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ORIGINAL ARTICLE

# Interaction of sorafenib and cytochrome P450 isoenzymes in patients with advanced melanoma: a phase I/II pharmacokinetic interaction study

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**Abstract**
*Background* In vitro data indicate that the sorafenib is a moderate inhibitor of cytochrome P450 (CYP) enzymes, including CYP3A4, CYP2C19, and CYP2D6. This phase I/II study in patients with advanced melanoma evaluated the potential effect of sorafenib on the pharmacokinetics of midazolam, omeprazole, and dextromethorphan, specific substrates of CYP3A4, CYP2C19, and CYP2D6, respectively.
*Methods* Twenty-one patients received sorafenib 400 mg twice daily for 28 consecutive days. On days 1 and 28, a cocktail containing midazolam 2 mg, omeprazole 20 mg, and dextromethorphan 30 mg was administered. Pharmacokinetic analyses were performed on day 1 without sorafenib and day 28 after steady-state sorafenib exposure; sorafenib pharmacokinetics were evaluated on day 28. We defined an interaction to be excluded if the 90% confidence interval of the ratio of all day 28:day 1 analyses fell within a range from 0.80 to 1.25.
*Results* In all, 18 patients were evaluable. On day 28, area under the plasma concentration–time curve from time 0 to 12 h ($AUC_{0-12}$) and maximum plasma concentration ($C_{max}$) for sorafenib were 38.1 mg h/l and 4.9 mg/l, respectively. Day 28:day 1 ratios for AUC from time 0 extrapolated to infinity ($AUC_{0-inf}$) and $C_{max}$ for midazolam were 0.85 and 0.98, respectively. Day 28:day 1 ratio for 5-OH-omeprazole:omeprazole plasma concentration at 3 h postdose was 1.26, slightly outside of the 0.80–1.25 range. Thus, an interaction could not be excluded, but is considered unlikely to be clinically significant. Day 28:day 1 ratio for dextromethorphan:dextrorphan concentration in urine was 0.94. Sorafenib had an acceptable safety profile. The most frequently observed grade 3–4 toxicities in cycle 1 included elevated lipase (19%) and hypertension (10%).
*Conclusions* In this patient population, our results demonstrate that exposures of probes of CYP3A4, CYP2D6, or CYP2C19 activity are potentially altered by administration of sorafenib at 400 mg twice daily. However, these differences are sufficiently small that a clinically significant inhibition or induction of these important drug metabolizing P450 isoenzymes is unlikely. Clinical and, where possible, drug level monitoring may still be appropriate for drugs of narrow therapeutic range co-administered with sorafenib.

**Keywords** Sorafenib · Midazolam · Omeprazole · Dextromethorphan · Cytochrome P450 · Probe substrate cocktail

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## Introduction

The small-molecule kinase inhibitor sorafenib inhibits multiple signaling kinases, including Raf, vascular endothelial growth factor receptors, and platelet-derived growth

factor receptors [1]. Single-agent sorafenib has been approved by the US Food and Drug Administration for the treatment of renal cell carcinoma and hepatocellular carcinoma [2, 3]. As combinations of sorafenib with chemotherapeutic agents are extensively tested in various solid tumors [4–8], including renal cell carcinoma [9–11], non-small-cell lung cancer [12, 13], melanoma [11, 14, 15], and metastatic breast cancer, a study of its potential interactions with other drugs is of great importance.

Sorafenib is primarily metabolized by cytochrome P450 (CYP) isoenzymes [16]. In turn, in vitro studies with human liver microsomes have demonstrated that sorafenib is a competitive inhibitor of several CYP isoenzymes, including CYP3A4, CYP2C19, and CYP2D6, with Ki values ranging from 17 μM to 29 μM [17]. At the conventional clinical dose of 400 mg twice daily (b.i.d.), the mean maximum plasma concentration ($C_{max}$) of sorafenib ranges from 11.6 to 21.5 μM (5.4–10.0 mg/l) [18]. Therefore, sorafenib has the potential in vivo to inhibit CYP isoenzymes involved in drug metabolism, resulting in interactions with concomitant medications that are metabolized by CYP. The primary purpose of this phase I/II study was to evaluate the effect of sorafenib on the pharmacokinetics of midazolam (CYP3A4 substrate), omeprazole (CYP2C19 substrate), and dextromethorphan (CYP2D6 substrate) in patients with advanced melanoma. In addition, safety and antitumor activity of sorafenib as well as biomarker response to sorafenib activity were investigated. The current paper reports on the drug interaction data obtained in the study.

We defined an interaction to be excluded if the 90% confidence interval of the ratio of all day 28:day 1 analyses fell within a range from 0.80 to 1.25. In cases, where this was not observed, the magnitude of the observed effect was considered in the context of published drug–drug interaction studies to determine whether there was precedent for a given degree of interaction to be subsequently associated with clinically significant alterations in concomitantly administered medications in clinical practice.

## Patients and methods

### Patients

Patients with biopsy-amenable metastatic melanoma that was measurable as defined by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were included in the study. In addition, eligible patients were ≥18 years of age, with an Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥12 weeks, and adequate bone marrow, hepatic, and renal function. Patients with previous exposure to Ras inhibitors were excluded. Patients were not allowed to take potent drug metabolism inducers or inhibitors 14 days prior to treatment initiation or during the course of the study. The main excluded medical conditions were congestive heart failure, cardiac arrhythmia, active coronary artery disease or ischemia, active clinically serious infection, history of human immunodeficiency virus infection or chronic hepatitis B or C, and active metastatic brain or leptomeningeal tumors. (Toxicity, efficacy and pharmacodynamic data will be presented in a separate report.) The protocol was reviewed and approved by the University of Pennsylvania Institutional Review Board, and all patients signed informed consent.

### Treatment plan

This phase I/II, single-center, pharmacokinetic interaction study was conducted in the investigational unit of the Developmental Therapeutics Program of the Abramson Cancer Center of the University of Pennsylvania. Sorafenib at a dose of 400 mg b.i.d. was administered starting on day 1 in continuous 28-day cycles until the occurrence of disease progression or unacceptable toxicity or on withdrawal of consent. Protocol-defined dose modifications and delays were allowed except during the first 28-day cycle (pharmacokinetic phase of the study), wherein dose modifications were permitted only if mandated by toxicity or on withdrawal of patient consent. During the pharmacokinetic phase, fasting patients received the "probe substrate cocktail" (midazolam 2 mg solution + omeprazole 20 mg capsule + dextromethorphan 30 mg syrup along with approximately 240 ml water) on days 1 and 28 .

Sorafenib tablets were supplied by Bayer HealthCare Pharmaceuticals. The probe substrate drugs midazolam (Versed®), omeprazole (Prilosec®), and dextromethorphan (Robitussin Maximum Strength®) were supplied through Bayer HealthCare Pharmaceuticals. The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws and regulations; written informed consent was obtained from all patients.

### Safety

All patients who had taken at least one dose of sorafenib and had posttreatment data were eligible for inclusion in the safety analysis. Safety assessments were conducted on day 1 of each sorafenib treatment cycle, within 2 weeks of study discontinuation, and at follow-up, i.e., 30 days after last dose of sorafenib. Safety evaluations included complete physical examination, electrocardiogram, and clinical laboratory variables (e.g., hematology, blood biochemistry, coagulation parameters, and urinalysis). Adverse events were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [20].

Pharmacokinetic variables and sampling schedules

*Sorafenib*

Blood samples for the determination of the steady-state plasma concentration of sorafenib and its metabolites, M2 (BAY 67-3472), M4 (BAY 43-9007), and M5 (BAY 68-7769), were collected on day 28 (0, 0.5, 1, 2, 4, 8, and 12 h postdose). Urine samples for the determination of the concentration of sorafenib and its metabolites, M2, M7 (glucuronide of sorafenib), and M8 (glucuronide of M2), were collected on day 28 (over a 12-h period postdose). For sorafenib and its metabolites, the following pharmacokinetic parameters were calculated: area under the plasma concentration–time curve from time 0 to 12 h ($AUC_{0-12}$), maximum plasma concentration ($C_{max}$), time at which $C_{max}$ was achieved ($t_{max}$), and the amount excreted in urine over a period of 12 h postdose.

*Midazolam*

Blood samples for the determination of plasma concentrations of midazolam and its metabolite 1-OH-midazolam were collected on days 1 and 28 (0, 0.5, 1, 2, 4, 8, and 12 h postdose on both days). The following pharmacokinetic parameters were calculated on both days: AUC from time zero extrapolated to infinity ($AUC_{0-inf}$) for midazolam, AUC from time zero to the last data point ($AUC_{0-tn}$) for 1-OH-midazolam (as only 11 patients had definable $AUC_{0-inf}$ values), $C_{max}$, and $t_{max}$.

*Omeprazole and 5-OH-omeprazole*

Blood samples for the determination of plasma concentrations of omeprazole and its metabolite 5-OH-omeprazole were collected on days 1 and 28 (0 and 3 h postdose on both days). The ratio of the concentrations of 5-OH-omeprazole to omeprazole at 3 h postdose was calculated on both days.

*Dextromethorphan*

Urine samples for the determination of concentrations of dextromethorphan and its metabolite dextrorphan were collected on days 1 and 28 (over a 12-h period postdose). The ratio of the concentrations of dextromethorphan and dextrorphan was calculated on both days.

*Bioanalytical methods*

All assays were performed using validated high-performance liquid chromatography methods. Each of the analytical methods met standard acceptance criteria for precision (mean coefficient of variation [CV]) and accuracy (percent of control concentration).

*Sorafenib and its metabolites*

The assays for sorafenib and its metabolites in plasma were performed at Bayer HealthCare AG (Wuppertal, Germany). Sorafenib, M2, M4, and M5 concentrations in plasma were determined by LC–MS/MS after protein precipitation with acetonitrile/methanol (50/50, v/v). Mass spectrometric detection was in the positive ion multiple reaction monitoring (MRM) mode on an API 3000 tandem mass spectrometer (AB Sciex, Foster City, CA). Sorafenib-[D4,15N] and M2-[D4,15N] served as the internal standards.

The calibration range in plasma was 0.01–12 mg/l for sorafenib and 0.01–2.5 mg/l for the metabolites M2, M4, and M5. The precision (%CV) for all analytes was between 0.9 and 7.11%, and the accuracy ranged from 92.1 to 105.2%.

Sorafenib and its metabolites in urine were analyzed at NorthEast BioAnalytical Laboratories (West Haven, CT, USA). Urine samples were analyzed for sorafenib and M2 before enzymatic hydrolysis, while M7 and M8 concentrations were determined indirectly after enzymatic cleavage of the conjugates in urine. After enzyme hydrolysis, the samples were diluted with a mixture of acetonitrile/water/acetic acid and then analyzed by LC–MS/MS in the positive ion MRM mode on an AB Sciex API-365 tandem mass spectrometer. In urine, M7 and M8 were measured after hydrolysis as sorafenib and M2 with calibration ranges of 10.21–5104 μg/l and 10.47–5234 μg/l, respectively. The precision was between 4.0 and 14.3%, and the accuracy ranged from 95.5 to 100.4%.

*Midazolam and 1-OH-midazolam*

The concentrations of midazolam and 1-OH-midazolam were measured by an LC–MS/MS positive ion electrospray method as described previously [19]. The calibration concentrations for both midazolam and 1-OH-midazolam were 0.20–100 ng/mL; alprazolam and diazepam served as the internal standards for 1-OH-midazolam and midazolam, respectively. The precision was between 6.4 and 13.9%, and the accuracy ranged from 96.4 to 107%.

*Omeprazole and 5-OH-omeprazole*

Omeprazole and 5-OH-omeprazole concentrations in plasma were determined by LC–MS/MS. Briefly, the analytes and internal standard (omeprazole-D3) were extracted from plasma at an alkaline pH by liquid–liquid extraction with ethyl acetate. Extracts were reconstituted and then analyzed by LC–MS/MS in the positive ion MRM mode on

an AB Sciex API-365 tandem mass spectrometer. The calibration ranges for omeprazole and 5-OH-omeprazole in plasma were 0.10–106.16 μg/l and 0.10–105.47 μg/l, respectively. The assay was performed at NorthEast Bio-Analytical Laboratories. The accuracy ranged from 97.8 to 114.5%, and the precision was between 2.8 and 14.7%.

*Dextromethorphan and dextrorphan*

The concentrations of dextromethorphan and its metabolite dextrorphan were measured by LC–MS/MS. Briefly, samples were pipetted into a 96-deep-well plate to which was added buffer (100 mM sodium acetate, pH 4.5) and *β*-glucuronidase/arylsulfatase enzyme solution. The plate was incubated at 37°C for 20 h. After incubation, proteins were precipitated by the addition of methanol. The plates were vortex-mixed briefly, centrifuged, and then samples were analyzed by LC/MS/MS. Urine samples were analyzed at NorthEast BioAnalytical Laboratories. The calibration curves were based on peak area versus the nominal concentration (no internal standard); the calibration ranges for dextromethorphan and dextrorphan in urine were 1.06–261.84 μg/l and 2.52–249.64 μg/l, respectively. The accuracy ranged from 94.3 to 105.4%, and the precision was between 3.5 and 22.4%.

*Pharmacokinetic and statistical analyses*

Summary statistics for the pharmacokinetic parameters of sorafenib and its metabolites, midazolam, 1-OH-midazolam, omeprazole, 5-OH-omeprazole, dextromethorphan, and dextrorphan, are reported. Plasma pharmacokinetic parameters were calculated using standard noncompartmental methods for sorafenib, M2, M4, and M5 (KINCALC® version 2.5, Bayer AG, Leverkusen, Germany) and for midazolam and 1-OH-midazolam (WinNonlin® version 4.0, Pharsight Corporation, Mountain View, CA, USA). The effect of sorafenib administration on the pharmacokinetic parameters of the probe substrates was evaluated using analysis of variance; 90% confidence intervals (CIs) of the day 28:day 1 ratios were estimated. If the 90% CI of the ratio was between 0.80 and 1.25, a lack of pharmacokinetic interaction was concluded. If the 90% CI was outside of the interval between 0.80 and 1.25, the clinical relevance of the interaction was evaluated. As this was a descriptive study to evaluate the drug–drug interaction potential of BAY 43–9006, no formal sample size estimation was performed prospectively for PK evaluations. In retrospect, and with the distribution of PK parameters available for the patients included in this analysis, this study was well powered (>90% power) to rule out a 20% decrease or 25% increase in AUC or $C_{max}$ comparing day 28 PK values to baseline with 90% confidence. Only the dextromethorphan: dextrorphan ratio was not as well powered (78%) at the same level of confidence.

## Results

Twenty-one patients were enrolled in this study. In all, 18 patients were evaluable for the primary pharmacokinetic endpoints of the study, 3 patients who withdrew from the study prior to collection of day 28 samples were not included in the pharmacokinetic analysis, 2 patients withdrew due to disease progression, and 1 patient withdrew due to dosing noncompliance. All 21 patients were included in the safety analysis. The demographic and baseline characteristics of the patients are reported in Table 1.

Pharmacokinetics

*Sorafenib*

The plasma pharmacokinetic data of sorafenib and its metabolites on day 28 are summarized in Table 2. Sorafenib and M2 were not detected in any postdose urine samples of day 28 except one that had a small amount (0.078 mg) of unchanged sorafenib. The mean amounts (standard deviation) of M7 and M8 in the urine were 13.17 mg (7.68) and 1.05 mg (0.68), respectively.

*Midazolam*

The plasma pharmacokinetic results of midazolam and 1-OH-midazolam on days 1 and 28 are presented in Table 3 and Fig. 1. On day 28, there was a 15% decrease in mean midazolam $AUC_{0-inf}$ compared with day 1, but no change in mean $C_{max}$. For 1-OH-midazolam, there was no change in $AUC_{0-tn}$, and a 20% increase in $C_{max}$.

*Omeprazole*

A summary of the metabolic ratio results for omeprazole on days 1 and 28 is shown in Table 4. There was a mean increase of 26% in 5-OH-omeprazole:omeprazole

**Table 1** Demographics and baseline characteristics of patients

| Characteristics | No. of patients | % |
|---|---|---|
| Patients enrolled | 21 | |
| Sex | | |
| Men | 17 | 81 |
| Women | 4 | 19 |
| Ethnic group | | |
| White | 21 | 100 |

**Table 2** Plasma pharmacokinetic parameters of sorafenib and its metabolites on day 28

| Analyte | Parameter | *n* | Geometric mean | %CV |
|---|---|---|---|---|
| Sorafenib | $AUC_{0-12}$ (mg h/l) | 15 | 38.13 | 34.31 |
| | $C_{max}$ (mg/l) | 18 | 4.86 | 36.89 |
| | $t_{max}$ (h) | 18 | 4.00[a] | (0.0, 4.0)[b] |
| M2 | $AUC_{0-12}$ (mg h/l) | 15 | 5.32 | 72.48 |
| | $C_{max}$ (mg/l) | 18 | 0.67 | 74.43 |
| | $t_{max}$ (h) | 18 | 4.00[a] | (0.0, 8.0)[b] |
| M4 | $AUC_{0-12}$ (mg h/l) | 15 | 1.73 | 79.00 |
| | $C_{max}$ (mg/l) | 18 | 0.22 | 78.96 |
| | $t_{max}$ (h) | 18 | 2.33[a] | (0.0, 12.0)[b] |
| M5 | $AUC_{0-12}$ (mg h/l) | 14 | 1.46 | 85.71 |
| | $C_{max}$ (mg/l) | 18 | 0.16 | 96.69 |
| | $t_{max}$ (h) | 18 | 2.33[a] | (0.0, 4.0)[b] |

*$AUC_{0-12}$* area under the plasma concentration–time curve from 0 to 12 h; *$C_{max}$* maximum plasma concentration; *CV* coefficient of variance; *$t_{max}$* time at which $C_{max}$ was achieved

[a] Median

[b] Range

concentration at 3 h on day 28 compared with day 1. This was the only ratio that fell outside of our prespecified range of 0.8–1.25, but only slightly so, and the 90% confidence interval around this estimate significantly overlapped with this range, which was our a priori basis for excluding a significant interaction.

*Dextromethorphan*

The dextromethorphan urinary metabolic ratios on days 1 and 28 are presented in Table 4. There was a 6% decrease in the dextromethorphan:dextrorphan phenotypic index on day 28 compared with day 1.

*Safety*

Grade 4 toxicities observed during cycle 1 included elevated lipase ($n = 1$). Grade 3 toxicities observed during cycle 1 included elevated lipase ($n = 3$) and hypertension ($n = 2$). Neither elevated amylase nor clinical evidence of pancreatitis was seen in patients with lipase elevations. Grade 2 toxicities observed during cycle 1 included hand–foot syndrome ($n = 2$), hypertension ($n = 3$), and pruritus ($n = 1$). No dose alterations were required prior to day 29. On or following day 28, there was no clinical evidence of adverse effects from the probe substrates.

## Discussion

Several kinase inhibitors developed previously have been shown to enhance the toxicity of chemotherapeutic agents. In combination with gefitinib, for example, the dose of irinotecan had to be decreased due to increase in toxicity [21]. Similarly, increased toxicity of irinotecan was observed in combinations with lapatinib and erlotinib [22, 23]. Although it is not clear if the increase in toxicity was due to pharmacokinetic interactions, the results nonetheless indicate the potential for such interactions. More than half the drugs on the market are metabolized by CYP3A4, and many drugs are metabolized by CYP2C19 and CYP2D6. The following Ki values were observed for sorafenib and these CYPs and others: CYP 1A2: 232 μM, CYP 2C8: 2.4 μM, CYP2C9: 7.3 μM, CYP2C19: 17 μM, CYP 2D6: 4.2 μM, CYP 3A4: 4.9 μM and CYP2B6: 6.2 μM. These data are consistent with sorafenib being a moderate inhibitor of these isoenzymes. Therefore, the present clinical study was performed to evaluate its drug–drug interaction potential with these important CYP enzymes.

The plasma pharmacokinetic data of sorafenib in the present study were similar to those reported in phase I sorafenib multiple-dose trials [18]. The amounts of M7 and M8 in the urine when normalized to the observed $AUC_{0-12}$ values were also consistent with those reported in a previous mass balance study [16]. Midazolam, omeprazole, and dextromethorphan were used to investigate the effect of sorafenib on the activities of CYP3A4, CYP2C19, and CYP2D6, respectively [24–27]. Evidence in the literature indicates that there is no metabolism-based interaction among midazolam, omeprazole, and dextromethorphan. Thus, these drugs can be administered simultaneously

**Table 3** Plasma pharmacokinetic parameters of midazolam and 1-OH-midazolam

| Analyte | Parameter | *n* | GM, day 1 | GM, day 28 | GMR, day 28:day 1 | 90% CI |
|---|---|---|---|---|---|---|
| Midazolam | $AUC_{0-inf}$ (μg h/l) | 17 | 36.69 | 31.05 | 0.85 | 0.75–0.95 |
| | $C_{max}$ (μg/l) | 18 | 12.05 | 11.81 | 0.98 | 0.88–1.09 |
| 1-OH-midazolam | $AUC_{0-tn}$ (μg h/l) | 18 | 10.69 | 11.08 | 1.04 | 0.85–1.27 |
| | $C_{max}$ (μg/l) | 18 | 4.62 | 5.53 | 1.20 | 0.98–1.46 |

*$AUC_{0-inf}$* area under the plasma concentration–time curve from time zero extrapolated to infinity; *$AUC_{0-tn}$* area under the plasma concentration–time curve from time zero to the last data point; *$C_{max}$* maximum plasma concentration; *CI* confidence intervals; *GM* geometric mean; *GMR* geometric mean ratio

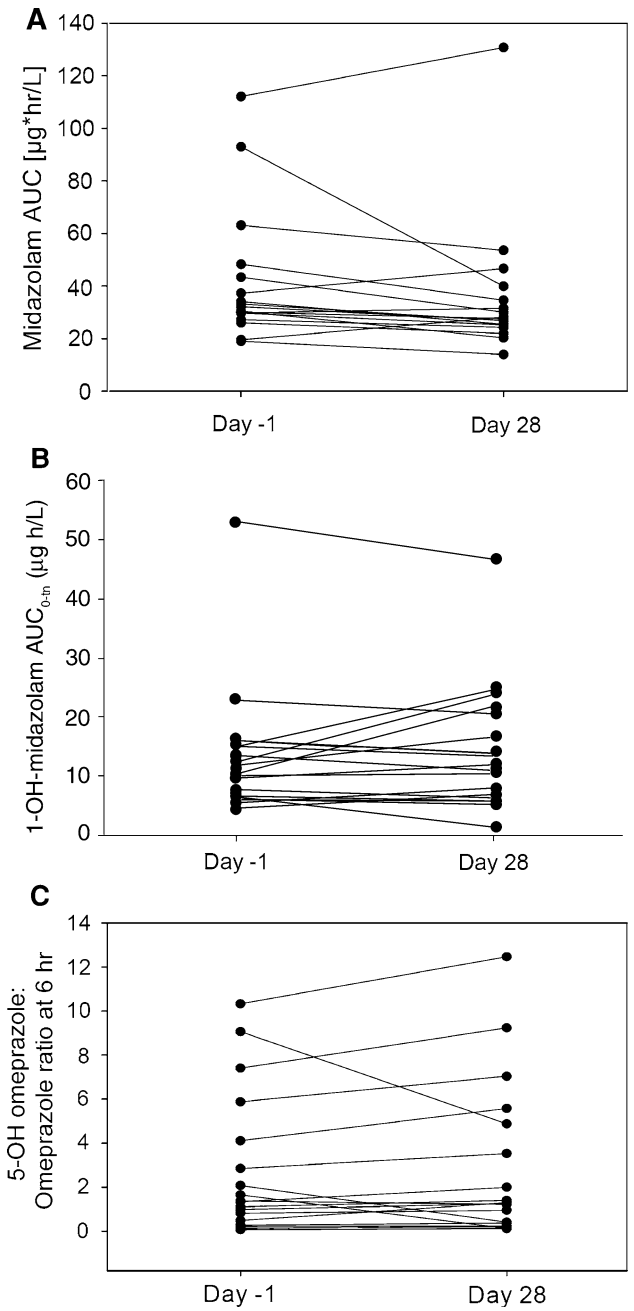


**Fig. 1** **a** $AUC_{0-inf}$ of midazolam on days 1 and 28 for each patient; **b** $AUC_{0-tn}$ of 1-OH-midazolam on days 1 and 28 for each patient; **c** 5-OH-omeprazole:omeprazole concentration ratio at 3 h for each patient. $AUC_{0-inf}$ area under the plasma concentration–time curve from time zero extrapolated to infinity; $AUC_{0-tn}$ area under the plasma concentration–time curve

("cocktail" approach) to evaluate the effects on multiple metabolic enzyme systems in the same study [28]. The pharmacokinetic values for midazolam and the phenotypic indices for omeprazole and dextromethorphan reported in this study were similar in range to those reported in the literature [29–33].

The results of this study indicate that sorafenib has a weak inducing effect on CYP3A activity, as demonstrated by an average decrease of 15% in the AUC of midazolam. The effect is considered "weak" as defined by a less than a twofold difference in midazolam exposure [34]. Although the 90% CIs for the mean decrease were not within the hypothesized target interval of 0.80–1.25, the effect was not considered clinically important. The magnitude of inductive effect observed is smaller than that produced by the weak CYP3A inducer pioglitazone, which decreased midazolam AUC by 26% [35], and very small relative to that produced by the potent CYP3A inducers carbamazepine and rifampin, which decrease midazolam AUC by >90% [36]. Thus, except for CYP3A substrates that have a narrow therapeutic range, the risk of a clinically relevant interaction with CYP3A substrates appears to be low.

Sorafenib produced modest induction of CYP2C19 activity as reflected by the 26% increase in the omeprazole metabolic ratio. The geometric mean ratio and 90% CI values were not contained within the target interval of 0.80–1.25, which are conservative limits used in this study to define no inhibition or induction. However, as with CYP3A, the effect is considered clinically unimportant and is much smaller than the twofold increase with lopinavir/ritonavir [37] and the fourfold increase caused by rifampin [38]. The dextromethorphan metabolic mean ratio (0.94) was close to 1; however, the CIs were outside the predetermined no-effect boundaries. The distribution of baseline dextromethorphan:dextrorphan ratios in our population is similarly broad compared to previously published reports. [39]. Based on these results, it appears that sorafenib is not a clinically significant inhibitor or inducer of CYP2C19 or CYP2D6.

While we evaluated the most common pathways of drug metabolism, other CYPs such as CYP1A2 and CYP2C9, which are important in drug metabolism, were not evaluated in this study. And our small patient population was of uniform ethnicity and did not contain any rapid or slow metabolizers based on the observed baseline clearance of

**Table 4** Ratio of the concentrations of 5-OH-omeprazole to omeprazole (in plasma) and dextromethorphan to dextrorphan (in urine)

| Analyte ratio | Sample | *n* | GM, day 1 | GM, day 28 | GMR, day 28:day 1 | 90% CI |
|---|---|---|---|---|---|---|
| 5-OH-omeprazole:omeprazole | 3-h sample | 17 | 0.62 | 0.77 | 1.26 | 1.11–1.42 |
| Dextromethorphan:dextrorphan | Over a 12-h period | 18 | 0.0053 | 0.0050 | 0.94 | 0.70–1.30 |

*CI* confidence interval, *GM* geometric mean, *GMR* geometric mean ratio

the probe substrates. Such individuals are known to exist at a low frequency in the general population on the basis germ-line polymorphisms in these drug metabolizing genes (namely CYP2C19 and CYP2D6). Our data show that sorafenib does not alter the disposition of substrates via the most common CYP metabolic pathways to a clinically relevant extent. Although interactions with compounds that are substrates for other CYP enzymes are as yet undefined, the potential for drug interactions with sorafenib and drugs metabolized through the common pathways of the CYP isoenzyme system are unlikely at standard recommended drug doses. Still, as larger patient populations are treated and a broader array of concomitant medications used, physicians should remain vigilant for potential interactions, particularly in drugs with a notoriously narrow therapeutic index such as anticoagulants and antiepileptic agents.

In conclusion, the results of this study indicate that clinically important interaction between sorafenib and drugs metabolized primarily by CYPs 3A4, 2C19, or 2D6 are not expected. On the basis of these results, combination studies with CYP-metabolized drugs such as paclitaxel, docetaxel, and erlotinib may safely incorporate sorafenib with the combination drug at full doses, assuming that non-CYP mechanisms of clearance are not inhibited by sorafenib. Similarly, it appears unlikely that sorafenib would significantly affect the metabolism of other nononcologic drugs that are substrates for these three CYP enzymes.

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**Conflict of interest** Chetan Lathia–employee, Bayer Healthcare Pharmaceuticals.

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