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Pharmacokinetic results of a phase I trial of sorafenib in combination with dacarbazine in patients with advanced solid tumors

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Abstract (Limit: ~250 words; actual: 249)

Purpose Sorafenib, a multikinase inhibitor of Raf and several growth factor receptors, is under investigation in combination with dacarbazine, a commonly used chemotherapeutic agent for treatment of many cancers. The current phase I study investigates the effects of sorafenib on the pharmacokinetic (PK) profile of dacarbazine and its metabolite 5-amino-imidazole-4-carboxamide (AIC). (AIC is formed in amounts equimolar to the active alkylating moiety, methane diazohydroxide, which is undetectable by known validated assays.)

Methods Patients with advanced solid tumors received intravenous dacarbazine 1,000 mg/m^2 on day 1 of a 21-day cycle to evaluate the PK of dacarbazine alone. Sorafenib 400 mg was administered twice daily continuously starting day 2 of cycle 1. The PK of dacarbazine in the presence of sorafenib was assessed on day 1 of cycle 2. Sorafenib PK was also assessed at steady state.

Results PK data were available for 15 of 23 patients. With concomitant administration of sorafenib, the mean AUC and C_{max} values of dacarbazine were reduced by 23% and 16%, respectively. Mean AUC and C_{max} values of AIC were increased by 41% and 45%, respectively, with individual increases of up to 106% and 136%, respectively. The apparent terminal half-lives of the two compounds were not significantly influenced by sorafenib. Based on coefficients of variation, the AUC and C_{max} values for sorafenib and its three metabolites were highly variable with dacarbazine coadministration.

Conclusions Concomitant administration of sorafenib and dacarbazine as described above may result in decreased dacarbazine exposure but increased AIC exposure.

Keywords Sorafenib, Dacarbazine, AIC, Pharmacokinetics, Phase I

Introduction

Sorafenib is a multikinase inhibitor of Raf, vascular endothelial growth factor (VEGF) receptors, and platelet-derived growth factor receptors [1, 2]. It has been approved as a single agent by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma. In addition, sorafenib is being tested in combination with other agents in a variety of advanced solid tumors such as melanoma, breast cancer, renal cell carcinoma, hepatic cancer, and non-small cell lung cancer [3-16]. Dacarbazine is the most commonly used FDA- and EMEA-approved chemotherapeutic agent for the treatment of advanced melanoma. Dacarbazine is metabolized by various cytochrome P450 (CYP) isoenzymes such as CYP1A2, CYP1A1, and CYP2E1 [17]. Sorafenib is primarily metabolized in the liver by CYP3A4 [18]. Therefore, concomitant sorafenib administration is not expected to affect dacarbazine metabolism, and the likelihood of a pharmacokinetic (PK) drug-drug interaction between sorafenib and dacarbazine is low.

An earlier phase I study estimated that the maximum tolerated dose of sorafenib in combination with dacarbazine 1,000 mg/m^2 was 400 mg twice daily (the standard single-agent doses for each agent) [19]. The primary objective of this study was to evaluate the PK profiles of dacarbazine with and without concomitant sorafenib under steady-state conditions. A secondary objective was to determine the steady-state PK profiles of sorafenib and its metabolites BAY 67-3472 (M2), BAY 43-9007 (M4), and BAY 68-7769 (M5) in the presence of dacarbazine. This paper reports on PK and safety data. A separate manuscript (in preparation) [20] reports on efficacy and functional analysis using dynamic contrast-enhanced ultrasonography (DCE-US) representing the blood volume and microarray analyses of gene expression obtained in sequential tumor biopsies.

Patients and methods

Patients

Patients with metastatic, histologically confirmed solid tumors were included in this study. Eligible patients had at least one lesion that could be accurately and serially measured per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [21]; were ≥18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; had adequate bone marrow, liver, and renal functions; and had a life expectancy of at least 12 weeks. Patients were excluded if they had previous or concurrent cancer that was distinct from the tumor being evaluated in this study, unless the other cancer was curatively treated more than 3 years prior to study entry; clinically evident congestive heart failure; cardiac arrhythmias; active coronary heart disease or ischemia; uncontrolled hypertension; active clinically serious infections; or active brain metastases. Anticancer chemotherapy, immunotherapy, or vaccine therapy was not permitted during or within 30 days prior to the start of study treatment. Prior treatment with inhibitors of Raf, VEGF, or mTOR signaling pathways or farnesyl transferase inhibitors was not permitted.

Study design

This phase I, single-center, open-label, uncontrolled study was conducted in France between September 2005 (date of first patient first visit) and August 2006 (data cutoff date). On day 1 of a 21-day cycle, dacarbazine 1,000 mg/m^2 was administered as a 1-h infusion. Sorafenib 400 mg was administered twice daily continuously starting on day 2 of cycle 1. Toxicity-related dose modifications of sorafenib and dacarbazine were performed in accordance with protocol-specified guidelines. Treatment continued until the occurrence of unacceptable toxicity, tumor progression, or death.

Sorafenib tablets were supplied by Bayer HealthCare AG (Leverkusen, Germany); dacarbazine was supplied by Faulding Pharmaceuticals SA (Asnieres, France). The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, the EU-Directive 2001/20/EC, and local applicable laws. All patients provided signed informed consent before starting study treatment.

Study outcomes

The primary endpoint was determination of the PK profile of dacarbazine with and without sorafenib. Secondary endpoints included evaluation of the PK profile of sorafenib in the presence of dacarbazine, safety and efficacy of the combination treatment, novel biomarker analyses using DCE-US, and gene profile analyses. This paper reports on PK and safety data; the other results are reported in a separate manuscript (in preparation) [20].

Pharmacokinetic variables and sampling schedules

Dacarbazine is a prodrug from which the active alkylating moiety methane diazohydroxide is formed by metabolization. In this metabolic process, the inactive metabolite is 5-amino-imidazole-4-carboxamide (AIC) that is formed in equimolar quantities as methane diazohydroxide, which cannot be analytically measured [17]. Therefore, in addition to the PK of dacarbazine, we also studied the PK of AIC to understand the changes in the exposure of the active alkylating moiety in the presence of sorafenib.

On day 1 of cycle 1, plasma samples were obtained prior to dacarbazine administration and at 0.5, 1.0, 1.25, 1.5, 2.0, 4.0, 8.0, 12.0, and 24.0 h following dacarbazine administration to assess the PK of dacarbazine and AIC in the absence

of sorafenib. On day 1 of cycle 2, samples were collected from the same patients to assess the PK of dacarbazine in the presence of sorafenib at the same time points as above. Additional samples were collected at the same time points on day 1 of cycle 2 prior to sorafenib dosing and at 0.5, 1.0, 2.0, 4.0, 8.0, 10.0, and 12.0 h thereafter to evaluate the PK profile of sorafenib and its main metabolites, M2, M4, and M5 in the presence of dacarbazine. Samples for dacarbazine measurements were stored at or below –70°C; samples for sorafenib measurements were stored below –15°C. Stability data indicated that all analytes were stable during analysis.

The following PK variables were determined for dacarbazine and AIC on day 1 of cycle 1 and day 1 of cycle 2: area under the plasma concentration–time curve (AUC) from zero to infinity after a single dose [AUC(0–inf)], AUC from time zero to the last data point [AUC(0–tn)], maximum concentration of drug in plasma (C_{max}), time to reach maximum drug concentration in plasma (t_{max}), and apparent terminal half-life ($t_{1/2}$). The following variables were determined for sorafenib, M2, M4, and M5 on day 1 of cycle 2: AUC from time zero to 12 hours after dose at steady state [$AUC(0–12)_{ss}$], $AUC(0–12)_{ss}$ normalized with respect to dose (in mg) per kg body weight [$AUC(0–12)_{ss,norm}$], C_{max} at steady state ($C_{max,ss}$), $C_{max,ss}$ normalized with respect to dose (in mg) per kg body weight ($C_{max,ss,norm}$), and t_{max} at steady state ($t_{max,ss}$).

Pharmacokinetic assay methods and analyses

All analytes in plasma samples were quantified using a fully validated liquid chromatography–tandem mass spectrometry assay method with a lower limit of quantification of 40.6 µg/L for dacarbazine, 40.7 µg/L for AIC, and 0.01 mg/L for sorafenib and its metabolites. The assay for each sample set was performed once. Mean inter-assay precision ranges as determined by analysis of quality control

samples were 7.0–8.7% for dacarbazine, 2.8–9.3% for AIC, 1.5–12.4% for sorafenib, 2.6–4.5% for M2, 3.9–5.2% for M4, and 3.2–6.7% for M5. Corresponding mean inter-assay accuracy ranges were 97.1–104.7% for dacarbazine, 99.3–105.3% for AIC, 102.3–107.0% for sorafenib, 97.9–103.2% for M2, 98.1–100.3% for M4, and 95.5–101.0% for M5. The parameters AUC, AUC(0–tn), and C_{max} of dacarbazine and AIC were analyzed after logarithmic transformations applying an analysis of variance assuming a log-normal distribution.

Safety

Safety was evaluated in all patients who had received at least one dose of either study treatment. Safety was assessed through observed adverse events (AEs) and results of physical examination, laboratory tests, and vital signs measurement. Safety assessment took place at baseline and weekly starting from day 1 of cycle 1. AEs were coded and graded using version 3.0 of the National Cancer Institute Common Toxicity Criteria.

Determination of sample size

As this was a descriptive PK and safety phase I study, no formal sample size estimation was performed. The planned enrolment of approximately 25 patients was based on the requirements of relevant PK data sampling in a phase I trial.

Results

The study enrolled 24 patients, one of whom developed progressive disease before study treatment. The remaining 23 patients underwent treatment and were evaluable for safety analysis. Twenty-one patients (91%) discontinued treatment owing to progressive disease and two patients (9%) discontinued owing to AEs. Complete PK data were available for 15 patients. The other 8 patients had incomplete or no PK

data on sorafenib and/or dacarbazine and were not included in the PK evaluation. The baseline characteristics of patients are reported in Table 1. Detailed dosing and drug exposure data are reported in the supplementary table.

Pharmacokinetics

The 15 patients included in the PK analysis did not undergo any dose modifications during the PK evaluation period. For 13 of the 15 patients, the PK profile of dacarbazine was determined on day 1 of cycle 1 in the absence of sorafenib and repeated on day 1 of cycle 2 following a 20-day treatment period of sorafenib, as planned. For two patients, the second dacarbazine PK sampling was done on day 1 of cycle 3 and day 1 of cycle 6. For all the PK analyses, these were combined with data obtained from other patients on day 1 of cycle 2. Sorafenib PK sampling was performed in all patients during the second dacarbazine PK sampling.

Geometric mean plasma concentration–time data for dacarbazine, AIC, and sorafenib are shown in Figures 1a, 1b, and 1c, respectively. While plasma concentrations of dacarbazine were slightly lower in cycle 2 at 4 hours after start of infusion and following times when compared with those in cycle 1, the corresponding mean plasma concentrations of AIC were distinctly higher in cycle 2 compared with cycle 1. The apparent $t_{1/2}$ of either dacarbazine or AIC was not altered on concomitant administration of sorafenib. Mean plasma concentrations of sorafenib ranged between 1.7 mg/L and 3.0 mg/L.

Table 2 summarizes the PK results for dacarbazine and AIC. While the mean AUC and C_{max} of dacarbazine were reduced by 23% and 16%, respectively, mean AUC and C_{max} of AIC were increased by 41% and 45%, respectively, with individual increases of up to 106% and 136%, respectively. The apparent $t_{1/2}$ of either compound was not significantly influenced by concomitant administration of

sorafenib. Table 3 reports the steady-state PK data for sorafenib and its metabolites. Sorafenib contributes approximately 83% to the sum of $AUC(0–12)_{ss}$ values, while the metabolites contribute approximately 9% (M2), 4% (M4), and 3% (M5). From the values of the coefficients of variation, it is evident that the PK parameters of sorafenib and its metabolites showed a high degree of variability.

Safety

Overall, toxicities were manageable, with the vast majority of grade 3/4 AEs improving or resolving upon transient study drug dose reduction or discontinuation. No patient died of treatment-related causes; 10 patients (43.5%) died of progressive disease, 5 within 30 days after the last dose of a study drug and 5 thereafter.

Table 4 summarizes the incidence of treatment-emergent AEs related to one or both of the study drugs and affecting at least two patients. The most common grade 3/4 toxicities included amylase or lipase elevation, which was attributed to sorafenib and asymptomatic in all cases. The hematologic toxicities were attributed to both study drugs. The most common drug-related toxicities of any grade were fatigue, nausea, diarrhea, hand-foot skin reaction, and rash/desquamation, each affecting a minimum of just under half of the patients. The most common categories of toxicities of any grade were gastrointestinal (19 patients [83%]), constitutional (18 patients [78%]), and dermatologic (15 patients [65%]).

In Table 5, we report selected PK parameters of AIC in each of the 15 patients included in the PK analysis and the associated percent changes in hematologic parameters (i.e. platelet, leukocyte, and neutrophil levels). It can be seen that four patients (reference numbers 01, 06, 11, and 14) with grade 4 platelets and grade 3/4 neutrophils showed an increase in C_{max} and AUC(0–inf) of AIC on concomitant sorafenib administration. However, we also see an increased incidence of

hematologic toxicities without an associated increase in the C_{max} and AUC(0–inf) on concomitant administration of sorafenib (patients with reference numbers 12 and 13) as well as an increase in C_{max} and AUC(0–inf) without an associated increase in hematologic toxicities (patient with reference number 09).

Discussion

In this paper, we report PK and safety data from the combination of sorafenib and dacarbazine in patients with advanced solid tumors. Our results indicate that while concomitant administration of sorafenib and dacarbazine decreased dacarbazine exposure, it resulted in increased AIC exposure. We also found that increased AIC exposure might be associated with an increased incidence of hematologic toxicities, likely because of the interference of methane diazohydroxide with erythropoiesis [22-24]. However, because of the small sample size, no statistically significant correlations between increased AIC exposure and hematologic toxicities could be established. Because of the study design, we could obtain PK profiles of sorafenib and its metabolites only in the presence of dacarbazine. Similar to other studies, we found that the PK parameters of sorafenib and its metabolites showed a high degree of variability [25]. Our data also show that sorafenib contributes approximately 83% to the sum of $AUC(0–12)_{ss}$ values, while the metabolites contribute approximately 9% (M2), 4% (M4), and 3% (M5). This is comparable with data obtained from previous single-agent studies (data on file, Bayer HealthCare AG).

The combination of sorafenib and dacarbazine was associated with a clinically acceptable toxicity profile, with the vast majority of the grades 3/4 AEs improving or resolving upon transient discontinuation and/or dose reduction of the study drugs. No unexpected serious adverse reactions were reported. The sorafenib-dacarbazine combination has also been investigated in randomized [14] and open-label [26]

phase II studies, and in another phase I study [19] with similar safety results. Currently, the combination is being investigated in a phase II trial for sarcoma (Clinicaltrials.gov identifier: NCT00837148)

In conclusion, the combined treatment with sorafenib and dacarbazine may result in an increased exposure to AIC, which may be considered an indicator for the exposure to the active alkylating agent methane diazohydroxide. IDue to the small number of patients in the present study, a statistically significant correlation between AIC exposure and observed hematologic toxicities, even if present, could not be established. Further studies may be necessary to more clearly characterize this potential drug-drug interaction.

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Figure legends

Fig. 1a Plasma concentrations (geometric means/geometric standard deviation) of dacarbazine after a 1-h intravenous infusion of 1,000 mg/m^2 dacarbazine without (cycle 1) or with (cycle 2) concomitant multiple oral doses of 400 mg bid sorafenib (geometric means; *n* = 15)

Fig. 1b Plasma concentrations (geometric means/geometric standard deviation) of AIC after a 1-h intravenous infusion of 1,000 mg/m^2 dacarbazine without (cycle 1) or with (cycle 2) concomitant multiple oral doses of 400 mg bid sorafenib (geometric means; *n* = 15)

Fig. 1c Plasma concentrations (geometric means/geometric standard deviation) of sorafenib after multiple oral doses of 400 mg bid sorafenib and following a concomitant 1-h intravenous infusion of 1,000 mg/m^2 dacarbazine on day 1 of cycle 2 (geometric means; *n* = 15)

Table 1 Patient baseline characteristics

Characteristics	Patients included in the PK analysis (*n* = 15)	Patients included in the safety analysis (*n* = 23)
Sex, *n* (%)		
Male	10 (67)	11 (48)
Female	5 (33)	12 (52)
Age at enrollment, mean ± SD[a] (year)	59.3 ± 7.5	57.2 ± 8.9
Primary cancer type, *n* (%)		
Malignant melanoma	4 (27)	4 (17)
Leiomyosarcoma	3 (20)	4 (17)
Adenocarcinoma	2 (13)	5 (22)
Neuroendocrine carcinoma	2 (13)	2 (9)
Carcinoid tumor	1 (7)	1 (4)
Epithelioid mesothelioma	1 (7)	3 (13)
Hemangiopericytoma	1 (7)	1 (4)
Hepatocarcinoma	1 (7)	1 (4)

Nesidioblastoma	0	1 (4)
Sarcoma	0	1 (4)
AJCC[b] stage at study entry, *n* (%)		
Stage Ⅳ	14 (93)	22 (96)
Unknown	1 (7)	1 (4)
ECOG performance status, *n* (%)		
0	6 (40)	10 (44)
1	8 (53)	12 (52)
Missing	1 (7)	1 (4)
Prior anticancer therapy, *n* (%)		
Systemic adjuvant therapy		
Antineoplastic agents	3 (20)	5 (22)
Immunostimulants	1 (7)	1 (4)
Systemic palliative therapy		

Antineoplastic agents	11 (73)	19 (83)
Endocrine therapy	1 (7)	3 (13)
Other	1 (7)	2 (9)
Radiotherapy	6 (40)	10 (43)
Prior anticancer regimens, *n* (%)		
0	1 (7)	1 (4)
1	7 (47)	10 (44)
≥2	7 (47)	12 (52)
Time since initial diagnosis, mean ± SD[a] (week)		
Malignant melanoma	141.2 ± 145.0	141.2 ± 145.0
Other tumor types	245.4 ± 331.7	197.9 ± 261.3

[a] Standard deviation

[b] American Joint Committee on Cancer

Table 2 PK data for dacarbazine and AIC after a 1-h intravenous infusion of 1,000 mg/m^2 dacarbazine without (day 1, cycle 1) or with (day 2, cycle 2) administration of concomitant multiple oral doses of 400 mg bid sorafenib (*n* = 15)

Parameters	Dacarbazine			AIC		
	Cycle 1	Cycle 2	Cycle 2/Cycle 1	Cycle 1	Cycle 2	Cycle 2/Cycle 1
AUC(0–inf) (mg h/L)						
GM[a] (%CV[b])	65.0 (31)	50.0 (36)		20.6 (35)	28.9 (26)	
Range	29.4–111.5	24.5–87.8		11.3–33.2	21.8-56.0	
Ratio			0.769			1.408
(90% CI[c])			(0.629–0.941)			(1.167–1.699)
AUC(0–tn) (mg h/L)						
GM[a] (%CV[b])	62.9 (29)	49.0 (35)		19.1 (35)	27.1 (25)	
Range	29.0–105.3	23.8–84.3		10.5–29.7	19.8–50.4	
C_{max} (mg/L)						
GM[a] (%CV[b])	28.9 (26)	24.4 (26)		4.96 (39)	7.16 (26)	
90% CI[c]	14.4–45.3	13.6–35.8		2.30–9.29	4.18–10.20	

Ratio (90% CI[c])			0.843 (0.718–0.990)			1.445 (1.184–1.765)
$t_{1/2}$ (h) GM[a] (%CV[b]) Range	 1.87 (29) 1.34–3.76	 1.72 (22) 1.31–2.87		 2.27 (27) 1.30–3.73	 2.17 (26) 1.50–3.21	
t_{max} (h) Median Range	 1.00 0.50–1.08	 1.00 0.50–1.17		 1.17 0.50–1.58	 1.17 1.00–2.00	

[a] Geometric mean

[b] Coefficient of variation

[c] Confidence interval

Table 3 PK parameters of sorafenib and its metabolites BAY-67 3472 (M2), BAY 43-9007 (M4), and BAY 68-7769 (M5) after multiple oral doses of 400 mg bid sorafenib and following a concomitant 1-h intravenous infusion of 1,000 mg/m^2 dacarbazine on day 1 of cycle 2

Parameters	Sorafenib (n = 15)[a]	M2 (n = 15)[a]	M4 (n = 15)[b]	M5 (n = 13)[c]
$AUC(0–12)_{ss}$ (mg h/L)				
GM[d] (%CV[e])	28.3 (84)	3.01 (207)	1.46 (202)	1.17 (225)
Range	6.13–85.7	0.195–17.6	0.176–14.0	0.218–9.31
$AUC(0–12)_{ss,norm}$ (kg h/L)				
GM[d] (%CV[e])	4.75 (93)	0.489 (228)	0.254 (207)	0.200 (238)
Range	0.934–16.1	0.029–3.15	0.026–2.23	0.024–1.44
$C_{max,ss}$ (mg/L)				
GM[d] (%CV[e])	3.67 (77)	0.371 (197)	0.149 (237)	0.137 (225)
Range	0.905–9.66	0.035–2.03	0.016–1.48	0.022–0.943
$C_{max,ss,norm}$ (kg/L)				
GM[d] (%CV[e])	0.620 (84)	0.061 (211)	0.026 (244)	0.023 (245)

Range	0.155–1.81	0.005–0.367	0.003–0.236	0.002–0.146
$t_{max,ss}$ (h) Median (range)	8.3 (0.5–12.0)	4.0 (0–12.0)	8.3 (0.5–12.0)	4.0 (0–12.0)

[a] n = 14 for $AUC(0–12)_{ss}$ and $AUC(0–12)_{ss,norm}$

[b] n = 13 for $AUC(0–12)_{ss}$ and $AUC(0–12)_{ss,norm}$

[c] n = 12 for $AUC(0–12)_{ss}$ and $AUC(0–12)_{ss,norm}$

[d] Geometric mean

[e] Coefficient of variation

Table 4 Incidence of drug-related treatment-emergent AEs associated with dacarbazine, sorafenib, or both, and affecting at least two patients

	Total incidence, *n* (%) (*n* = 23)		
	All grades	Grade 3[a]	Grade 4[a]
Blood/Bone marrow			
Hemoglobin	5 (22)	5 (22)	0
Lymphopenia	2 (9)	2 (9)	0
Neutrophils	5 (22)	3 (13)	2 (9)
Platelets	7 (30)	1 (4)	4 (17)
Constitutional symptoms			
Fatigue	17 (74)	4 (17)	0
Fever	7 (30)	0	0
Weight loss	2 (9)	0	0
Dermatology/Skin			
Alopecia	8 (35)	0	0

Hand-foot skin reaction	11 (48)	1 (4)	0
Pruritus	5 (22)	0	0
Rash/Desquamation	11 (48)	2 (9)	0
Gastrointestinal			
Anorexia	11 (48)	1 (4)	0
Constipation	3 (13)	0	0
Diarrhea	11 (48)	0	0
Mucositis (symptomatic)	2 (9)	0	0
Nausea	15 (65)	1 (4)	0
Taste alteration	2 (9)	0	0
Vomiting	10 (44)	2 (9)	0
Metabolic/Laboratory			

Amylase	4 (17)	4 (17)	0
Lipase	5 (22)	2 (9)	3 (13)
Pain			
Headache	2 (8)	0	0

[a] Worst grade

Table 5 Individual patient parameters of AIC after a 1-h infusion of 1,000 mg/m^2 dacarbazine without (cycle 1) or with (cycle 2) concomitant administration of multiple oral doses of 400 mg sorafenib bid and percent changes in hematologic parameters in patients valid for PK analysis (*n* = 15)

Reference #	C_{max} (mg/L)		AUC(0–inf) (mg h/L)		Percent change from baseline (NCI CTCAE v3.0[a] grade)		
	C1; C2	C2/C1	C1; C2	C2/C1	Platelets	Leukocytes	Neutrophils
01	4.23; 7.22[a]	1.70	14.5; 27.2[b]	1.87	–89.3 (G4)	–70.4 (G3)	–74.9 (G3)
03	9.29; 10.23	1.10	30.9; 33.9	1.10	–41.1 (G1)	–44.9 (G1)	–57.0
05	6.36; 7.44	1.17	23.7; 27.3	1.15	–72.8 (G1)	–75.2 (G2)	–81.2 (G2)
06	2.30; 5.43	2.36	11.3; 23.4	2.06	–96.6 (G4)	–94.9 (G4)	–97.2 (G4)
07	3.21; 4.18	1.30	15.2; 26.0	1.71	–24.7 (G1)	–36.8 (G1)	–46.5
09	3.94; 7.77	1.97	16.2; 31.0	1.92	–24.4 (G1)	–35.8	–37.0
11	3.87; 6.76	1.75	13.5; 21.9	1.62	–88.9 (G4)	–63.7 (G2)	–80.0 (G3)
12	6.05; 8.67	1.43	29.0; 39.8	1.37	–71.3 (G1)	–72.1 (G3)	–83.7 (G3)
13	5.48; 5.89	1.08	21.8; 28.7	1.31	–73.3 (G2)	–74.0 (G3)	–85.4 (G3)
14	5.32; 9.78	1.84	33.2; 56.0	1.68	–95.0 (G4)	–90.5 (G4)	–98.3 (G4)

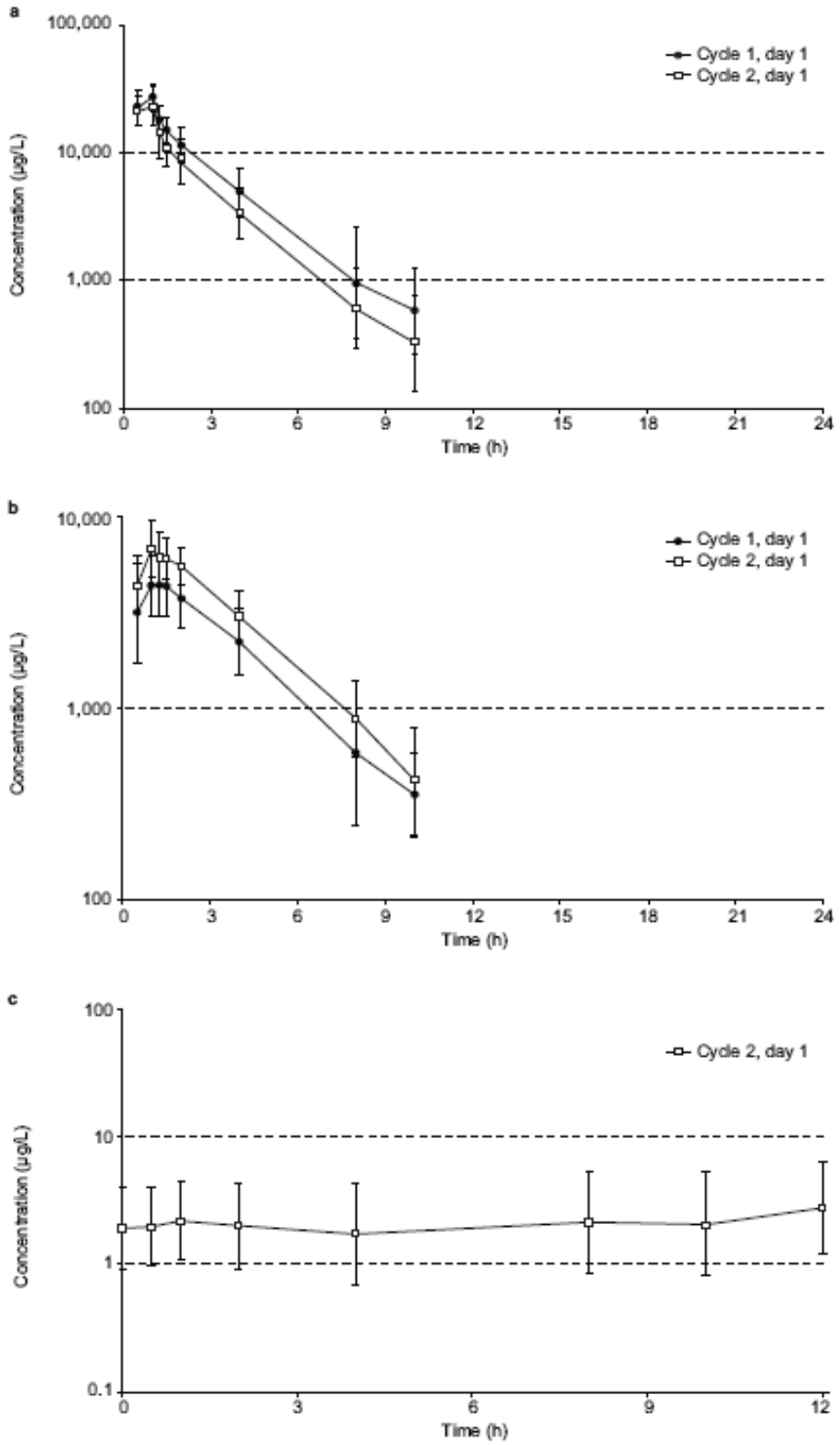
15	7.55; 9.54	1.26	27.2; 32.7	1.20	–50.4 (G1)	–55.4 (G2)	–55.6 (G2)
17	5.40; 6.84	1.27	21.4; 24.9	1.16	–52.9 (G1)	–37.9	–42.6
22	7.88; 9.07	1.15	24.6; 22.5	0.91	–85.0 (G2)	–66.7 (G3)	–65.8 (G2)
23	4.97; 6.53	1.32	27.8; 31.7	1.14	–83.2 (G1)	–70.1 (G2)	–77.3 (G1)
24	3.37; 5.29[c]	1.57	14.7; 21.8[b]	1.49	–13.7	–15.9	–40.6

[a] National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0

[b] Data from cycle 3

[c] Data from cycle 6

Fig 1


a
100,000
10,000
1,000
100
Concentration (µg/L)
Cycle 1, day 1
Cycle 2, day 1
0
3
6
9
12
15
18
21
24
Time (h)
b
10,000
1,000
100
Concentration (µg/L)
Cycle 1, day 1
Cycle 2, day 1
0
3
6
9
12
15
18
21
24
Time (h)
c
100
10
1
0.1
Concentration (µg/L)
Cycle 2, day 1
0
3
6
9
12
Time (h)

Supplementary Table Dosing and drug exposure

Drug	No. of patients (*n* = 23)
Sorafenib	
Planned daily dose (mg)	800
Actual daily dose, mean ± SD[a] (mg)	659 ± 133
Duration of treatment, median (range) (week)	14.7 (2.9–99.9)
Percent of planned dose received, *n* (%)	
30–<50%	2 (9)
50–<70%	9 (39)
70–<90%	9 (39)
≥90%	3 (13)
Dose reduction, *n* (%)	18 (78)
Due to AEs	18 (78)
Dose interruption, *n* (%)	14 (61)
Due to AEs	13 (57)
Dacarbazine	
Planned dose per cycle (mg/m^2)	1,000
Actual dose per cycle, mean ± SD[a] (mg/m^2)	967 ± 69
Number of cycles, median (range)	4 (1–9)

Percent of planned dose received, *n* (%)	
>50–70%	3 (13)
>70–90%	12 (52)
>90–100%	8 (35)
Dose reduction, *n* (%)	5 (22)
Due to AEs	5 (22)
Dose interruption, *n* (%)	11 (48)
Due to AEs	8 (73)

[a] Standard deviation