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# A phase 1b/pharmacokinetic trial of PTC299, a novel post-transcriptional VEGF inhibitor, for AIDS-related Kaposi's sarcoma: AIDS Malignancy Consortium trial 059

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## Abstract

Vascular endothelial growth factor (VEGF) plays an important role in Kaposi's sarcoma (KS). We administered PTC299, a post-transcriptional inhibitor of pathogenic VEGF, to persons with HIV-related KS. Seventeen participants received three different doses of PTC299. Adverse events typically observed with VEGF-inhibition were absent. Three participants had partial tumor responses and 11 had stable disease. There were no differences in exposure to PTC299 by antiretroviral regimen. Serum VEGF, but not KSHV DNA, decreased on treatment. Given redundancies in the VEGF feedback loop, future trials should consider combining PTC299 with agents that inhibit different pathways implicated in KS and KSHV proliferation.

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**CONFLICT OF INTEREST**

RBI, JYL, AS, VK, DPD, RFA, MAR, and SEK declare no conflict of interest.

### Keywords

Kaposi's sarcoma (KS); Vascular Endothelial Growth Factor (VEGF); Vascular Endothelial Growth Factor Inhibitor (VEGF inhibitor); Kaposi's sarcoma-associated herpes virus (KSHV/HHV-8); HIV/AIDS-related malignancy; pharmacokinetics (PK)

## INTRODUCTION

Although Kaposi's sarcoma (KS), the most common AIDS-defining malignancy worldwide [1, 2], can be treated with antiretroviral therapy (ART) alone or with chemotherapy added [3-5], responses are often incomplete. Cytotoxic chemotherapy may induce acute and chronic adverse events and pharmacokinetic interactions with ART, and access to chemotherapy is limited in high-incidence, low-resource regions, especially sub-Saharan Africa [6, 7]. Thus, alternative treatments are needed.

Vascular endothelial growth factor (VEGF) is highly over-expressed in KS tumors and enhances KS-associated herpesvirus (KSHV) entry and KS gene expression within target cells [8, 9]. In laboratory studies, inhibiting VEGF expression or its signaling pathways results in tumor growth inhibition [10-14]. KSHV-encoded proteins promote vascular endothelial reprogramming and immortalization through up-regulation of VEGF and VEGF receptors (VEGFr) [15, 16]. Additionally, tumor hypoxia induces p53-mediated apoptosis and HIF-1α, further promoting VEGF production [17]. HIF-1α and hypoxemic responses are additionally modulated directly by KSHV, and hypoxia further promotes lytic KSHV replication [18-21].

PTC299 (PTC Therapeutics Inc, South Plainfield, NJ) an orally-bioavailable VEGF inhibitor, acts via post-transcriptional regulation of VEGF mRNA under conditions of cellular stress. Transcriptional regulation of VEGF in normal endothelial cells occurs mainly through cap-dependent translation of its mRNA. In contrast, cellular stress and hypoxemia augment transcription of VEGF in a cap-independent fashion [22-24]. Because PTC299 targets cap-independent pathways of mRNA translation that predominate during stress such as hypoxia and oncogenic transformation, VEGF production in normal endothelium is spared, potentially avoiding undesirable off-target effects of generalized VEGF blockade observed with other VEGF and VEGFr tyrosine kinase inhibitors (TKIs). PTC299 activity was demonstrated in a variety of tumor cell lines and mouse xenograft-tumor models and was safe and well tolerated in several phase I clinical trials [25-28].

These considerations led the AIDS Malignancy Consortium (AMC) to evaluate the safety, dosing, antitumor activity, and pharmacokinetics of PTC299 in patients with HIV-associated KS, and to describe its effects on VEGF expression and KSHV replication.

## METHODS

### Study Population

Eligible participants were HIV-infected adults with biopsy-proven KS not requiring urgent systemic chemotherapy for symptomatic visceral disease. Participants receiving ART were

required to be on a stable regimen ≥ 12 weeks without improvement in KS during that time, not pregnant or breastfeeding, and to have received no KS treatment within one month. Exclusions included Karnofsky score <60, life expectancy <3 months, history of bleeding or clotting diathesis, severe hepatic or renal dysfunction, or other active serious medical conditions.

After providing informed consent, three participants were sequentially enrolled into each of three oral dosage levels, 40mg twice daily (BID), 80mg BID, and 100mg BID, once the preceding dose had been administered without dose limiting toxicities (DLT) for one cycle. Eight additional participants then received 100mg BID. PTC299 was supplied as 20mg capsules. A plan to estimate the maximum tolerated dosage (MTD) was not performed because the sponsor suspended enrollment due to change in drug formulation. Each drug cycle lasted 28 days. KS response was assessed every 28 days as previously described [29, 30], and categorized as complete (CR), partial (PR), stable (SD) or progression (PD). Participants were considered evaluable for response if they completed 1 cycle of PTC299. Participants without CR or PR were removed from study after 6 cycles; treatment was likewise discontinued if KS progressed on therapy or DLT occurred. Participants were continued on therapy for an additional 2 cycles following CR, or up to 12 cycles for PR.

## Laboratory Methods

Biopsies of non-indicator KS lesions were performed at baseline and during week 4, cycle 1, and evaluated for changes in expression of viral, angiogenesis and proliferation markers (see Supplemental Material).

KSHV DNA was quantified in plasma at baseline, cycles 2 and 5, and treatment discontinuation, using competitive DNA PCR [31]. Whole blood CD4+ T cell counts and plasma HIV RNA levels were determined at these same time points.

VEGF-A and IL-6 levels were quantified by ELISA (Quest Laboratories, San Juan Capistrano, CA) in serum and plasma on Day 1 of cycles 1-6, on Cycle 1, Day 15 and at treatment discontinuation.

Serial blood samples for pharmacokinetic analysis were collected immediately preceding and at 1, 2, 3, 4, 5, 6, and 8 hours following the morning administration of PTC299 on Cycle 1, Days 1 and 28. Additional trough samples were obtained on Cycle 1, Day 15 and Cycle 2, Day 28. Samples were analyzed and pharmacokinetic parameters estimated as described (see Supplemental Material).

## Statistical Considerations

Descriptive statistics were used to summarize adverse events and response rates.

Effects of PTC299 on serum and plasma VEGF, VEGFR and cytokine profiles were evaluated comparing pre-treatment values with Day 28 and with the lowest value subsequent to Day 28, and differences tested with Wilcoxon signed rank tests. Methods for analyzing other correlative laboratory endpoints are described in Supplemental Materials.

## RESULTS

Seventeen volunteers were enrolled: 3 at 40 mg BID, 3 at 80 mg BID and 11 at 100 mg BID. Baseline characteristics, including extent of KS, ART regimen, HIV parameters, and prior KS therapy are described in Table 1, as are details of study treatment.

Five participants completed therapy per protocol, 6 terminated study treatment for KS progression, and 4 voluntarily withdrew after a median of 3 cycles. One patient died and one withdrew from study before the first response evaluation. PR was documented in 3 participants (18%), lasting for 2, 3, and 4 months respectively at doses of 40mg BID (n=1) and 100mg BID (n=2). Eleven participants showed SD lasting a median of 3 months (IQR 2-6.5). PD ultimately occurred in 6 participants, of whom 5 initially had either PR or SD.

### Safety Assessment

Common adverse events included nausea (41%), vomiting (18%), diarrhea (24%), limb pain (47%), and fatigue (29%); >90% of events were Grade 1 or 2. Limb pain, fatigue, and peripheral edema were prevalent at baseline and consistent with the primary disease. Hyperglycemia (29%), dyslipidemia (53%), elevated creatinine (18%), and proteinuria (18%), were the most frequent laboratory abnormalities. Three participants (18%), all receiving atazanavir, had elevated bilirubin. All participants with elevated creatinine and/or proteinuria received concurrent tenofovir. Serious adverse events were reported in 3 participants: one grade 3 nephrolithiasis, considered unlikely related to study drug; one grade 3 myalgia at the 100 mg/dose level, considered probably PTC299-related; and one death. The death was officially ascribed to hypertensive cardiovascular disease and reported as possibly study drug-related, although autopsy revealed detectable serum levels of several illicit and prescription opiates and sedatives; precise cause of death is therefore uncertain.

### Pharmacokinetics

**Pharmacokinetics—**Pharmacokinetic analysis was available for 15 patients. A post-hoc analysis categorizing participants on whether the ART regimen was known to induce CYP2C19 (ritonavir) or inhibit CYP2C19 (efavirenz) [32] showed no statistically significant alterations in pharmacokinetics of the parent compound, but significant alterations in exposure to the less-active metabolite, des-methyl PTC299 (see Supplemental Material)[33]. There was no correlation between treatment response and PTC-299 or metabolite exposure ($p > 0.05$)

### Effects of PTC299 on Biologic markers

Day 1, cycle 1 levels of serum VEGF were significantly higher than levels at all later time-points (Figure 1); plasma VEGF showed a less sustained decrease that was significant only at intermediate time-points. No changes were observed in serum or plasma IL-6.

There were no significant treatment-associated changes in KSHV viral loads, absolute and percent CD4, or immunohistochemical expression of VEGF, VEGFr, phospho-Akt, p53, HIF-1α, or Ki-67, or viral gene expression or cellular gene transcription in tumor biopsies.

## DISCUSSION

Recognition of the essential role of VEGF in KS development has prompted evaluation of several VEGF inhibitors in AIDS-associated KS. This study evaluated PTC299, a novel, orally-bioavailable small molecule that inhibits VEGF protein production by preventing translation of pathological VEGF. Because the study was halted early, we were unable to define the MTD in this population, but doses administered were similar to those tested in other Phase I and II studies. Those trials and ours demonstrated a pharmacokinetic profile for PTC299 consistent with maintenance of drug levels well above those required for efficacy in preclinical models.

Participants were allocated to PTC299 dosage levels without respect to the concurrent antiretroviral regimen. We observed no significant variation between participants receiving CYP2C19 inducers and inhibitors in the pharmacokinetics of the parent drug, nor correlation of treatment response with drug and metabolite exposure, although metabolite exposure and metabolite:parent drug ratio differed significantly between these two groups. Without stratified dosage assignments, such as those used in a subsequent AMC trial of sunitinib [34], we were unable to correlate adverse events by ART regimen effects on CYP2C19.

We did not observe many of the medically significant side effects of VEGF inhibitors and TKIs, such as bleeding, hypertension and renal vascular injury [35, 36]. Mild proteinuria was limited to persons receiving tenofovir and/or atazanavir, both known to cause renal tubulopathies [37] and all persons with elevated bilirubin levels were receiving atazanivir [38]. Fewer adverse events were observed than for other classes of VEGF inhibitors/TKIs, suggesting that drugs inhibiting VEGF by targeting tumor-specific mRNA rather than general kinase activity may be less likely to induce off-target effects. The short duration of PTC299 administration in some participants may, however, have precluded observation of potential adverse events.

Although we could not evaluate the planned dosage range of PTC299, moderate serum VEGF inhibition was achieved, though only modest effects on KS growth, consistent with results from other VEGF inhibitors. Many participants had previously received multiple KS treatments, but we did not note a pattern of response with respect to prior receipt of agents with anti-VEGF activity. Other studies of VEGF inhibitors in KS reported a 30% response rate for bevacizumab, 20% for sorafenib, and no better than SD for sunitunib [34, 39-41]. As such, this study highlights a persistent question in the search for improved therapies for KS and many soft tissue sarcomas (STS) which similarly over-express VEGF and its receptors [42]. It is unclear why, despite the apparent reliance of many such tumors on VEGF overproduction, VEGF inhibitors have not proven highly efficacious in these tumors. Five VEGF inhibitors have been studied in other STS, of which four received approval for this indication. However, single-agent PR rates were only 14% for sorafenib [43], 17% for bevacizumab [44], 6% for pazopanib [45] and metabolic PR in 47% of patients receiving sunitinib for varied STS [46]. Despite PTC299 activity in multiple pre-clinical *in vivo* sarcoma models [33], and a statistically significant decrease in serum VEGF levels in this trial, the response rate of 20% was similar to rates for other TKIs, but inferior to standard-of-care chemotherapy.

One reason that single-point blockade of the VEGF pathway may be insufficient to cause tumor regression, particularly in AIDS-related KS, is redundancy in the human VEGF pathway, which KSHV reinforces at several points [40]. Additionally, while VEGF is necessary for proliferation, it may not be necessary for tumor survival. This is similar to the mTOR pathway, an upstream regulator of VEGF and IL-6 expression [47-50]. Viral IL-6 and KSHV-mediated up-regulation of HIF-1α and VEGFrs may reinforce this autocrine-paracrine loop, such that single-point blockade of the VEGF pathway is easily circumvented. Virus-tumor interactions, allowing up-regulation of alternate pathways, may explain why objective responses to single agent VEGF inhibitors have been modest. Lastly, since pharmacologic growth factor depletion is seldom complete, the typical outcome of single-agent therapy in pre-clinical studies is growth arrest, translating to no better than SD in most patients.

Given the limited therapeutic results of VEGF monotherapy, a logical next step may be to combine mechanistically-distinct VEGF inhibitors [51] or VEGF inhibitors with agents that target either tumor or virus. A current example is an ongoing trial of bevacizumab with liposomal doxorubicin (NCT00923936). Additionally, nucleoside analog inhibitors of viral DNA polymerase with direct gamma herpesvirus activity, despite little anti-KS efficacy as single agents [52, 53], may provide adjuvant effects against virally-mediated paracrine stimulation to remove redundancy in the VEGF pathway. Furthermore, several HIV protease inhibitors have off-target effects on pathways regulating tumor growth, including Akt, NF-κB, and the 20S proteasome [54, 55]. Of particular interest is nelfinavir, which down-regulates HIF-1α and VEGF, and has direct anti-herpesvirus activity [56, 57].

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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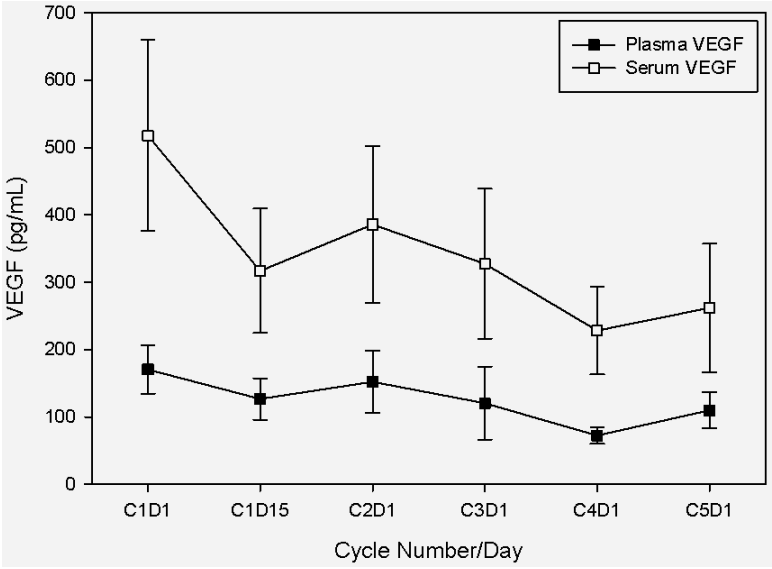


**Figure 1. Change in mean serum and plasma VEGF levels during treatment with PTC299**

Figure legend: This graph demonstrates mean VEGF levels in serum (open boxes) and plasma (closed boxes) with standard deviations denoted by brackets. Compared with the baseline (C1D1) mean level of 518.1 pg/ml, serum VEGF decreased significantly at all subsequent time points ( to 316.9 pg/ml, p=0.001 at C1D15; and to 261.81 pg/ml, p=0.026 at the final time point: C5D1). Baseline (C1D1) mean plasma VEGF was 170.4 pg/ml and was 126.7 pg/ml at C1D15 (p=0.061). Plasma VEGF decreased significantly between baseline and C3D1 (120.3 pg/ml, p=0.009) and C4D1 only (72.3 pg/ml,p=0.001) and but not at the final time point on C5D1 (109.9 pg/ml, p=0.432).

Abbreviations: VEGF, vascular endothelial growth factor; CxDx, cycle and day of PTC299 therapy

## Table 1

Baseline Participant Characteristics and Study Therapy Received

| Characteristic | | | | N=17 |
|---|---|---|---|---|
| **Age** median (range) | | | | 45 (31,57) |
| **Male** | | | | 17 (100%) |
| **Race/Ethnicity** | | | | |
| White, non-Hispanic | | | | 8 (47) |
| Black | | | | 4 (24) |
| Hispanic | | | | 3 (18) |
| Asian/Pacific Islander/Other | | | | 2 (12) |
| **KS Disease Characteristics** | | | | |
| Oral lesions | | | | 1 (6) |
| ≥50 lesions | | | | 16 (88) |
| Tumor-associated edema | | | | 16 (88) |
| **Prior treatment for KS*** | | | | **16 (94)** |
| Cytotoxic Chemotherapy | | | | 14 (82) |
| Local therapies (topical, radiation, or cryotherapy) | | | | 4 (24) |
| Imatinib | | | | 4 (24) |
| Other/experimental therapies | | | | 6 (35) |
| **Baseline KSHV Plasma Log-copies/ml, median (IQR)** | | | | **4.8 (2.5, 5.8)** |
| **CD4 T-cell Count, median (range)** | | | | **489 (133, 1132)** |
| **HIV Viral load undetectable** | | | | **13 (76)** |
| **Current Antiretroviral regimens** | | | | **N =17 (%)** |
| Nucleoside Analog Backbone | | | | |
| ABC/d4T | | | | 1 (6) |
| ABC/3TC/ddI | | | | 1 (6) |
| TDF/FTC or TDF/3TC | | | | 12 (71) |
| 3TC | | | | 1 (6) |
| AZT/3TC | | | | 1 (6) |
| Nucleoside-sparing regimen | | | | 1 (6) |
| Non-Nucleoside Agents | | | | 6 (35) |
| EFV | | | | 6 (35) |
| Protease Inhibitors** | | | | 10 (59) |
| Other Classes (raltegravir, maraviroc) | | | | 5 (29) |
| **PTC299 Cycles Received** | **40mg BID** | **80mg BID** | **100mg BID** | **Total** |
| | N=3 | N=3 | N=11 | **N=17** |
| median (range) | 7 (6,13) | 3 (2,5) | 4 (1,10) | **5 (1,13)** |

Abbreviations: KS, Kaposi sarcoma; HIV, human immunodeficiency virus; KSHV, Kaposi Sarcoma-associated herpes virus; IQR, interquartile range; ABC, abacavir; d4T, stavudine; 3TC, lamivudine; ddI, didanosine; TDF, tenofovir; FTC, emtricitabine; AZT, zidovodine; EFV, efavirenz.

*Prior treatments included (# of participants): cytotoxic therapies: liposomal doxorubicin (14), paclitaxel (7), vinblastine (1), etoposide (1), vincristine (1), daunomycin (1); Other/experimental therapies included: valproic acid (2), IM-862 (2), rapamycin (1), flavopiridol (1), Col-3 [incyclinide] (3), interferon-alpha (1), VEGF-antisense (1).

** Protease inhibitors included were lopinivir/ritonavir, darunavir/ritonavir, and atazanavir with and without ritonavir.