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A phase I/pharmacokinetic study of sunitinib in combination with highly active antiretroviral therapy (HAART) in HIV-positive patients with cancer: AIDS Malignancy Consortium Trial AMC 061

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Abstract

Background—Treatment of non-AIDS defining cancers (NADCs) may be complicated by drug interactions between highly active antiretroviral therapy (HAART) and chemotherapy. This trial is the first by the AIDS Malignancy Consortium assessing targeted therapies and HAART in HIV+ cancer patients ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00890747) NCT00890747).

Methods—Patients were stratified into two arms based on whether they were taking ritonavir, a potent CYP3A4 inhibitor, in a modified phase I study of sunitinib. Patients in arm 1 (non-ritonavir HAART) received standard sunitinib dosing (50mg/day). Arm 2 (ritonavir-based HAART) used a phase I, 3+3 dose escalation design (from 25 to 50mg/day). Cycles were with four weeks on treatment followed by a two week break (6 weeks total). Pharmacokinetics of sunitinib and its active metabolite (N-desethyl sunitinib) were assessed.

Results—Nineteen patients were enrolled and evaluable. Patients on Arm 1 tolerated treatment with one observed dose limiting toxicity (DLT). In Arm 2, a DLT was experienced at 37.5mg, and an additional 3 of 5 patients experienced grade 3 neutropenia, an uncommon toxicity of sunitinib. No patient had a response, but 10 had stable disease, including 8 with prolonged disease stability. Efavirenz, a potent inducer of CYP3A4, resulted in increased exposure of N-desethyl sunitinib, whereas ritonavir caused decreased exposure of the metabolite. Hand-foot syndrome was associated with higher steady-state trough concentrations of sunitinib.

Conclusions—Patients on non-ritonavir based HAART regimens tolerated standard dosing of sunitinib. Patients on ritonavir-based therapy treated with 37.5mg/day experienced higher toxicities. Dose reduction of sunitinib to 37.5mg may be warranted in patients on ritonavir.

Keywords

Phase I; sunitinib; HIV; clinical trial; HAART

Introduction

Since the advent of highly active antiretroviral therapy (HAART), patients diagnosed with HIV infection have seen a significant improvement in the mortality and morbidity from HIV disease.(1, 2) The incidence of AIDS and AIDS-defining illnesses, including opportunistic infection as well as AIDS-defining malignancies, have been on the decline since HAART therapy became widely prescribed in the mid to late 1990s.(1)

While incidences of AIDS-defining malignancies such as non-Hodgkin lymphoma (NHL) and Kaposi's sarcoma (KS) have dramatically decreased over the last two decades, the prevalence of Non-AIDS-Defining Cancers (NADCs) has been on the rise.(3) Epidemiology studies on the rates of cancers in the pre- and post-HAART era in patients residing in the United States, France, and Switzerland have shown increases in the incidence ratios in specific cancers, such as head and neck, lung, liver, anal, and kidney, as well as Hodgkin disease.(3–7) Viral co-infections may in part explain higher rates of some of these cancers such as Hodgkin lymphoma, liver, and anal cancer. However, for many of these diseases the higher incidence rates among HIV patients are not explained by viral co-infections or other risk factors.(8) For example, the increased incidence of head and neck and lung cancers are

not completely explained by a higher use of tobacco products among patients diagnosed with HIV.(3, 9)

HAART typically includes a three to four drug combination of protease inhibitors (PIs), nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or additional agents.(10, 11) A significant amount of research over the past decade has investigated how these HAART drugs are metabolized, including how these agents both induce and inhibit various enzymes involved in drug metabolism.(12) For example, to varying degrees all PIs inhibit CYP3A4, an enzyme that mediates the metabolism of over half of all drugs that undergo hepatic metabolism. Ritonavir is a strong inhibitor of CYP3A4, and this fact has been used to increase the drug delivery of other HAART agents via 'boosted' combination therapy.(13)

How to treat cancer in patients on HAART with chemotherapy for a NADC is complicated, and not well studied. In fact, an HIV diagnosis is often an exclusionary criterion in clinical trials of NADCs due to concerns of potential drug-drug interactions and a higher perceived risk for immune mediated complications. In 2009, the NCI-sponsored AIDS Malignancy Consortium began the first in a planned series of clinical trials to better understand the use, dosing, and toxicities of targeted chemotherapies when combined with HAART to better understand such potential interactions, and provide treatment recommendations when using such agents.

Sunitinib malate is an orally available multi-targeted tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma (RCC), gastrointestinal stromal tumors (GIST), as well as pancreatic neuroendocrine tumors (pNET), and has been assessed in a wide range of other solid tumor malignancies in clinical trials. The drug inhibits PDGFR, VEGFR1 and 3, KIT, FLT3, the receptor stem cell factor (SCF), and RET.(14–18) Sunitinib is metabolized by CYP3A4 to produce the primary active metabolite N-desethyl sunitinib via N-deethylation. Given the potential interactions between HAART agents and sunitinib at the level of CYP3A4, which could lead to reduced efficacy and/or increased toxicity, we conducted this phase I study.

Methods

Patients

Patients who were HIV-positive and had a diagnosis of a solid or hematologic malignancy were eligible if the patient had progressed following standard therapy and/or other curative options were not available. Patients were required to have a CD4+ T-lymphocyte count of 50 cells/ μ L or greater and be on a stable HAART for at least 4 weeks with a PI-based or NNRTI-based regimen of at least three drugs. Eligibility criteria included adequate bone marrow, liver, and renal function, a Karnofsky performance status of at least 60%, no opportunistic infection or uncontrolled medical condition, the ability to take oral medication, and a life expectancy >3 months. Written informed consent was obtained as per federal and institutional guidelines before treatment.

Given potential cardiac toxicity from sunitinib, patients were ineligible if they had clinically significant cardiovascular disease, including uncontrolled hypertension, unstable angina, cardiac arrhythmia, an abnormal left ventricular ejection fraction, a myocardial infarction, or other significant vascular disease related event in the previous six months. Patients could not be taking medications that were known to inhibit or induce CYP3A4 other than antiretroviral drugs used to treat HIV infection, and were asked to avoid grapefruit and star fruit juice. Medications known to have a proarrhythmic potential were also not allowed. Chemoprophylaxis for *Pneumocystis jirovecii* (PCP) pneumonia was required for patients with a CD4+ count less than 200 cells/ μ L. Erythropoietin and granulocyte colony-stimulating factors were allowed if clinically indicated but only after completion of cycle 1. Palliative radiotherapy to specific sites of disease was permitted after cycle 1 if considered medically necessary by the treating physician and the involved field was not considered to represent disease progression.

Study Design

This phase I trial was conducted to determine the safety and to investigate the pharmacological interactions of administering sunitinib in patients with cancer who were also HIV-positive on antiretroviral regimens containing PIs and/or NNRTIs. Secondary objectives included evaluating the efficacy of sunitinib in treating NADCs in these patients, and to detect alterations in immune parameters, including total leukocyte count, CD4+ lymphocyte count and HIV viral load during sunitinib therapy in HIV-positive patients. The original trial design stratified patients into one of three groups based on the type of HAART therapy they were receiving: (1) NNRTI-based therapy, (2) non-ritonavir PI-based therapy, and (3) ritonavir PI-based therapy. In December, 2009, the Center for Disease Control recommended against treating newly diagnosed HIV-positive patients with non-ritonavir containing PI-based therapies, and thus that arm was closed.

Patients on NNRTI-based therapy received the standard sunitinib dose of 50mg/day for 4 weeks, followed by a 2 week treatment break (6-week cycles). For patients on ritonavir, the sunitinib dose level was escalated from 25mg/day in 12.5mg/day increments up to the standard dose (50mg/day) utilizing a 3+3 phase I design. A total of six patients would be treated at the maximum tolerated dose (MTD) level. Patients were allowed to stay on therapy as long as they experienced clinical benefit and tolerable toxicities.

The protocol was approved by each site's Institutional Review Board. Data and safety monitoring including dose escalation decisions was overseen by an independent Medical Monitor.

Toxicity and Response

Toxicities were assessed using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A dose-limiting toxicity (DLT) was defined as an adverse event occurring during cycle 1 with a possible, probable, or definite relation to the study medication and fulfilled one of the following criteria: grade 4 neutropenia lasting 7 days or more; febrile neutropenia; neutropenic infection (grade 3 or 4); grade 4 thrombocytopenia lasting for 7 days or more; any grade 3 or 4 non-hematologic

toxicity lasting 7 days or more (except alopecia and grade 3 asymptomatic hypertension with adequately controlled blood pressure with medication); grade 3 or 4 nausea, vomiting or diarrhea lasting for longer than 24 hours despite maximal medical therapy; and any toxicity that precluded starting cycle 2 within 14 days of the protocol-specified date. Dose reductions were allowed for toxicities not meeting the definition of a DLT but only after cycle 1.

Patients were assessed for response after every two cycles (12 weeks) of therapy, using the same modality (e.g., computed tomographic scans, magnetic resonance imaging) by which the measurable disease was initially evaluated. Response was assessed utilizing criteria depending on the subject's primary disease, as follows: for solid tumors, the Response Evaluation Criteria in Solid Tumors (RECIST)(19); for prostate cancer, Serological Response Criteria for Prostate Cancer from the NCI Prostate Specific Antigen Working Group(20); for Kaposi's Sarcoma, AIDS Clinical Trials Group Criteria(21); for lymphoma, the International Working Group Criteria for Response for Lymphomas(22); for multiple myeloma, International Myeloma Working Group Response Criteria(23); and for leukemia, the International Working Group for Response Criteria for Acute Leukemias(24).

Pharmacokinetic Sampling, Assay, and Analysis

Serial blood samples for pharmacokinetic analysis were collected during Cycle 1 on Day 1, in addition to weekly trough samples through Day 29, with an optional half-life assessment to Day 42. Total and unbound plasma concentrations of sunitinib and N-desethyl sunitinib were determined using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.(25) Individual pharmacokinetic parameters were estimated by standard non-compartmental analysis using WinNonlin Professional Version 5.3 (Pharsight Corporation, Mountain View, CA). The following pharmacokinetic parameters were estimated: area under the plasma concentration-time curve (AUC_{0-24h}) from time zero to 24 hours on Day 1, peak plasma concentration (C_{max}), minimal plasma concentrations at steady-state ($C_{min,ss}$), half-life ($T_{1/2}$), average fraction unbound (F_u), and the relative systemic exposure to sunitinib for the metabolite N-desethyl sunitinib. $C_{min,ss}$ was calculated from Day 15–29 and Day 22–29 for sunitinib and N-desethyl sunitinib, respectively, based on the time to steady-state estimated based on reported half-life and dosing interval.(26) Dose-normalized C_{max} , $C_{min,ss}$, and AUC_{0-24h} values were calculated as the observed parameter divided by actual dose.

Statistical considerations

The primary objective of this study was to investigate the safety and pharmacological interactions of administering sunitinib to cancer patients on HAART therapy. No formal statistical hypothesis testing was planned for the primary analysis on the safety parameters due to the small sample size; instead results have been presented descriptively. Pharmacokinetic parameters were summarized using descriptive statistics. Differences in dose-normalized pharmacokinetic parameters across groups were evaluated using a two-sided Kruskal-Wallis test. Mann-Whitney U-tests were used to assess correlations between sunitinib and metabolite exposure and toxicity. The a priori level of significance was set at $p < 0.05$.

Results

Patients

Between August 2009 and April 2011, a total of 21 patients were enrolled, and 19 completed cycle one of therapy and were evaluable for toxicities. One enrolled patient did not start treatment, and another patient came off study per patient preference (not for toxicity) before completing cycle one. Demographic data on the 19 evaluable patients are summarized in Table 1. The one patient enrolled to the non-ritonavir PI arm was included for analysis purposes in arm 1 (NNRTI-based therapy) after that arm was closed. After six patients were enrolled to the NNRTI arm, the protocol was amended to allow another three patients (for a total of six patients) who were on efavirenz, a known inducer of CYP3A4, due to an interim pharmacokinetic assessment indicating a significant increase in N-desethyl sunitinib formation. Enrollment by arm and dose level are presented in Table 2.

Treatment and Toxicities

Treatment in the NNRTI arm was well tolerated, and no dose limiting toxicities were observed. On the ritonavir arm, four patients were treated at the 25mg dose level and three completed cycle 1 without any significant toxicities. One patient with non-small cell lung cancer experienced rapid tumor progression and was taken off study for clinical progression. At the 37.5mg dose level, one of the first three patients experienced a DLT (grade 3 wound complications), and the cohort was expanded to six patients. None of the remaining five patients experienced a protocol-defined DLT, though three experienced grade 3 neutropenia. Given this safety profile, further expansion to 50mg was not recommended by the medical monitor. The MTD for patients on ritonavir was thus determined to be 37.5mg.

Toxicities experienced during cycle 1 and throughout treatment that were thought to be related to treatment and experienced by at least 10% of patients are listed in Table 3. The most common toxicities observed besides hematological abnormalities were diarrhea, fatigue, nausea/vomiting, hand-foot syndrome, and hypertension. One patient was treated with local palliative radiation for pain control while on study, which was not deemed by the treating investigator to represent disease progression, nor did it account for any additional treatment-related toxicities.

Response

A total of 17 patients were evaluable for response. No patient experienced an objective response to therapy. A total of ten patients (56%) experienced stable disease as a best response, including eight patients (44%) who experienced prolonged stable disease lasting at least 4 cycles (24 weeks). Three of these patients were diagnosed with Kaposi's Sarcoma, while one patient each had diagnoses of melanoma, sarcoma, renal cell, salivary gland, and adenocystic carcinoma of the lung. The patient with salivary gland cancer (adenocarcinoma histology) had been heavily pretreated, and was on study for 14 cycles (20 months). Of the eight patients with stable disease on prolonged therapy, four had their dose of sunitinib reduced after cycle 1, including three on the NNRTI arm.

Effect of Sunitinib on HIV Disease Parameters

No significant effect was seen by treatment with sunitinib on CD4+ cell count and HIV viral load parameters, arguing against any sunitinib-induced effect of the pharmacology of HAART. The median change in the log CD4 count from baseline to the end of cycle two was -0.02 (range -0.23 to 0.25 , $n=13$ patients), and -0.03 (range -0.14 to 0.10 , $n=8$ patients) after cycle four. For those patients with detectable levels, the median change in log HIV viral load from base line to the end of cycle two was -0.18 (range -2.78 to 0.0 , $n=6$ patients), and -0.33 (range -2.05 to 0.0 , $n=4$ patients) after cycle four.

Pharmacokinetics

Pharmacokinetic analysis was evaluable on 18 patients (Table 4). One patient was excluded due to the pre-treatment sample containing significant sunitinib concentrations. Consistent with previous reports, pharmacokinetic analysis showed significant inter-patient variability of sunitinib and its active metabolite, N-desethyl sunitinib.(26, 27) Despite trends towards increased sunitinib exposure with ritonavir (AUC_{0-24h} $p=0.16$, C_{max} $P=0.08$, $C_{min,ss}$ $p=0.07$), there were no statistically significant alterations in sunitinib pharmacokinetics between the arms. However, there were significant alterations in N-desethyl sunitinib exposure. Efavirenz resulted in a 410% increase compared to NNRTI, whereas ritonavir caused a 48% decrease in N-desethyl sunitinib C_{max} , respectively ($p=0.0008$, efavirenz >ritonavir). A similar trend was noted with a 390% increase in N-desethyl sunitinib AUC_{0-24h} in the efavirenz arm compared to NNRTI with a 40% decrease in the ritonavir arm ($p=0.006$, efavirenz>ritonavir and NNRTI). At steady-state, the inhibitory effect of ritonavir on metabolite formation was not observed (12% increase) but efavirenz still resulted in a 234% increase in N-desethyl sunitinib $C_{min,ss}$ compared to NNRTI ($p=0.06$ for N-desethyl sunitinib; $p=0.07$ for sunitinib). The differences in N-desethyl sunitinib concentrations were significant to alter the ratio of metabolite:parent drug ($p=0.01$ for AUC_{0-24h} and $C_{min,ss}$ efavirenz>ritonavir and NNRTI) but not the sum total AUC_{0-24h} ($p=0.68$) when assessed on a dose-normalized basis. There was no alteration in protein binding across study arms ($p>0.05$). There was a correlation between hand-foot syndrome and elevated sunitinib $C_{min,ss}$ ($p=0.013$) but not sunitinib exposure after a single dose ($p>0.05$) nor with N-desethyl sunitinib exposure ($p>0.05$). There was not a significant correlation between any PK parameter and grade 3 neutropenia.

Discussion

Since HAART became widely prescribed beginning in 1996, there has been a dramatic change in the AIDS epidemic.(1,2) Patients with AIDS are no longer faced with an invariably terminal illness, but rather a chronic condition with improved life span.(1,2) As the use of HAART became more widespread in developed countries, the incidence of AIDS-defining cancers also declined.(3) Unfortunately, patients with HIV are now being diagnosed at high rates with NADCs.(3–7) As new targeted therapies have become available to treat these cancers, how best to use -- and dose -- these chemotherapy agents to treat HIV patients with NADCs who are on HAART remains an important research and clinical question.

One potential strategy given concerns for drug-drug interactions might be to stop HAART therapy while treating a malignancy. However, taking patients off of HAART therapy, including the use of 'structured treatment interruptions' that was hoped to reduce drug resistance and improve tolerability of HAART therapy, can lead to poorer outcomes, including higher rates of drug resistance and increased risk of death from any cause .(10, 28)

In this modified phase I trial, we found that patients on non-ritonavir containing HAART therapy tolerated standard dosing of sunitinib at 50mg/day using the 4 week on/2 week off cycle. However, patients on ritonavir based therapy experienced toxicity on the 37.5mg/day dose level comparable or higher than that seen in the non-ritonavir 50mg/day dose level, including higher rates of grade 3 neutropenia and grade 1/2 diarrhea, mucositis, and fatigue. Due to this toxicity profile, the recommended dose for patients on ritonavir is 37.5mg/day on the 4 week on/2 week off schedule.

Two previous clinical studies were conducted in healthy volunteers to investigate drug-drug interactions with sunitinib based on the effect of inhibition and induction of the CYP3A4 metabolic pathway, and are reported in the FDA-approved package insert of Sutent®.(29) Exposure was altered significantly by ketoconazole and rifampin with dosage recommendations to consider a starting dose of 37.5 mg when administered with a strong CYP3A4 inhibitor or increasing the dose in 12.5 mg increments to a maximum of 87.5 mg when administered with a strong CYP3A4 inducer. Our trial confirms these findings, and in the case of the potent CYP3A4 inhibitor ritonavir is in keeping with the dose modification recommended in the package insert. The dose escalation in the efavirenz arm was not explored due to concerns with the non-traditional toxicities being observed in our patient population. These findings also highlight the variability of exposure with CYP3A4 inhibitors/inducers of different strengths, and the need for further studies to guide the magnitude of adjustments needed in dosing drugs that may alter metabolism through this pathway.

Rates of grade 3 or 4 neutropenia in the phase III trials of sunitinib to treat renal cell carcinoma, gastrointestinal stromal tumors, and primitive neuroectodermal tumors using the dose of 50mg/day were 17%, 10%, and 16%, respectively, according to the Sutent® package insert.(29) The 60% rate seen on the ritonavir arm at the dose of 37.5mg/day (3 of 5 patients who completed cycle one of treatment) was unexpected, and proved to be the limiting toxicity for such patients. These were patients on a phase I trial and had received prior systemic cytotoxic chemotherapy (median of 1.7 regimens, with a range of 0 to 4). This may account in part for this higher rate of neutropenia. A contributing factor may be that sunitinib and N-desethyl sunitinib are substrates for the ABCB1 and ABCG2 drug transporters.(30, 31) Protease inhibitors including ritonavir have been found to inhibit ABCB1.(32) ABCB1 expression and function is important in myeloid stem cells.(33) Therefore, this high rate of neutropenia may be due to ritonavir inhibition of ABCB1-mediated sunitinib efflux out of myeloid stem cells, accumulating even higher concentrations in such cells, in turn inducing this hematologic toxicity. There was no correlation with systemic exposure to sunitinib and N-desethyl sunitinib.

This first trial of the AMC to better understand the use of targeted therapies in HIV-positive patients suggests HAART-based dosing recommendations that now can be used in other clinical trials, and by practicing medical oncologists. Given the rising rates of non-AIDS defining solid tumor and hematological malignancies, we hope that this and future studies will result in improved treatment information to guide the use of targeted anti-cancer agents in the care of HIV-positive patients.

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Table 1

Patient Demographics

Total	19
Age – median (range) years	54 (38 – 71)
Gender (male/female)	19 / 0
Ethnicity	
Caucasian	8 (42%)
African-American	4 (21%)
Hispanic	3 (16%)
Other/Unknown	4 (21%)
Duration of HIV infection – median (range) years	13.7 (1.2 – 21.5)
CD4+ Cell Count – median (cells/ μ L)	376
HIV Viral Load – median (copies/mL)	48
Primary Site of Malignancy (N)	
Kaposi's Sarcoma	6
Anal	2
Lung	3
Head and Neck	1
Sarcoma	1
Non-Hodgkin Lymphoma	1
Colorectal	1
Liver	1
Prostate	1
Melanoma	1
Renal	1
Prior systemic chemotherapy regimens --median (range)	1.7 (0 – 4)
Median Cycle Treatment Duration (range)	3 (1 – 14)

Table 2

Dose Levels and Patients Enrolled

Arm / Level	Sunitinib Dose (mg)	No. of Patients
Arm 1 – NNRTI / Non-Ritonavir PI		10
Non-Ritonavir P	50	1
NNRTI	50	3
Efavirenz	50	6
Arm 2 - Ritonavir PI		9
Level 1	25	3
Level 2	37.5	6
Level 3	50	n/a

Table 3

All treatment-related adverse events occurring in 10% or more of patients, according to cohort during Cycle 1 and for the duration of treatment

System	Arm 1 (NNRTI) (50 mg; n=10)		Arm 2 (Ritonavir) (25 mg; n=3)		Arm 2 (Ritonavir) (37.5 mg; n=6)		Total in Cycle 1		Total in All Cycles	
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	All Grade (%)	G3 (%)	All Grade (%)	G3 (%)
Hematology										
Neutropenia	4	1	1	1	0	3	10 (53)	5 (26)	10 (53)	6 (32)
Anemia	1	1	0	0	0	0	2 (11)	1 (5)	3 (16)	1 (5)
Thrombocytopenia	1	0	0	0	1	0	2 (11)	0 (0)	3 (16)	0 (0)
Gastrointestinal										
Abdominal Pain	1	0	1	0	0	0	2 (11)	0 (0)	2 (11)	0 (0)
Constipation	1	0	0	0	0	0	1 (5)	0 (0)	2 (11)	0 (0)
Diarrhea	3	0	2	0	3	0	8 (42)	0 (0)	9 (47)	1 (5)
Mucositis	0	0	0	0	2	0	2 (11)	0 (0)	3 (16)	0 (0)
Nausea/Vomiting	2	0	1	0	0	0	3 (16)	0 (0)	6 (32)	0 (0)
ALT/AST Elevation	2	0	0	0	0	0	2 (11)	0 (0)	2 (11)	0 (0)
Cardiac										
Hypertension	2	0	1	0	0	0	3 (16)	0 (0)	4 (21)	0 (0)
Constitutional										
Fatigue	3	0	1	0	3	0	7 (37)	0 (0)	8 (42)	0 (0)
Dermatological										
Rash	1	0	0	0	1	0	2 (11)	0 (0)	3 (16)	0 (0)
Hand-Foot Syndrome	1	0	0	0	1	0	2 (11)	0 (0)	6 (32)	1 (5)
Hypopigmentation	1	0	0	0	1	0	2 (11)	0 (0)	2 (11)	0 (0)
Musculoskeletal										
Myalgia/Limb Pain	2	0	0	0	0	0	2 (11)	0 (0)	2 (11)	0 (0)
Metabolism/Nutrition										
Anorexia	2	0	0	0	0	0	2 (11)	0 (0)	3 (16)	0 (0)
Hemorrhage/Bleeding										
Epistaxis	1	0	0	0	0	0	1 (5)	0 (0)	2 (11)	0 (0)

System	Arm 1 (NNRTI) (50 mg; n=10)		Arm 2 (Ritonavir) (25 mg; n=3)		Arm 2 (Ritonavir) (37.5 mg; n=6)		Total in Cycle 1		Total in All Cycles	
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	All Grade (%)	G3 (%)	All Grade (%)	G3 (%)
<i>Neurology</i>										
Headache	1	0	0	0	1	0	2 (11)	0 (0)	2 (11)	0 (0)
<i>Miscellaneous</i>										
Cough	0	0	0	0	0	0	0 (0)	0 (0)	2 (11)	0 (0)
Wound Dehiscence	1	0	0	0	0	1 [#]	2 (11)	1 (5) [#]	2 (11)	1 (5)

Toxicities with possible, probable, or definite relation to study treatment and graded per NCI CTCAE version 4.0. Patients with a recurrent toxicity were counted only once at the highest grade level that occurred during Cycle 1 or for the duration of therapy.

[#]DLT

ALT alanine amino-transferase; AST aspartate amino-transferase

Table 4

Plasma pharmacokinetics parameters of sunitinib and N-desethylsunitinib¹

Group/Dose (mg/day)	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-24h} (ng•h/mL)	Sum Total AUC _{0-24h} (ng•h/mL)	C _{min,ss} (ng/mL)	T _{1/2} (h)	F _u (%)
Sunitinib							
NNRTI/50	25.1±10.8 (4)	7.5 (3.1–8.2, 4)	315.2, 413.6 (2)	397.7, 469.9 (2)	42.1±3.1 (3)	63.6 (1)	6.9±2.1 (4)
Efavirenz/50	14.7±2.2 (5)	7.0 (3.9–24.0, 5)	263.6±49.7 (5)	534.2±193.9 (5)	17.7±7.7 (5)	71.1±33.5 (4)	5.0±4.0 (5)
Ritonavir/25	9.1±4.2 (3)	7.0 (6.1–24.4, 3)	102.2, 183.6 (2)	117.8, 199.5 (2)	6.0, 28.3 (2)	66.0 (1)	7.0±3.1 (3)
Ritonavir/37.5	19.9±5.9 (6)	7.5 (4.0–8.1, 6)	338.1±99.0 (4)	373.2±99.8 (4)	50.3±29.5 (5)	67.8, 86.8 (2)	6.7±2.1 (6)
N-desethyl sunitinib							
NNRTI/50	4.6±1.2 (4)	7.5 (4.1–8.2, 4)	56.3, 82.5 (2)	N.A.	17.8±9.9 (3)	100.1 (1)	12.2±4.3 (4)
Efavirenz/50	18.7±15.8 (5)	24.0 (3.9–24.0, 5)	270.5±147.4 (5)	N.A.	41.5±17.9 (5)	89.7±19.3 (5)	7.7±3.5 (5)
Ritonavir/25	1.1±0.4 (3)	6.1 (5.0–24.4, 3)	15.6, 15.9 (2)	N.A.	2.3, 10.1 (2)	102.0 (1)	8.8±0.8 (3)
Ritonavir/37.5	1.9±0.4 (6)	16.0 (7.0–24.1, 6)	35.0±2.1 (4)	N.A.	21.9±6.4 (3) ²	97.4, 105.2 (2)	11.6±3.2 (6)
N-desethyl sunitinib:sunitinib Ratio (%)							
NNRTI/50	N.A.	N.A.	14.0, 26.0% (2)	N.A.	291.3±150.7% (3)	N.A.	N.A.
Efavirenz/50	N.A.	N.A.	98.0±34.8% (5)	N.A.	47.4±19.5% (5)	N.A.	N.A.
Ritonavir/25	N.A.	N.A.	9.0, 15.0% (2)	N.A.	260.0, 280.0% (2)	N.A.	N.A.
Ritonavir/37.5	N.A.	N.A.	11.0±2.9% (4)	N.A.	298.3±53.7 (3)	N.A.	N.A.

¹ Data are presented in the table as mean±SD (n). T_{max} is presented as median (range, n). If n<3, the actual values are reported.

² One patient did not have sufficient samples to calculate the average C_{min,ss} for N-desethyl sunitinib.

Abbreviations: AUC area under the plasma concentration-time curve to 24 h; C_{max} peak plasma concentration; C_{min,ss} average plasma trough concentration; N.A. not applicable; T_{1/2} half-life; T_{max} time to peak concentration; F_u unbound fraction.