP) was determined as the time from baseline until disease progression. All continuous measurements were summarised by mean (or median for non-normal data), standard deviation and minimum and maximum values. Categorical data were summarised by frequency counts and percentages.

2.3.5. Inhibition of docetaxel hydroxylation in vitro

During this study, the PK analysis revealed that docetaxel exposure was increased by pre-treatment with sorafenib. The knowledge of these PK results prompted an *in vitro* sub-study, to elucidate the observed clinical–PK interaction between docetaxel and sorafenib.

Human hepatocytes, isolated from surgical waste tissues from patients undergoing partial liver resections, were supplied by Hepacult GmbH (Unterföehring, Germany) or Cytonet GmbH (Heidelberg, Germany). Docetaxel (Taxotere®) was purchased from Fluka (Taufkirchen, Germany).

Incubation mixtures contained 1×10^6 cells/mL, William's medium E (sterile and carbogen gas treated for 15 min), 0.292 g/L L-glutamine, docetaxel (5 μM) as substrate and various concentrations of sorafenib tosylate as potential inhibitor (0, 2, 5, 10 and 20 μM) in a final volume of 4–5 mL. Following incubation at 37 °C for 45 min, reaction mixtures were stopped by the addition of methanol, and precipitated proteins were removed by centrifugation (8000 RPM, 3 min). The supernatants were analysed for hydroxy docetaxel and docetaxel by LC–MS with a Gemini C18 column (3 μm, 100 × 2.0 mm, Phenomenex, Aschaffenburg, Germany) coupled via TurboIonSpray interface to an atmospheric pressure ionisation tandem mass spectrometer API 3000 (Applied Biosystems MDS Sciex, Concord, Canada). Mobile phase A consisted of 10 mmol/L ammonium formate (pH 4) and mobile phase B was acetonitrile. Elution was conducted at a flow rate of 0.4 mL/L using a ratio of 55:45 of mobile Phase A to mobile Phase B.

3. Results

3.1. Patient characteristics

Twenty-seven patients (11 male), aged 27–75 years (median 53 years), were enrolled and received at least one dose of both sorafenib and docetaxel (Table 1). The majority of patients (96%) had an ECOG performance status of 0–1, one patient in Cohort 3 was enrolled in the study despite having an ECOG performance status of 2. The most common malignancies included breast (19%), prostate (15%), pancreas (11%) and ovary (11%). Most patients had received prior systemic anticancer chemotherapy (93%), surgery (78%) and/or radiotherapy (63%).

3.2. Safety

All 27 patients were evaluable for the safety analyses. All patients had at least one AE, and 26 (96%) patients had at least one AE rated Grade 3–5 (Table 2). The most frequent treatment-emergent Grade 3–5 AEs included abnormal neutrophils (89%), decreased leukocytes (81%), HFSR (30%) and fatigue (30%).

The most common drug-related AEs leading to dose reduction/interruption or permanent discontinuation were dermatologic (41%), gastrointestinal (26%) and constitutional (22%) in nature (Table 3). DLTs occurring during the first 42 days of study included cutaneous rash/HFSR, noted in one of six patients in Cohort 1 (sorafenib 200 mg bid + docetaxel 75 mg/m^2), and leukopaenia/neutropenia, noted in one of six patients in Cohort 2 (sorafenib 200 mg bid + docetaxel 100 mg/m^2). In Cohort 3 (sorafenib 400 mg bid + docetaxel 100 mg/m^2), DLTs were reported in three of five patients, and in Cohort 4 (sorafenib 400 mg bid + docetaxel 75 mg/m^2), DLTs were reported in four of 10 patients. The most commonly reported DLTs occurring in the first 42 days of study in Cohorts 3 and 4 included mainly HFSR and neutropenia, and to a lesser extent mucositis, diarrhoea, neutropenia-related events and fatigue. It should be mentioned that in Cohort 4, 10 patients were enrolled to evaluate the toxicity at this dose level in more detail.

AEs as the primary reason for a permanent discontinuation from the study occurred in five patients. Two patients in Cohort 2 experienced either HFSR ($n = 1$) or weight loss combined with diarrhoea ($n = 1$), leading to permanent discontinuation. One patient in Cohort 3 experienced febrile neutropenia and leucopaenia (both Grade 4) with dysphagia and mucositis leading to permanent discontinuation. Two patients in Cohort 4 experienced either an allergy to sorafenib ($n = 1$) or erythema combined with mucositis, vomiting, anorexia and fatigue ($n = 1$), leading to discontinuation. Other reasons for treatment discontinuations were PD ($n = 21$) and withdrawal of consent ($n = 1$). One subject in Cohort 3 died of progressive disease, which was reported as an adverse event.

3.3. Pharmacokinetics

Analysis of docetaxel PK parameters is based on data from 15 of 27 patients, who completed at least one

Table 1
Baseline and demographic characteristics.

	Cohort 1 ($n = 6$) DTX 75 mg/m^2 + SOR 200 mg bid *n* (%)	Cohort 2 ($n = 6$) DTX 100 mg/m^2 + SOR 200 mg bid *n* (%)	Cohort 3 ($n = 5$) DTX 100 mg/m^2 + SOR 400 mg bid *n* (%)	Cohort 4 ($n = 10$) DTX 75 mg/m^2 + SOR 400 mg bid *n* (%)	Total ($n = 27$) *n* (%)
Gender					
Male	3 (50)	2 (33)	2 (40)	4 (40)	11 (41)
Female	3 (50)	4 (67)	3 (60)	6 (60)	16 (59)
Median age, years (range)	57 (40–75)	49 (27–69)	48 (42–74)	56 (31–68)	53 (27–75)
ECOG PS					
0	1 (17)	0 (0)	1 (20)	5 (50)	7 (26)
1	5 (83)	6 (100)	3 (60)	5 (50)	19 (70)
2	0 (0)	0 (0)	1 (20)	0 (0)	1 (4)
Malignancy type					
Breast	2 (33)	2 (33)	1 (20)	0 (0)	5 (19)
Prostate	2 (33)	1 (17)	1 (20)	0 (0)	4 (15)
Ovary	1 (17)	1 (17)	0 (0)	1 (10)	3 (11)
Pancreas	1 (17)	0 (0)	0 (0)	2 (20)	3 (11)
Oesophagus	0 (0)	0 (0)	1 (20)	1 (10)	2 (7)
Kidney	0 (0)	1 (17)	0 (0)	1 (10)	2 (7)
Skin	0 (0)	0 (0)	1 (20)	1 (10)	2 (7)
Other	0 (0)	1 (17)	1 (20)	4 (40)	6 (22)
Prior treatment					
Systemic	6 (100)	5 (83)	4 (80)	10 (100)	25 (93)
Radiotherapy	5 (83)	3 (50)	5 (100)	4 (40)	17 (63)
Surgery	6 (100)	4 (67)	4 (80)	7 (70)	21 (78)
Number of prior regimens					
0	0 (0)	1 (17)	1 (20)	0 (0)	2 (7)
1–2	1 (17)	2 (33)	1 (20)	8 (80)	12 (44)
3–4	2 (33)	1 (17)	1 (20)	1 (10)	5 (19)
$\geqslant 5$	3 (50)	2 (33)	2 (40)	1 (10)	8 (30)

Bid, twice daily; DTX, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; SOR, sorafenib.

Table 2
Incidence of treatment-emergent adverse events (AEs) in $\geqslant 10\%$ of all patients in at least one Cohort.

	Cohort 1 ($n = 6$) DTX 75 mg/m^2 + SOR 200 mg bid *n* (%)		Cohort 2 ($n = 6$) DTX 100 mg/m^2 + SOR 200 mg bid *n* (%)		Cohort 3 ($n = 5$) DTX 100 mg/m^2 + SOR 400 mg bid *n* (%)		Cohort 4 ($n = 10$) DTX 75 mg/m^2 + SOR 400 mg bid *n* (%)		Total ($n = 27$) *n* (%)	
	All grades	Grade 3–5	All grades	Grade 3–5	All grades	Grade 3–5	All grades	Grade 3–5	All grades	Grade 3–5
Any adverse event	6 (100)	5 (83)	6 (100)	6 (100)	5 (100)	5 (100)	10 (100)	10 (100)	27 (100)	26 (96)
Blood/bone marrow-related	5 (83)	4 (67)	6 (100)	6 (100)	5 (100)	5 (100)	10 (100)	10 (100)	26 (96)	25 (93)
Neutrophils/ granulocytes[a]	5 (83)	4 (67)	6 (100)	6 (100)	4 (80)	4 (80)	10 (100)	10 (100)	25 (93)	24 (89)
Leucocytes (total WBC)	4 (67)	3 (50)	6 (100)	6 (100)	5 (100)	5 (100)	9 (90)	8 (80)	24 (89)	22 (81)
Dermatology/skin-related	6 (100)	1 (17)	6 (100)	2 (33)	5 (100)	2 (40)	10 (100)	3 (30)	27 (100)	8 (30)
Hand–foot skin reaction	3 (50)	1 (17)	5 (83)	2 (33)	4 (80)	2 (40)	9 (90)	3 (30)	21 (78)	8 (30)
Constitutional symptoms	6 (100)	1 (17)	6 (100)	0 (0)	4 (80)	3 (60)	10 (100)	6 (60)	26 (96)	10 (37)
Fatigue	5 (83)	0 (0)	6 (100)	0 (0)	4 (80)	2 (40)	10 (100)	6 (60)	25 (93)	8 (30)
Gastrointestinal-related	5 (83)	1 (17)	6 (100)	0 (0)	5 (100)	2 (40)	8 (80)	4 (40)	24 (89)	7 (26)
Anorexia	3 (50)	0 (0)	5 (83)	0 (0)	3 (60)	2 (40)	5 (50)	1 (10)	16 (59)	3 (11)
Infection/febrile neutropenia	3 (50)	1 (17)	2 (33)	0 (0)	3 (60)	2 (40)	3 (30)	2 (20)	11 (41)	5 (19)
Infection without neutropenia	1 (17)	0 (0)	1 (17)	0 (0)	2 (40)	1 (20)	3 (30)	2 (20)	7 (26)	3 (11)
Pain	6 (100)	1 (17)	2 (33)	1 (17)	3 (60)	1 (20)	6 (60)	1 (10)	17 (63)	4 (15)

Note: the grading of AEs was according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) v2.0 category.
DTX, docetaxel; SOR, sorafenib; WBC, white blood cells.
[a] ANC/AGC = absolute granulocyte count/absolute neutrophil count.

Table 3
Incidence of drug-related adverse events (AEs), summarised in categories, leading to dose reduction, interruption or permanent discontinuation.

	Cohort 1 ($n = 6$) DTX 75 mg/m^2 + SOR 200 mg bid n (%)	Cohort 2 ($n = 6$) DTX 100 mg/m^2 + SOR 200 mg bid n (%)	Cohort 3 ($n = 5$) DTX 100 mg/m^2 + SOR 400 mg bid n (%)	Cohort 4 ($n = 10$) DTX 75 mg/m^2 + SOR 400 mg bid n (%)	Total ($n = 27$) n (%)
Dermatologic toxicity	2 (33)	1 (17)	2 (40)	6 (60)	11 (41)
Gastrointestinal toxicity	1 (17)	1 (17)	2 (40)	3 (30)	7 (26)
Constitutional symptoms	1 (17)	1 (17)	1 (20)	3 (30)	6 (22)
Infection/febrile neutropenia	0 (0)	0 (0)	1 (20)	1 (10)	2 (7)
Blood/bone marrow-related	0 (0)	0 (0)	1 (20)	1 (10)	2 (7)
Neurological toxicities	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)

Bid, twice daily; DTX, docetaxel; SOR, sorafenib.

treatment cycle and had no missing PK measurements (Table 4). Mean $AUC_{0–24}$ values for 75 and 100 mg/m^2 docetaxel alone (Cycle 1 of Cohorts 1 and 2) were of similar magnitude (1991 μg h/L and 2096 μg h/L, respectively), despite the 33% increase in dose. In contrast, mean C_{max} increased from 1309 to 2343 μg/L after infusion of 75 and 100 mg/m^2 docetaxel, respectively. Mean $AUC_{0–24}$ values for 100 mg/m^2 docetaxel alone (Cycle 1) were similar in Cohorts 2 and 3 (2096 and 2080 μg h/L, respectively). However, mean $AUC_{0–24}$ (3006 μg h/L) and C_{max} (2728 μg/L) for 75 mg/m^2 docetaxel alone (Cycle 1) in Cohort 4 were notably higher compared with those in Cohorts 2 and 3. The apparent non-linearity for docetaxel PK parameters may be explained by the low number of patients in each cohort and the high interpatient variability of docetaxel PK.

Pre-treatment with 200 mg bid sorafenib had little effect on $AUC_{0–24}$ of 75 mg/m^2 docetaxel (Cycle 2, Cohort 1). However, the $AUC_{0–24}$ for 100 mg/m^2 docetaxel (Cohort 2) was increased on average by 54% (from 2096 to 3228 μg·h/L) in the presence of 200 mg sorafenib (Table 5). Similarly, mean $AUC_{0–24}$ of docetaxel was increased by 36% in Cohort 3 and by 80% in Cohort 4 when the patients were pre-treated with 400 mg sorafenib. C_{max} of docetaxel was increased by pre-treatment with sorafenib in the range of 16–32%, independent of the doses of both docetaxel and sorafenib.

3.3.1. Inhibition of docetaxel hydroxylation in vitro

Docetaxel (5 μM) was incubated with hepatocytes of four different donors in the absence and presence of sorafenib (0–20 μM). The amount of hydroxy docetaxel decreased in a concentration-dependent manner when sorafenib was co-incubated. Sorafenib was capable of inhibiting hydroxy docetaxel formation with an IC_{50} value of 17.2 μM (range: 15.0–18.8 μM) *in vitro*.

3.4. Efficacy

Twenty-five patients were evaluable for tumour response. Three (11%) patients achieved partial response (PR), and 14 (52%) patients had SD as best response

Table 4
Pharmacokinetics (PK) parameters of docetaxel (75 or 100 mg/m^2) without (Cycle 1) or with (Cycle 2) previous multiple dosing with sorafenib (200 or 400 mg twice daily) for 15 patients in Cohorts 1–4 (geometric means/geometric standard deviation [%CV] [range]).

	Cycle 1 (without sorafenib)				Cycle 2 (with sorafenib)			
	$AUC_{0–24}$ (μg·h/L) Mean (%CV) Range	C_{max} (μg/L) Mean (%CV) Range	$t_{½}$ (h) Mean (%CV) Range	t_{max} (h) Median Range	$AUC_{0–24}$ (μg·h/L) Mean (%CV) Range	C_{max} (μg/L) Mean(%CV) Range	$t_{½}$ (h) Mean (%CV) Range	t_{max} (h) Median Range
Cohort 1 ($n = 3$)	1991 (68.7)	1309 (22.9)	21.0 (22.1)	1.0	2090 (43.6)	1734 (34.1)	12.3 (82.8)	1.0
SOR 200 mg bid + DTX 75 mg/m^2	980–3130	1043–1640	18.5–27.1	0.5–1.0	1298–2820	1185–2175	5.86–24.8	1.0–1.0
Cohort 2 ($n = 5$)	2096 (26.3)	2343 (23.7)	4.94 (43.7)	0.6	3228 (31.7)	2717 (33.3)	7.44 (59.3)	0.5
SOR 200 mg bid + DTX 100 mg/m^2	1554–3126	1744–3256	3.18–9.42	0.5–1.0	2346–5127	2053–4085	3.63–14.8	0.5–1.0
Cohort 3 ($n = 2$)	2080 (31.9)	1793 (5.7)	5.78 (110.1)	1.1	2823 (9.7)	2201 (29.9)	10.6 (111.9)	0.5
SOR 400 mg bid + DTX 100 mg/m^2	1669–2591	1722–1866	3.08–10.9	1.0–1.1	2636–3023	1789–2707	5.62–20.1	0.5–0.5
Cohort 4 ($n = 5$)	3006 (24.5)	2728 (23.2)	11.7 (326.2)	0.6	5416 (33.9)	3408 (14.4)	15.7 (150.4)	1.0
SOR 400 mg bid + DTX 75 mg/m^2	2259–4092	2184–3970	2.45–80.4	0.5–1.0	3788–8156	2931–4207	3.25–59.8	0.6–1.1

$AUC_{0–24}$, area under the concentration–time curve; C_{max}, maximum plasma concentration; %CV, coefficient of variation; DTX, docetaxel; SOR, sorafenib. t_{max},time to maximum concentration; $t_{½}$, elimination half-life.

Table 5
Ratios of AUC_{0-24} and C_{max} values of docetaxel in Cycle 2 (administration of docetaxel after prior administration of sorafenib) versus Cycle 1 (administration of doectaxel without prior administration of sorafenib) and corresponding 90% confidence intervals (CI) for 15 patients in Cohorts 1–4.

	AUC_{0-24} (μg·h/L)		C_{max} (μg/L)	
	Ratio	90% CI	Ratio	90% CI
Cohort 1 ($n = 3$) SOR 200 mg bid + DTX 75 mg/m^2	1.05	0.68–1.62	1.32	0.95–1.85
Cohort 2 ($n = 5$) SOR 200 mg bid + DTX 100 mg/m^2	1.54	1.41–1.68	1.16	0.98–1.37
Cohort 3 ($n = 2$) SOR 400 mg bid + DTX 100 mg/m^2	1.36	0.52–3.53	1.23	0.43–3.52
Cohort 4 ($n = 5$) SOR 400 mg bid + DTX 75 mg/m^2	1.80	1.18–2.74	1.25	1.12–1.39

AUC_{0-24}, area under the concentration–time curve; C_{max}, maximum plasma concentration; DTX, docetaxel; SOR, sorafenib.

during the study (Table 6). Of the patients who achieved SD, four received sorafenib/docetaxel for less than 3 months, three received sorafenib/docetaxel for more than 3 months but less than 6 months, and seven were treated with sorafenib/docetaxel for more than 6 months. The patients with PR had breast, lung and oesophageal cancers (all $n = 1$). Patients with SD had prostate ($n = 4$), breast ($n = 3$), ovarian ($n = 2$), melanoma ($n = 2$), RCC ($n = 1$), cervical ($n = 1$) and skin (epidermoid epithelioma, $n = 1$) tumour types. Overall median TTP was 128 days (Cohort 1), 165 days (Cohort 2), 179 days (Cohort 3) and 127 days (Cohort 4).

4. Discussion

The combination of sorafenib with docetaxel was tolerable, and no unexpected toxicities associated with sorafenib treatment in combination with docetaxel were reported. The most frequently observed toxicity was myelotoxicity, with greater than 80% of patients reporting neutropenia and leucopaenia of Grade 3–5. Myelotoxicity is typically associated with single-agent docetaxel, and rates of Grade 4 neutropenia as high as 76–95% with docetaxel 100 mg/m^2 given every 3 weeks have been reported in the literature.[36–38] Historical data show that 93–95% of breast cancer patients given docetaxel 100 mg/m^2 every 3 weeks experienced Grade 4 neutropenia,[37,38] with Grade 3–4 skin reactions reported in up to 10% of patients.[39] The increase in docetaxel exposure upon coadministration with sorafenib was not reflected by an increased frequency of myelotoxicity compared with historical data from single-agent docetaxel studies.

Although single-agent sorafenib is associated with dermatologic toxicities,[40] sorafenib is not known to cause clinically relevant myelotoxicity. In the present study, there were no unexpected toxicities associated with sorafenib treatment in combination with docetaxel.[41] This is consistent with previous reports that have suggested sorafenib is generally well tolerated in combination with other anticancer therapies, including oxaliplatin,[25] gemcitabine,[26] interferon-alpha 2a,[27] carboplatin/paclitaxel[28] and doxorubicin.[22] The sorafenib 400 mg bid continuous dosing regimen has been associated with HFSR, and Grade 3 or 4 HFSR has been reported in 6% of RCC patients[14,42] and 8% of HCC patients.[23] In the present study, the pattern of DLT occurrence reflects the toxicity profile of docetaxel and sorafenib. However, DLTs associated with skin toxicity were more frequent with the combination than expected,[42] based on historical single-agent therapy data – possibly due to the higher PK exposure of docetaxel. It must be noted that these results are based on a relatively small patient population with a variety of advanced solid tumours. Currently, 400 mg bid is generally accepted as the recommended dose for sorafenib therapy as a single agent or in combination with other agents.[25,26,42–44] Therefore, as cutaneous toxicity is not a life-threatening AE and can be resolved with appropriate management (including topical treatments and/or periodic dose interruptions or

Table 6
Best tumour response and median time to progression.

	Cohort 1 ($n = 6$) DTX 75 mg/m^2 + SOR 200 mg bid *n* (%)	Cohort 2 ($n = 6$) DTX 100 mg/m^2 + SOR 200 mg bid *n* (%)	Cohort 3 ($n = 5$) DTX 100 mg/m^2 + SOR 400 mg bid *n* (%)	Cohort 4 ($n = 10$) DTX 75 mg/m^2 + SOR 400 mg bid *n* (%)	Total ($n = 27$) *n* (%)
Partial response	0 (0.0)	1 (16.7)	0 (0.0)	2 (20.0)	3 (11.1)
Stable disease	4 (66.7)	3 (50.0)	4 (80.0)	3 (30.0)	14 (51.9)
Progressive disease[a]	2 (33.3)	2 (33.3)	0 (0.0)	2 (20.0)	6 (22.2)
Progressive disease[b]	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	2 (7.4)
Not assessable	0 (0.0)	0 (0.0)	1 (20.0)	1 (10.0)	2 (7.4)
Median TTP, days (range)	128 (29–772)	165 (30–393)	179 (64–246)	127 (51–268)	N/A

Bid, twice daily; DTX, docetaxel; N/A, not applicable; SOR, sorafenib; TTP, time to progression.
[a] Measurement proven.
[b] By clinical judgement.

reductions), patients could begin treatment with sorafenib 400 mg bid + docetaxel 75 mg/m^2 with down titration to 200 mg bid sorafenib in the event of significant dermatologic toxicity.

The PK analyses were similar to those previously reported[42] and suggested that concomitant administration of these agents may lead to an increase in the exposure of docetaxel. Cohort 4 had the highest mean increase (80%) in the AUC_{0-24} of docetaxel. In Cohort 3, there was a mean increase in AUC_{0-24} of docetaxel of 36%. Similarly, AUC_{0-24} of docetaxel increased on average by 54% following the combination regimen of docetaxel 100 mg/m^2 and sorafenib 200 mg bid. This lack of a dose-dependent increase in AUC_{0-24} and C_{max} of docetaxel alone (Cycle 1) may be a consequence of the small number of patients evaluable for PK in this trial and the significant interpatient docetaxel PK variability.

Docetaxel is subject to oxidative metabolic pathways catalysed primarily by CYP3A4.[29,30] Furthermore, studies in cancer patients that use the probe substrates erythromycin, midazolam and cortisol showed that CYP3A4 activity is the most significant predictor of docetaxel clearance, with lower clearance and greater toxicity in patients with the lowest CYP3A4 activity.[31–33]

Although docetaxel is predominantly metabolised by CYP3A, data on potential clinical drug–drug interactions with CYP3A inhibitors are rare. The potent CYP3A inhibitor ketoconazole produces a 49% decrease in docetaxel clearance.[45] Moderate inhibitors of CYP3A4 have a low potential to affect the PK profile of docetaxel.

Flaherty et al. evaluated the inhibitory potential of sorafenib *in vivo*. A clinical study was conducted to investigate the effect of 400 mg bid sorafenib (at steady-state sorafenib concentrations) on probe substrates of CYP2C19 (omeprazole), CYP2D6 (dextromethorphan) and CYP3A4 (midazolam).[46] There was no increase of midazolam exposure and no significant change in 1-hydroxy midazolam plasma levels, indicating that sorafenib is not a clinically relevant inhibitor of CYP3A4.

As co-medication of sorafenib with midazolam did not alter midazolam PK, it seems to be unlikely that the observed increase in docetaxel exposure (1.3–1.8-fold) following sorafenib coadministration is due to CYP3A4 inhibition. This interpretation is further supported by the *in vitro* drug–drug interaction data. Using human hepatocytes, sorafenib inhibited hydroxy docetaxel formation with an IC_{50} value of 17.2 μM (range: 15.0–18.8 μM).

In vitro, sorafenib also exhibited only small inhibitory effects on CYP3A4 using testosterone and midazolam as representative substrates and human liver microsomes as enzyme source. The K_i values were 28.9 and 26.3 μM for the inhibition of midazolam and testosterone hydroxylation, respectively.[35]

The inhibitory effect of sorafenib on docetaxel hydroxylation *in vitro* is in the same range as its effects on midazolam and testosterone hydroxylation, indicating CYP3A4 inhibition by sorafenib to be moderate and almost independent of the probe substrate. Therefore, it is unlikely that the increase in docetaxel exposure when coadministered with sorafenib is due to CYP3A4 inhibition.

Likewise, *in vitro* data indicated that docetaxel is a substrate for P-glycoprotein (P-gp). However, although sorafenib is capable of inhibiting P-gp-mediated efflux of other substrates (e.g. dipyridamole and loperamide had IC_{50} of 1.3 and 0.8 μM in L-MDR-1 cells, respectively), there was no considerable inhibition of docetaxel efflux [data on file]. Thus P-gp inhibition does not appear to account for the increase in docetaxel exposure when coadministered with sorafenib.

Drug–drug interactions with sorafenib (400 mg bid) have been investigated in other Phase I trials; concomitant administration of sorafenib resulted in increased exposures of doxorubicin and irinotecan, although there were no apparent increases in clinical toxicities.[22,47] In the majority of Phase I trials, no significant PK interactions were observed when sorafenib was coadministered with other anticancer therapies, including carboplatin/paclitaxel,[28] gemcitabine[26] or oxaliplatin.[25]

The reason for exploring a combination approach in cancer therapy is because such combinations of chemotherapeutic agents may help overcome tumour drug-resistance mechanisms that are commonly associated with single-agent therapies and thus enhance the therapeutic potential of each individual agent.[5] Promising anti-tumour activity has been demonstrated with sorafenib in combination with gemcitabine,[26] doxorubicin[22] or oxaliplatin[25] in a variety of solid tumours. Although not a primary objective of this study, anti-tumour activity of sorafenib in combination with docetaxel was demonstrated across all Cohorts in this largely pre-treated patient population. Three (11%) patients achieved a PR (median duration 178 days) and 14 (52%) patients experienced SD (median duration 208 days), resulting in a disease control rate of 63%. These data are to be compared with those from a Phase I trial of single-agent docetaxel (at a slightly higher exposure) in treatment-refractory solid tumours, in which one (4%) patient achieved a complete response, eight (35%) patients had PRs and six (26%) patients had SD, for a disease control rate of 65%).[48] All responses were observed in patients with metastatic breast cancer. Further studies are required to elucidate the advantages of the combination therapy. The preliminary anti-tumour activity and median TTP observed in our study also compare favourably with that reported in several randomised Phase III trials of docetaxel in solid tumours, including metastatic breast, lung, ovarian, gastric and prostate cancer.[2]

In summary, the results of this Phase I trial demonstrated that the coadministration of sorafenib with docetaxel lead to a significant gastro intestinal, fatigue and skin toxicity but remains feasible. There were no unexpected toxicities associated with sorafenib when coadministered with docetaxel. Despite a possible increase in docetaxel exposure with concomitant sorafenib, the data suggest that there was no apparent increase in myelotoxicity (e.g. neutropenia or leukopaenia) and no suggestion that sorafenib is a clinically significant inhibitor of CYP3A4. Preliminary efficacy was observed across all doses. These results suggest that Phase II studies investigating the anti-tumour activity of sorafenib and docetaxel in combination should be considered, with sorafenib 400 mg bid administered in combination with docetaxel 75 mg/m^2 as the starting dose for Phase II investigation. We propose that the reduction of sorafenib dose or an interruption in the case of significant skin or gastro intestinal toxicity should be implemented.

Conflict of interest statement

Fellows of the American College of Clinical Pharmacology: none. Ahmad Awada has no disclosures. Alain Hendlisz has no disclosures. Olaf Christensen is employed by Bayer HealthCare Pharmaceuticals Inc. Chetan Lathia is employed by Bayer HealthCare Pharmaceuticals Inc. Sylvie Bartholomeus has no disclosures. Fabienne Lebrun has no disclosures. Dominique de Valeriola has no disclosures. Erich Brendel is employed by Bayer HealthCare AG. Martin Radtke is employed by Bayer HealthCare AG. Thierry Delaunoit has no disclosures. Martine Piccart-Gebhart has no disclosures. Thierry Gil has no disclosures.

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