

A Phase Ib Study of Sorafenib (BAY 43-9006) in Patients with Kaposi Sarcoma

THOMAS S. ULDRICK,^a PRISCILA H. GONÇALVES,^a KATHLEEN M. WYVILL,^a CODY J. PEER,^b WENDY BERNSTEIN,^a KAREN ALEMAN,^a MARK N. POLIZZOTTO,^a DAVID VENZON,^c SETH M. STEINBERG,^c VICKIE MARSHALL,^e DENISE WHITBY,^e RICHARD F. LITTLE,^a JOHN J. WRIGHT,^d MICHELLE A. RUDEK,^f WILLIAM D. FIGG,^b ROBERT YARCHOAN^a

^aHIV and AIDS Malignancy Branch, ^bClinical Pharmacology Program, ^cBiostatistics and Data Management Section at the Center for Cancer Research, and ^dCancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland, USA; ^eViral Oncology Section, AIDS and Cancer Virus Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA; ^fAnalytical Pharmacology Core, Sidney Kimmel Comprehensive Cancer Center and Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT00287495
- **Sponsor(s):** Bayer Health Care Corporation and NCI Cancer Therapy Evaluation Program
- **Principal Investigator(s):** Robert Yarchoan
- **IRB Approved:** Yes

LESSONS LEARNED

- Oral targeted agents are desirable for treatment of Kaposi sarcoma (KS); however, in patients with HIV, drug–drug interactions must be considered. In this study to treat KS, sorafenib was poorly tolerated at doses less than those approved by the U.S. Food and Drug Administration for hepatocellular carcinoma and other cancers, and showed only modest activity.
- Sorafenib's metabolism occurs via the CYP3A4 pathway, which is inhibited by ritonavir, a commonly used antiretroviral agent used by most patients in this study. Strong CYP3A4 inhibition by ritonavir may contribute to the observed sorafenib toxicity.
- Alternate antiretroviral agents without predicted interactions are preferred for co-administration in patients with HIV and cancers for which sorafenib is indicated.

ABSTRACT

Background. We conducted a phase Ib study of sorafenib, a vascular epithelial growth factor receptor (VEGFR), c-kit, and platelet derived growth factor receptor (PDGFR)-targeted treatment in Kaposi sarcoma (KS). We evaluated drug–drug interactions between sorafenib and ritonavir, an HIV medication with strong CYP3A4 inhibitory activity.

Methods. Two cohorts were enrolled: HIV-related KS on ritonavir (Cohort R) and HIV-related or classical KS not receiving ritonavir (Cohort NR). Sorafenib dose level 1 in cohort R (R1) was 200 mg daily and 200 mg every 12 hours in cohort NR (NR1). Steady-state pharmacokinetics were evaluated at cycle 1, day 8. KS responses and correlative factors were assessed.

Results. Ten patients (nine HIV⁺) were enrolled: R1 (eight), NR1 (two). Median CD4⁺ count (HIV⁺) was 500 cells/μL.

Dose-limiting toxicities (DLTs) were grade 3 elevated lipase (R1), grade 4 thrombocytopenia (R1), and grade 3 hand-foot syndrome (NR1). Two of seven evaluable patients had a partial response (PR; 29%; 95% CI 4%–71%). Steady-state area under the curve of the dosing interval (AUC_{TAU}) of sorafenib was not significantly affected by ritonavir; however, a trend for decreased AUC_{TAU} of the CYP3A4 metabolite sorafenib-N-oxide (3.8-fold decrease; $p = .08$) suggests other metabolites may be increased.

Conclusion. Sorafenib was poorly tolerated, and anti-KS activity was modest. Strong CYP3A4 inhibitors may contribute to sorafenib toxicity, and ritonavir has previously been shown to be a CYP3A4 inhibitor. Alternate antiretroviral agents without predicted interactions should be used when possible for concurrent administration with sorafenib. *The Oncologist* 2017;22:505–e49

Correspondence: Thomas S. Uldrick, M.D., HIV and AIDS Malignancy Branch, National Cancer Institute, 10 Center Drive, Room 6N106, MSC 1868, Bethesda, Maryland 20892, USA. Telephone: 301-402-6296; e-mail: uldrickts@mail.nih.gov Received December 5, 2016; accepted for publication December 16, 2016; published Online First on March 24, 2017. ©AlphaMedPress; the data published online to support this summary is the property of the authors. <http://dx.doi.org/10.1634/theoncologist.2016-0486>

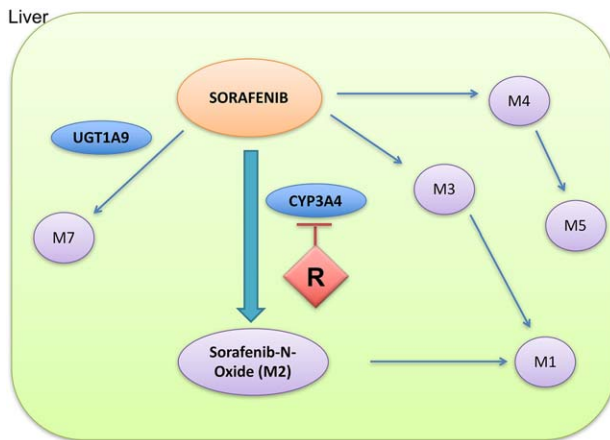


Figure 1. Hepatic metabolism of sorafenib. Elimination of sorafenib occurs mainly in the liver through CYP3A4 oxidative metabolism. M2 is produced by oxidation of sorafenib via CYP3A4 and is the major circulating active metabolite. M7 is produced through the glucuronidation of the parent compound by UGT1A9. Ritonavir is a strong inhibitor of the CYP3A4 pathway, and inhibition of CYP3A4 may lead to the increased production of other metabolites through alternate pathways. Figure modified from PharmGKB pathway with permission from PharmGKB and Stanford University (<https://www.pharmgkb.org/pathway/PA165959537>).

Abbreviations: M, metabolite; M2, Sorafenib N-oxide; R, ritonavir.

DISCUSSION

Preclinical data supported evaluation of sorafenib in KS. Our primary objective was to evaluate the safety of sorafenib in KS patients and ritonavir–sorafenib pharmacokinetic (PK) interactions [1]. Sorafenib was poorly tolerated, with two patients experiencing DLTs at the first dose level (one in each cohort). The overall response rate (ORR) in seven evaluable patients was 29% (95% CI 4%–71%). Although the maximum tolerated dose (MTD) was not determined, accrual was terminated after review of Cohort R1 safety and efficacy data.

Importantly, patients had well-controlled HIV and preserved CD4 counts. Such patients generally tolerate standard

chemotherapy dosing when co-administered with appropriate antiretroviral therapy (ART). Poor tolerability was most likely due to drug–drug interactions. Maximum plasma concentration (C_{MAX}) and AUC_{0-12h} of sorafenib following a 200 mg dose at steady state observed in this trial were within reported ranges [2–4]. The effects of drug–drug interactions and genetic variants on hepatic metabolism are important [5–7], and co-administration with ritonavir, a strong CYP3A4 inhibitor, is a possible contributor to the poor tolerability in Cohort R1 [7, 8]. A phase I study of sunitinib, another CYP3A4-metabolized drug, in patients with HIV and cancer demonstrated that HIV patients not taking ritonavir tolerated standard dosing, whereas patients receiving ritonavir had higher toxicities at lower doses. Ritonavir was associated with decreases in the sunitinib active metabolite but not the parent drug [7]. In our study, we demonstrated a similar trend toward a 3.8-fold decrease in the CYP3A4 main active metabolite sorafenib-N-oxide [9] in patients receiving ritonavir, while parent sorafenib exposures were only modestly affected. Shunting of metabolism towards other pathways yielding more toxic metabolites may alter tolerability (Fig. 1) and explain the toxicity observed. A limitation of this study is the small sample size, and conclusions on the use of sorafenib with ritonavir cannot be based on PK data alone. Nonetheless, our findings suggest that sorafenib has modest activity and does not have a favorable activity/toxicity profile in patients with KS, and that use of concurrent ritonavir-based ART and sorafenib should be avoided.

Although these results do not support its further study or use in KS, our PK and safety findings inform treatment of patients with HIV and cancers for which sorafenib is indicated, particularly those with hepatocellular carcinoma, a tumor with increasing incidence [10]. Caution in using sorafenib in patients with HIV and cancers for which it is approved is advised. Although this study did not conclusively show that ritonavir affected sorafenib metabolism, the results are suggestive, and concurrent ritonavir or other strong CYP3A4 inhibitors should be avoided. ART without predicted strong CYP3A4 interactions should be preferred for concurrent treatment of HIV in patients with cancers best treated by sorafenib.

TRIAL INFORMATION

Disease	Kaposi's sarcoma
Stage of disease/treatment	Any
Prior Therapy	No designated number of regimens
Type of study – 1	Phase I
Type of study – 2	3 + 3 phase I design
Primary endpoint	Toxicity
Primary endpoint	Pharmacokinetics
Primary endpoint	Pharmacodynamic
Primary endpoint	Safety
Secondary endpoint	Efficacy

Additional details of endpoints or study design

Eligibility and treatment. Adults with histologically confirmed KS and at least five evaluable cutaneous lesions or non-cutaneous measurable disease were eligible, regardless of HIV status. HIV-positive subjects must have been on ART ≥ 3 months with progressive disease (PD) or ≥ 4 months without disease regression and willing to adhere to concurrent ART during this study of sorafenib. Patients with symptomatic visceral KS, except oral cavity disease, were excluded. There was no CD4⁺ T-cell count criterion. The initial dosing was less frequent in cohort R because of concerns of the effect of CYP3A4 inhibition on drug metabolism. Sorafenib was given continuously over 21-day cycles. Dose escalation by 100% was planned in each cohort up to the recommended dose of 400 mg every 12 hours.

Safety monitoring and dose-limiting toxicity evaluation. Safety was evaluated by history and physical and laboratory investigations at baseline every 7 days during cycle 1 (C1), then on day 1 of subsequent cycles. CD4⁺ T-cell counts and HIV RNA levels in HIV-positive patients were obtained at the end of C1 and every 3 months. Adverse events (AEs) were evaluated using NCI Common Terminology Criteria for Adverse Events version 3.0; after January 1, 2011, version 4.0 was utilized. DLTs were determined over 12 weeks on sorafenib, with a minimum 6-week evaluation required for a participant not taken off treatment for a DLT. Any grade 4 AE was considered a DLT except for lymphopenia, CD4⁺ T-cell lymphocytopenia, neutropenia, anemia, or transient creatine phosphokinase (CPK) elevation; these required the following additional criteria to be considered a DLT: absolute neutrophil count < 500 cells/mm³ for ≥ 5 days and/or accompanied by \geq grade 2 fever; CD4⁺ T-cell decrease $> 80\%$ and ≥ 50 cell/mm³ from entry on two successive determinations despite controlled HIV; anemia unresponsive to erythropoietin within 1 week and no other identified causes; and CPK elevation occurring in the absence of causal exercise or trauma. Grade 3 AEs at least possibly due to sorafenib were considered DLTs with the exception of elevation of hepatic transaminases < 500 IU, total bilirubin < 4.8 mg/dL (direct < 0.3 mg/dL and indirect < 4.5 mg/dL) in patients on a protease inhibitor, asymptomatic hyperuricemia or hypophosphatemia, amylase elevation due to non-pancreatic origin, grade 3 rash that decreases to grade 1 by week 6 and does not recur on drug rechallenge, or hypertension managed with modification of medications. Preexisting manifestations of HIV, KS, or HIV therapy were not considered DLTs. A dose was considered not tolerable if two or more of six evaluable patients developed a DLT. The MTD was defined as the highest dose level where \leq fewer than one of six patients experienced a DLT.

Pharmacokinetics (PK) methods. Steady-state PKs were evaluated C1, day 8. Blood was collected pre-dose and at 1, 2, 4, 8, and 12 hours (before the next dose if on a every 12 hour dosing) and 16 and 24 hours (before the next dose) after sorafenib. Plasma concentrations of sorafenib and its major active CYP3A4 metabolite sorafenib N-oxide were measured by liquid chromatography-tandem mass spectrometry as previously described. Noncompartmental PK assessment was performed using Phoenix WinNonlin v6.4 (Certara Pharsight Corp, Cary, NC). Maximum plasma concentration (C_{MAX}) was recorded as observed values, and the area under the plasma-concentration time curve was calculated using the Linear Trapezoidal rule. AUC_{TAU} was calculated to compare the two groups and normalize the additive effect of twice daily versus once daily dosing.

Pharmacodynamics. Sorafenib's effect on select serum factors, Kaposi sarcoma-associated herpes virus (KSHV) viral load (VL) and CD4⁺ T-cell count were evaluated. Correlative assays were performed on biospecimens collected at baseline and the end of C1. Serum IL-1b, IL-6, IL-8, IL-10, IL-12p40, IL-12p70, IFN- γ , TNF-alpha, MCP1, MIP1A, bFGF, IP-10, GM-CSF, FIT-1, PIGF, VEGF-A, VEGF-C, and VEGF-D were evaluated using a custom V-Plex Assay (Meso-Scale Discovery, Gaithersburg, MD) and Sector Imager (Meso-Scale Discovery). Peripheral blood mononuclear cell (PBMC)-associated KSHV VL was measured using previously described methods.

Statistical considerations. The primary objectives were to assess safety and pharmacokinetics of sorafenib in both cohorts. The study allowed for closure after primary objectives were met in Cohort R and did not require completion of Cohort NR. A secondary objective was to preliminarily assess antitumor effect. ORR, defined as the proportion of patients whose best response was PR or better with exact 95% confidence intervals, was calculated for all patients and for evaluable patients. PK parameters were compared between cohorts to assess the effects of ritonavir on sorafenib. Nonparametric Mann-Whitney test was applied to compare differences in sorafenib, sorafenib-N-oxide, the ratio sorafenib-N-oxide:sorafenib, and AUC_{TAU} between patients administered 200 mg sorafenib daily with 200 mg ritonavir or sorafenib twice daily alone. Association between grade 3–4 AEs and AUC_{TAU} was evaluated by unpaired t test. For comparisons between cohorts, $p < .05$ was considered significant while $.05 < p < .1$ would indicate a trend. Sorafenib's effect on serum factors, KSHV VL, and CD4⁺ T-cell count was evaluated by comparing differences from baseline to the end of C1 using Wilcoxon signed rank test. Analytes with serum levels below the lower limit of detection in a majority of samples were excluded. Analyses were repeated excluding one patient subsequently diagnosed with KSHV-associated multicentric Castlemann disease (KSHV-MCD), which is associated with abnormalities in human IL-6 and IL-10. Analyses were considered exploratory without formal adjustment for multiple comparisons. A p -value $< .01$ was considered to reflect a significant change while $.01 < p < .05$ would indicate a trend.

Investigator's analysis

Active but too toxic as administered in this study

DRUG INFORMATION**Drug 1**

Generic/Working name	Sorafenib
Trade name	Nexavar
Company name	Bayer
Drug type	Small molecule
Dose	milligrams (mg) per flat dose
Route	oral (po)
Schedule of administration	Cohort R - dose level 1 was 200 mg orally once daily. Cohort NR- dose level 1 was 200 mg twice daily. In all cohorts, sorafenib was given orally continuously over 21-day cycles.

PATIENT CHARACTERISTICS	
Number of patients, male	10
Number of patients, female	0
Stage	
In HIV infected patients	KS prognostic factors ¹ : n (%)—T1: 6 (67%); I1: 1 (11%), S1: 1 (11%) Revised TS stage ² (AIDS KS prognostic criteria): Good, 8 (89%); Poor, 1 (11%) ¹ Risk factors based on AIDS Clinic Trials Group (ACTG) staging criteria. T1: edema or ulceration, extensive oral mucosa KS, or visceral KS; I1: CD4 ⁺ T-cells <150 cells/mL; S1: history of opportunistic infections or thrush, and/or "B" symptoms present, and/or Karnofsky Score <70%, and/or other HIV-related disease. ² Revised AIDS KS prognostic criteria, excludes CD4 ⁺ as a risk factor.
Age	Median (range): 49 years (35–72 years)
Number of prior systemic therapies	Median (range): 2 (0–4)
Performance Status: ECOG	0 — 4 (40%) 1 — 6 (60%) 2 — 0 3 — 0 unknown —
Other	Patients accrued between January 2006 and February 2012. Patient characteristics are as follows:
All patients	Race: Black 2 (20%); White 8 (80%) Detectable circulating KSHV: 7 (70%) Tumor associated edema: 6 (60%) Greater than 50 KS lesions: 10 (100%) Prior therapy for KS: 8 (80%) HIV seropositive: 9 (90%) Median time since last KS treatment (months): 22 (range 2–108)
In HIV infected patients	CD4 ⁺ (cells/microL) median (range): 500 (35–747) CD4 ⁺ <200 cells/microL: 1 (11%) HIV VL <50 copies/mL: 7 (78%) Median time on antiretroviral therapy (ART) (months*): 22 (range 3.5–108) *Defined as months on specific ART regimen used at the time of screening visit.
Cancer types or histologic subtypes	Kaposi sarcoma, HIV-associated: 9 Classic Kaposi sarcoma, HIV-negative: 1
PRIMARY ASSESSMENT METHOD	
Control Arm: Total Patient Population	
Number of patients screened	29
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	7
Evaluation method	Modified AIDS Clinical Trial Group Criteria
Response assessment CR	n = 0
Response assessment PR	n = 2
Response assessment SD	n = 4
Response assessment PD	n = 1
(Median) duration assessments response duration	3 months
Note:	Seven patients (five in Cohort R1, two in Cohort NR1) were evaluable for response. Best responses were PR in two patients (R1), stable disease (SD) in four (three in R1, one in NR1), and progressive disease (PD) in one (NR1). The ORR was 2/10 (20%; 95% CI 3%–56%) in all patients and 2/7 (29%; 95% CI 4%–71%) in patients evaluable for response. Duration of PR was 3 months in the two responding patients. Median duration of SD was 4 cycles (range 1–5). Of six patients with tumor-associated edema, five showed objective improvement with ≥2 cm decrease (range 2–5 cm) in circumference of affected limbs at the end of treatment, and one of these obtained a PR. One with severe tumor-associated edema had improved range of motion in affected limbs, decreased weight, and decreased serous ooze after 1 cycle.

ADVERSE EVENTS							
All Dose Levels, All Cycles							
Name	NC/NA	1	2	3	4	5	All Grades
Alopecia	90%	10%	0%	0%	0%	0%	10%
Palmar-plantar erythrodysesthesia syndrome	70%	10%	0%	20%	0%	0%	30%
Anemia	80%	20%	0%	0%	0%	0%	20%
Lymphocyte count decreased	90%	0%	10%	0%	0%	0%	10%
Neutrophil count decreased	90%	0%	10%	0%	0%	0%	10%
Activated partial thromboplastin time prolonged	83%	17%	0%	0%	0%	0%	17%
Platelet count decreased	70%	10%	0%	10%	10%	0%	30%
Hyperkalemia	90%	10%	0%	0%	0%	0%	10%
Hemoglobinuria	90%	10%	0%	0%	0%	0%	10%
Proteinuria	70%	10%	20%	0%	0%	0%	30%
Mucositis oral	90%	0%	10%	0%	0%	0%	10%
Anorexia	90%	10%	0%	0%	0%	0%	10%
Abdominal pain	50%	50%	0%	0%	0%	0%	50%
Dyspepsia	90%	10%	0%	0%	0%	0%	10%
Diarrhea	50%	50%	0%	0%	0%	0%	50%
Flatulence	90%	10%	0%	0%	0%	0%	10%
Serum amylase increased	90%	0%	10%	0%	0%	0%	10%
Lipase increased	60%	20%	10%	10%	0%	0%	40%
Aspartate aminotransferase increased	40%	60%	0%	0%	0%	0%	60%
Alanine aminotransferase increased	70%	30%	0%	0%	0%	0%	30%
Alkaline phosphatase increased	90%	10%	0%	0%	0%	0%	10%
Hypoalbuminemia	90%	10%	0%	0%	0%	0%	10%
Arthralgia	90%	0%	10%	0%	0%	0%	10%
Myalgia	90%	10%	0%	0%	0%	0%	10%
Ischemia cerebrovascular	90%	0%	0%	10%	0%	0%	10%
Hypertension	60%	0%	10%	30%	0%	0%	40%
Infections and infestations—other	80%	10%	10%	0%	0%	0%	20%
Fatigue	70%	20%	10%	0%	0%	0%	30%
Insomnia	90%	10%	0%	0%	0%	0%	10%
Voice alteration	60%	30%	10%	0%	0%	0%	40%
Respiratory, thoracic, and mediastinal disorders—nasal cavity/paranasal sinus reaction	90%	10%	0%	0%	0%	0%	10%

Adverse events represent the worst grade for each patient that was possibly, probably, or definitely related to sorafenib during the entire course of treatment.

Abbreviations: NA, no adverse event; NC, no change from baseline.

DOSE-LIMITING TOXICITY					
Dose Level	Dose of Drug: Sorafenib	Number Enrolled	Number Evaluable for Toxicity	Number with a DLT	DLT Information
R1	200 mg po qd	8	8	1	Grade 3 lipase, grade 4 thrombocytopenia
NR1	200 mg po bid	2	2	1	Grade 3 palmar-plantar erythrodysesthesia syndrome

PHARMACOKINETICS/PHARMACODYNAMICS		
Dose Level	Dose of Drug: Sorafenib	Number Enrolled
R1	200 mg po qd	8
NR1	200 mg po bid	2

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study terminated before completion

Investigator's Assessment

Active but too toxic as administered in this study

KS is an angioproliferative tumor caused by Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus-8 [11–13]. HIV infection substantially increases KS risk [14] and accounts for more than 80% of KS in the U.S. High prevalence of HIV and KSHV coinfection has led to a high incidence of KS in areas of sub-Saharan Africa [16]. In AIDS-associated KS, combination ART is indicated but often insufficient. Current therapies for KS are limited by cumulative toxicities. Effective and less toxic approaches are needed. Oral agents are particularly desirable for resource-limited settings.

Paracrine stimulation by pro-angiogenic factors produced in part by KSHV-infected cells contributes to KS pathogenesis. KS spindle cells express vascular epithelial growth factor (VEGF) receptors (R) types 2 and 3 (VEGFR-2, VEGFR-3), platelet-derived growth factor (PDGF)-R [17–20], and c-kit [21]. In vitro, spindle cells derived from KS patients proliferate in response to VEGF, VEGF-C (a ligand for VEGFR-3), and PDGF [17, 19, 20]. Sorafenib is a tyrosine kinase inhibitor (TKI) of VEGFR2, VEGFR3, PDGFR, and c-kit [17–20, 22], making it a rational agent to treat KS. However, prospective evaluation of novel cancer therapies in people with HIV for safety and PK interactions with antiretroviral agents is important [23].

Our primary objective in this phase Ib study was to evaluate the safety and tolerability of sorafenib in KS patients and the effect of ritonavir on levels of sorafenib [1]. Overall, sorafenib was poorly tolerated, with two patients experiencing DLTs at the first dose level (one in R1 and one in NR1). Additionally, five patients had grade 3 toxicities that did not meet DLT criteria and found the drug difficult to tolerate. The ORR in seven evaluable patients was 29% (95% CI 4%–71%). Although the MTD was not determined, accrual was terminated after review of Cohort R1 safety and efficacy data. Our safety and PK data suggest ritonavir, a strong CYP3A4 inhibitor, affects sorafenib metabolism by decreasing production of sorafenib-N-oxide and shunting the metabolism towards more toxic metabolites.

Although small, this phase Ib study provides valuable information to help inform treatment decisions for medical oncologists treating HIV-associated tumors. Sorafenib [24] is indicated for the treatment of hepatocellular carcinoma (HCC) and other tumors in people with HIV [25, 26]. Increased toxicity has been described in a limited number of patients co-administered ritonavir [27, 28], while other studies report that sorafenib was relatively well tolerated [29–31]. The largest retrospective series included 27 patients with HIV and HCC treated with 400 mg sorafenib twice daily. In that study, 93% were co-administered ART. No information on number of patients on ritonavir was available, although protease inhibitor-based therapy was common during that study time period (2007–2010). AEs were graded retrospectively, a source of bias and underreporting. Nonetheless, diarrhea, palmar-plantar erythrodysesthesia syndrome, and hypertension were the most common grade 3–4 AEs, observed in 15%, 15%, and 11% of patients, respectively,

higher than reported in the phase III trial that helped establish approval of sorafenib in HCC (8%, 8% and 2%) [24] and consistent with potential drug–drug interactions.

Despite our inability to escalate to standard doses, the ORR of 29% with sorafenib was comparable to observed response rates with other anti-angiogenic agents and TKIs for KS. For example, ORRs in studies evaluating imatinib and bevacizumab in KS were 33% and 31%, respectively [21, 32]. Interestingly, there was evidence of a clinical effect related to decreased tumor-associated edema in most patients with edema at baseline [32]. However, it is unclear why only modest tumor regression is observed, given the strong rationale. One possibility is redundancy of angiogenic pathways in KS. Better results may require combination with agents that target KS through other mechanisms.

KSHV-infected dendritic cells overproduce IL-12p40, a common subunit for IL-12 and IL-23. Despite modest antitumor effect, evaluating 14 serum factors associated with KS pathogenesis, we found a statistically significant decrease in the amount of IL-12p40 between baseline and the end of cycle 1 ($p = .002$), suggesting that sorafenib has some effect on KSHV-induced signaling [33]. Signal transducer and activator of transcription 3 (STAT3) activation by KSHV in endothelial and dendritic cells [34, 35] has been implicated in increased immunosuppressive cytokines, including IL-23 [35], and indirect downregulation of phospho-STAT3 by sorafenib [36] is a potential mechanism for our observed IL-12p40 findings. Further evaluation of STAT3 inhibition in KSHV-associated diseases is warranted [37]. We also noted a potential trend towards decreased bFGF ($p = .018$), a growth factor implicated in KS pathogenesis [18]. Our results are similar to findings in non-small-cell lung cancer [38] and consistent with a potential role for bFGF downregulation by sorafenib in the treatment of HCC [39, 40].

In summary, sorafenib is relatively poorly tolerated in patients with KS when co-administered with ritonavir and has modest activity. Although these results do not support its further study or use in KS, findings from this study inform treatment of patients with HIV and cancers for which sorafenib is indicated, particularly those with HCC, a tumor with increasing incidence [10]. Prospective data on co-administration of ART and cancer therapeutics are important, as concerns regarding toxicity contribute to treatment disparities in patients with HIV and cancer [10]. Caution in using sorafenib in patients with HIV and cancers for which it is approved is advised. Although this study did not conclusively show that ritonavir affected sorafenib metabolism, the results are suggestive, and concurrent ritonavir or other strong CYP3A4 inhibitors should be avoided. Antiretroviral agents without predicted strong CYP3A4 interactions are available and preferred for concurrent treatment of HIV in patients with cancers best treated by sorafenib. Sorafenib dose modification may be required even if an alternate ART regimen is used.

ACKNOWLEDGMENTS

This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute and gift funds from Johns Hopkins University. Further support was provided by a Clinical Trials Agreement between Bayer Health Care Corporation and the NCI Cancer Therapy Evaluation Program and by NCI Contract No. HHSN261200800001E. We thank the patients who volunteered to participate; the

medical, nursing, and support staffs of the HIV and AIDS Malignancy Branch, the Medical Oncology Service, and the NIH Clinical Center; and Adam Rupert and Randy Stevens and colleagues in Leidos, NCI-Frederick, Frederick, Maryland.

DISCLOSURES

The authors indicated no financial relationships.

REFERENCES

- Sevrioukova IF, Poulos TL. Structure and mechanism of the complex between cytochrome p4503a4 and ritonavir. *Proc Natl Acad Sci USA* 2010;107:18422–18427.
- Shacham-Shmueli E, Geva R, Figer A et al. Phase I trial of sorafenib in combination with 5-fluorouracil/leucovorin in advanced solid tumors. *J Clin Pharmacol* 2012;52:656–669.
- Desar IM, Timmer-Bonte JN, Burger DM et al. A phase I dose-escalation study to evaluate safety and tolerability of sorafenib combined with sirolimus in patients with advanced solid cancer. *Br J Cancer* 2010;103:1637–1643.
- Azad N, Dasari A, Arcaroli J et al. Phase I pharmacokinetic and pharmacodynamic study of cetuximab, irinotecan and sorafenib in advanced colorectal cancer. *Invest New Drugs* 2013;31:345–354.
- Peer CJ, Sissung TM, Kim A et al. Sorafenib is an inhibitor of UGT1a1 but is metabolized by UGT1a9: Implications of genetic variants on pharmacokinetics and hyperbilirubinemia. *Clin Cancer Res* 2012;18:2099–2107.
- Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet* 2005;44:111–145.
- Rudek MA, Moore PC, Mitsuyasu RT et al. A phase 1/pharmacokinetic study of sunitinib in combination with highly active antiretroviral therapy in human immunodeficiency virus-positive patients with cancer: AIDS malignancy consortium trial AMC 061. *Cancer* 2014;120:1194–1202.
- Lathia C, Lettieri J, Cihon F et al. Lack of effect of ketoconazole-mediated CYP3a inhibition on sorafenib clinical pharmacokinetics. *Cancer Chemother Pharmacol* 2006;57:685–692.
- Keating GM, Santoro A. Sorafenib: A review of its use in advanced hepatocellular carcinoma. *Drugs* 2009;69:223–240.
- Suneja G, Boyer M, Yehia BR et al. Cancer treatment in patients with HIV infection and non-AIDS-defining cancers: A survey of US oncologists. *J Oncol Pract* 2015;11:e380–e387.
- Chang Y, Cesarman E, Pessin MS et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994;266:1865–1869.
- Gao SJ, Kingsley L, Li M et al. KSHV antibodies among Americans, Italians, and Ugandans with and without Kaposi's sarcoma. *Nat Med* 1996;2:925–928.
- Biggar RJ, Chaturvedi AK, Goedert JJ et al. AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst* 2007;99:962–972.
- Engels EA, Biggar RJ, Hall HI et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008;123:187–194.
- Shiels MS, Pfeiffer RM, Gail MH et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011;103:753–762.
- Mosam A, Carrara H, Shaik F et al. Increasing incidence of Kaposi's sarcoma in black South Africans in KwaZulu-Natal, South Africa (1983–2006). *Int J STD AIDS* 2009;20:553–556.
- Skobe M, Brown LF, Tognazzi K et al. Vascular endothelial growth factor-C (VEGF-C) and its receptors KDR and flt-4 are expressed in AIDS-associated Kaposi's sarcoma. *J Invest Dermatol* 1999;113:1047–1053.
- Enslin B, Gendelman R, Markham P et al. Synergy between basic fibroblast growth factor and HIV-1 Tat protein in induction of Kaposi's sarcoma. *Nature* 1994;371:674–680.
- Marchiò S, Primo L, Pagano M et al. Vascular endothelial growth factor-C stimulates the migration and proliferation of Kaposi's sarcoma cells. *J Biol Chem* 1999;274:27617–27622.
- Stürzl M, Brandstetter H, Zietz C et al. Identification of interleukin-1 and platelet-derived growth factor-B as major mitogens for the spindle cells of Kaposi's sarcoma: A combined in vitro and in vivo analysis. *Oncogene* 1995;10:2007–2016.
- Koon HB, Krown SE, Lee JY et al. Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. *J Clin Oncol* 2014;10:402–408.
- Masood R, Cai J, Zheng T et al. Vascular endothelial growth factor/vascular permeability factor is an autocrine growth factor for AIDS-Kaposi sarcoma. *Proc Natl Acad Sci USA* 1997;94:979–984.
- Persad GC, Little RF, Grady C. Including persons with HIV infection in cancer clinical trials. *J Clin Oncol* 2008;26:1027–1032.
- Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
- Sulkowski MS. Viral hepatitis and HIV coinfection. *J Hepatol* 2008;48:353–367.
- Rosenthal E, Roussillon C, Salmon-Céron D et al. Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: The Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalité 2010 survey. *HIV Med* 2015;16:230–239.
- Chelis L, Ntinou N, Souftas V et al. Complete response after sorafenib therapy for hepatocellular carcinoma in an HIV-HBV co infected patient: Possible synergy with HAART? A case report. *Med Oncol* 2011;28(suppl 1):S165–S168.
- Ozenne V, Gervais A, Peytavin G et al. Suspected interaction between sorafenib and HAART in an HIV-1 infected patient: A case report. *Hepatogastroenterology* 2011;58:161–162.
- Berretta M, Di Benedetto F, Dal Maso L et al. Sorafenib for the treatment of unresectable hepatocellular carcinoma in HIV-positive patients. *Anti-cancer Drugs* 2013;24:212–218.
- De Nardo P, Viscione M, Corpolongo A et al. Treatment of recurrent hepatocellular carcinoma with sorafenib in a HIV/HCV co-infected patient in HAART: A case report. *Infect Agent Cancer* 2012;7:15.
- Perboni G, Costa P, Fibbia GC et al. Sorafenib therapy for hepatocellular carcinoma in an HIV-HCV coinfecting patient: A case report. *The Oncologist* 2010;15:142–145.
- Uldrick TS, Wyvill KM, Kumar P et al. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. *J Clin Oncol* 2012;30:1476–1483.
- Hensler HR, Rappocciolo G, Rinaldo CR et al. Cytokine production by human herpesvirus 8-infected dendritic cells. *J Gen Virol* 2009;90:79–83.
- Punjabi AS, Carroll PA, Chen L et al. Persistent activation of STAT3 by latent Kaposi's sarcoma-associated herpesvirus infection of endothelial cells. *J Virol* 2007;81:2449–2458.
- Santarelli R, Gonnella R, Di Giovenale G et al. STAT3 activation by KSHV correlates with IL-10, IL-6 and IL-23 release and an autophagic block in dendritic cells. *Sci Rep* 2014;4:2421.
- Shiels MS, Pfeiffer RM, Hall HI et al. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980–2007. *JAMA* 2011;305:1450–1459.
- Aoki Y, Feldman GM, Tosato G. Inhibition of STAT3 signaling induces apoptosis and decreases survivin expression in primary effusion lymphoma. *Blood* 2003;101:1535–1542.
- Kelly RJ, Rajan A, Force J et al. Evaluation of KRAS mutations, angiogenic biomarkers, and DCE-MRI in patients with advanced non-small-cell lung cancer receiving sorafenib. *Clin Cancer Res* 2011;17:1190–1199.
- Wang L, Park H, Chhim S et al. A novel monoclonal antibody to fibroblast growth factor 2 effectively inhibits growth of hepatocellular carcinoma xenografts. *Mol Cancer Ther* 2012;11:864–872.
- Cheng AL, Shen YC, Zhu AX. Targeting fibroblast growth factor receptor signaling in hepatocellular carcinoma. *Oncology* 2011;81:372–380.

FIGURES AND TABLES

Table 1. Select pharmacokinetic parameters for sorafenib and sorafenib N-oxide

	Sorafenib			Sorafenib N-Oxide			Sorafenib N-oxide/Sorafenib Ratio		
	+ Rit. (n = 8)	– Rit. (n = 2)	p value	+ Rit. (n = 8)	– Rit. (n = 2)	p value	+ Rit. (n = 8)	– Rit. (n = 2)	p value
C _{MAX} (ng/mL)	2,581 ± 430.7 ^a	6,505 ± 2,875	.089	77.83 ± 21.02	452.5 ± 223.5	.044	2.86 ± 0.59	10.5 ± 8.09	.533
AUC _{TAU} (hr ^a ng/mL)	39,900 ± 6,267	55,188 ± 19,045	.711	1,158 ± 301.3	4,378 ± 2,411	.089	2.68 ± 0.45	10.7 ± 8.07	.533

^aNumbers displayed as mean ± standard error of the mean. Comparisons used Mann–Whitney test.

Abbreviations: AUC_{TAU}, area under the curve of the dosing interval; C_{MAX}, maximum plasma concentration; Rit, ritonavir.

Table 2. Baseline characteristics

Feature	Result
All patients (n = 10)	
Median age in years, n (range)	49 (35–72)
Sex	
Men, n (%)	10 (100%)
Race	
Black, n (%)	2 (20%)
White, n (%)	8 (80%)
Detectable circulating KSHV, n (%)	7 (70%)
ECOG performance status, n (%)	
0	4 (40%)
1	6 (60%)
Tumor-associated edema, n (%)	6 (60%)
Greater than 50 KS lesions, n (%)	10 (100%)
Prior therapy for KS, n (%)	8 (80%)
Chemotherapy	6 (60%)
Liposomal doxorubicin	5 (50%)
Paclitaxel	2 (20%)
Biologic therapy	5 (50%)
Interferon alpha	2 (20%)
Bevacizumab	3 (30%)
Thalidomide	1 (10%)
Alitretinoin	2 (20%)
Radiation	2 (20%)

(continued)

Table 2. (continued)

Feature	Result
Median time since last treatment in months, n (range)	22 (3–108)
HIV seropositive, n (%)	9 (90%)
HIV-infected patients (n = 9)	
KS prognostic factors ^a , n (%)	
T ₁	6 (67%)
I ₁	1 (11%)
S ₁	1 (11%)
Revised TS ^b , n (%)	
Good (T ₀ S ₀ , T ₁ S ₀ , or T ₀ S ₁)	8 (89%)
Poor (T ₁ S ₁)	1 (11%)
CD4 (cells/μL) median, n (range)	500 (35–747)
CD4 < 200 cells/μL, n (%)	1 (11%)
Median time on ART in months ^c , n (range)	22 (3.5–108)
Ritonavir-based ART regimen, n (%)	8 (89%)
HIV viral load < 50 copies/mL, n (%)	7 (78%)

^aRisk factors based on ACTG staging criteria. T₁: Edema or ulceration, extensive oral mucosa KS, or visceral KS, I₁: CD4 < 150 cells/mL, S₁: History of opportunistic infections or thrush, and/or “B” symptoms present, and/or Karnofsky Score < 70%, and/or other HIV-related disease.

^bRevised AIDS KS Prognostic Criteria, excludes CD4 as risk factor.

^cMonths on the specific ART regimen used at time of the screening visit.

Abbreviations: ART, antiretroviral therapy; ECOG, Eastern Cooperative Oncology Group; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma-associated herpes virus.

Click here to access other published clinical trials.