Safety, Activity, and Long-term Outcomes of Pomalidomide in the Treatment of Kaposi Sarcoma among Individuals with or without HIV Infection

Ramya Ramaswami[1], Mark N. Polizzotto[1], Kathryn Lurain[1], Kathleen M. Wyvill[1], Anaida Widell[1], Jomy George[1], Priscila Goncalves[1], Seth M. Steinberg[2], Denise Whitby[3], Thomas S. Uldrick[1], and Robert Yarchoan[1]

ABSTRACT

Purpose: Kaposi sarcoma (KS) is caused by Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8). KS, which develops most frequently among people with HIV, is generally treated with chemotherapy, but these drugs have acute and cumulative toxicities. We previously described initial results of a trial of pomalidomide, an oral immunomodulatory derivative of thalidomide, in patients with KS. Here, we present results on the full cohort and survival outcomes.

Patients and Methods: Participants with KS with or without HIV were treated with pomalidomide 5 mg once daily for 21 days per 28-day cycle with aspirin 81 mg daily for thromboprophylaxis. Participants with HIV received antiretroviral therapy. Response was defined by modified version of the AIDS Clinical Trial Group KS criteria. We evaluated tumor responses (including participants who had a second course), adverse events, progression-free survival (PFS), and long-term outcomes.

Results: Twenty-eight participants were enrolled. Eighteen (64%) were HIV positive and 21 (75%) had advanced (T1) disease. The overall response rate was 71%: 95% confidence interval (CI) 51%–87%. Twelve of 18 HIV-positive (67%; 95% CI, 41–87%) and 8 of 10 HIV-negative participants (80%; 95% CI, 44%–97%) had a response. Two of 4 participants who received a second course of pomalidomide had a partial response. The median PFS was 10.2 months (95% CI: 7.6–15.7 months). Grade 3 neutropenia was noted among 50% of participants. In the follow-up period, 3 participants with HIV had other KSHV-associated diseases.

Conclusions: Pomalidomide is a safe and active chemotherapy-sparing agent for the treatment of KS among individuals with or without HIV.

Introduction

Kaposi sarcoma (KS) is a multicentric tumor that is caused by Kaposi sarcoma herpesvirus (KSHV; also known as human herpesvirus 8) and characterized by the proliferation of KSHV-infected spindle cells and abnormal vasculature (1–4). KS commonly manifests as skin lesions but can also involve the lymph nodes and visceral organs, including gastrointestinal and respiratory systems (2, 5). KS was originally described by Moritz Kaposi in 1872 as novel tumor developing in elderly men; this relatively indolent form occurring in Eastern Europe and the Mediterranean region is now called classic KS (6). Several other epidemiologic types have been described, including endemic KS in sub-Saharan Africa and epidemic KS, arising in HIV-infected individuals (5, 7, 8). KS was one of the harbingers of the HIV epidemic, and its incidence is substantially higher among people living with HIV (PLWH) in the United States as compared with the general population (8). KS remains a leading cause of mortality overall in sub-Saharan Africa, due to the high prevalence of both HIV and KSHV (9).

KSHV is known for its molecular piracy of cellular genes (10, 11) and its modulation of cellular survival and immune regulatory pathways (12, 13). A virus-encoded constitutively activated G-protein–coupled receptor encoded by open reading frame (ORF) 74 that induces production of a variety of chemokines and cytokines is believed to play an important role in KS pathogenesis. Also, two KSHV-encoded proteins (K3 and K5) are membrane-bound ubiquitin E3 ligases that suppress expression of surface major histocompatibility complex class I (MHC-1) proteins and render infected cells relatively invisible to T cells. In patients with KSHV infection, KS most often develops in the setting of impaired host immunity. In PLWH, KS is typically observed at lower $CD4^+$ T-cell counts and uncontrolled HIV. However, KS can also emerge and remain persistent among individuals with well-controlled HIV and higher $CD4^+$ T-cell counts (7). In this type of KS and classic KS, markers of immunologic aging (immunosenscence) are usually observed (14).

Among PLWH, antiretroviral therapy (ART) is the cornerstone of KS therapy as HIV control enables at least partial restoration of KSHV-directed cellular immunity and reduces the inflammatory cytokine milieu (15). However, in patients with extensive disease, ART alone leads to regression of KS in only a minority of patients and is generally insufficient to address visceral manifestations of KS (16). In addition to ART, chemotherapy options include liposomal doxorubicin and paclitaxel. Response rates of these agents range between 55% and 70%; however, responses may not be sustained in all cases and KS can relapse following a period of remission (16–19). Patients often need to be periodically retreated. Although KS often responds to retreatment with chemotherapy, patients can suffer from immediate and cumulative

[1]HIV and AIDS Malignancy Branch, Center for Cancer Research, NCI, NIH, Bethesda, Maryland. [2]Biostatistics and Data Management Section, Center for Cancer Research, NCI, NIH, Bethesda, Maryland. [3]Viral Oncology Section, AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research, NCI, NIH, Bethesda, Maryland.

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Corresponding Author: Ramya Ramaswami, HIV and AIDS Malignancy Branch, Center for Cancer Research, 10 Center Drive, Bethesda, MD 20892. Phone: 240-506-1088; E-mail: ramya.ramaswami@nih.gov

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Translational Relevance

Kaposi sarcoma (KS) is a multicentric tumor caused by Kaposi sarcoma herpesvirus (KSHV). Worldwide, among patients with KSHV infection, emergence of KS is closely linked to impaired immunity and HIV infection. Chemotherapy-sparing options that are oral and deliverable in resource-limited settings are important goals for the management of KS. Pomalidomide is an oral immunomodulatory derivative of thalidomide. An initial report of the first 22 participants of a clinical trial of pomalidomide in KS demonstrated safety and activity in participants with or without HIV. In this report of all 28 participants, we evaluated tumor responses, cytokine changes, adverse events, and long-term outcomes. This trial led to accelerated approval of pomalidomide by the FDA for patients with KS without HIV infection and as initial KS-specific therapy for patients with HIV whose KS does not respond to ART alone.

long-term toxicities ranging from cytopenias, reduction in $CD4^+$ T-cell counts, and potential anthracycline-induced cardiotoxicity (19). New chemotherapy-sparing options are needed for patients with KS.

Pomalidomide is an oral immunomodulatory derivative of thalidomide. Thalidomide was initially tested against KS because of reports of its antiangiogenic activity (20) and was found to have substantial activity (21, 22). However, it has not been widely used due to significant central nervous system toxicity. Pomalidomide is one of several analogs of thalidomide. We now know that this class of agents acts by targeting cereblon, a cellular E3 ubiquitin ligase (23, 24) with downstream effects that enhance $CD4^+$ and $CD8^+$ T-cell costimulation, enhance natural killer (NK) cell activity, and modulate tumor necrosis factor-α, IL6, and VEGF. Preclinical studies from our group have shown that pomalidomide reverses the virus-induced downregulation of immune surface markers including MHC-1, ICAM-1, and B7 in a variety of KSHV-infected lymphoid cells, rendering them more visible to the immune system (25, 26). A phase I/II trial of pomalidomide was initiated by our group in 2012. The initial report of the first 22 participants demonstrated safety and activity in both HIV-infected and uninfected participants with KS (22). Here, we provide data on all 28 participants, describe long-term outcomes, and summarize the activity (including the benefit of a second course of pomalidomide) and duration of response of pomalidomide in KS.

Patients and Methods

Study population

This single-center study (NCT01495598) opened in 2012. This protocol was approved by the NCI Institutional Review Board. All enrolled participants gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. Eligible participants were HIV-infected or uninfected adults with pathologically confirmed KS with at least five measurable cutaneous KS lesions. To isolate the effect of pomalidomide on KS from those who may experience a response to ART alone, participants with HIV had to be receiving ART at the time of entry and either demonstrate KS progression despite HIV suppression and ART for ≥2 months or stability of KS lesions despite ART for ≥3 months. There was no $CD4^+$ T-cell count eligibility requirement. All participants required an absolute neutrophil count (ANC) ≥1,000 cells/μL, hemoglobin ≥10 g/dL, platelets ≥ 75,000 cells/μL, liver function tests (serum alanine aminotransferase and aspartate aminotransferase) ≤2.5 times of upper limit of normal, and creatinine clearance > 60 mL/minute. All participants were required to have an Eastern Cooperative Oncology Group performance status ≤ 2 and life expectancy ≥ 6 months. Cisgender female participants were required to either abstain from heterosexual intercourse or begin two acceptable methods of birth control at the same time at least 28 days prior to initiating pomalidomide on the study, and have pregnancy testing within 24 hours before starting study treatment and also over the course of treatment. All males (even those who had a vasectomy) were required to use a latex condom during sexual intercourse with a person of childbearing potential. Exclusion criteria included individuals with symptomatic visceral KS, specific procoagulant disorders, or previous thromboembolic disease. Individuals with a history of malignant tumors who were not in remission for ≥1 year were excluded, except for resected basal cell carcinoma or *in situ* squamous cell carcinoma.

Study design

Participants received 5 mg of oral pomalidomide for 21 days of a 28-day cycle. All participants were counseled on the teratogenic effects of pomalidomide and were enrolled onto a risk evaluation and mitigation strategy (REMS) drug safety program when it was incorporated during the study (Amendment F: 01/2014). Aspirin 81 mg was provided daily as thromboprophylaxis with treatment and continued for 30 days beyond the last dose of pomalidomide on the study. The initial phase I portion of the study allowed for a dose deescalation of pomalidomide for prespecified dose-limiting toxicity (DLT) criteria. However, patients did not experience any DLTs at 5 mg of pomalidomide, and this dose was used for all participants on the study.

Treatment cycles continued if the following laboratory criteria were met: ANC ≥ 1,000 cells/μL, hemoglobin ≥ 10 g/dL, and platelets ≥ 50,000 cells/μL. If these thresholds were not met, or in the event of febrile neutropenic or severe infection, pomalidomide was held until resolution. Daily granulocyte colony stimulating factor (GCSF) was recommended for ANC < 1000 cells/μL. For ANC <500 cells/μL, therapy was held and GCSF was required. Pegylated GCSF was not used. Opportunistic infection prophylaxis was started in accordance with guidelines (27). Pomalidomide was initially administered for 24 weeks unless discontinued earlier for toxicity, pregnancy, complete remission (CR), progressive disease (PD), patient preference, inability to maintain HIV control, or nonadherence. Participants deriving benefit could be treated for an additional 24 weeks (48 weeks total). KS tends to wax and wane, and the protocol allowed patients to continue treatment on study even if they met the criteria for PD if the progression was not clinically significant. During the study (Amendment D: 01/2013), an option for a second course of pomalidomide was introduced; participants who had clinical response (complete or partial response) or other clinical benefit with the initial course of pomalidomide and still met the study eligibility criteria were able to receive a second course of pomalidomide if they had progression of KS during the follow-up period. Participants were required to keep a daily diary of pomalidomide administration, including the time of administration and any clinical toxicities as an *aide memoire*.

Response assessment and adverse event (AE) assessment

KS responses were evaluated every cycle and assessed using modified AIDS Clinical Trials Groups criteria as previously described (22, 28). Responses had to be sustained for 4 weeks, and at least 8 weeks of therapy (or two cycles) were required to assess

responses. Response assessments included measurement of the sum product of the diameters of five indicator lesions, and a count of the total number of lesions and nodular lesions (for patients with 50 or more lesions, the lesion counts were assessed in one to three representative areas). In short, a CR required clinical resolution of all lesions and tumor-associated edema; participants with some residual pigmentation required biopsy confirmation of a representative pigmented area demonstrating no residual malignant cells (i.e., KSHV-infected spindle cells). Patients who had resolution of all lesions except for some residual pigmentation but who did not have a biopsy of a representative pigmented area were assessed as having a clinical CR (cCR). A partial response (PR) required a ≥50% decrease in the number of lesions and/or number of nodular lesions and/or sum of the product of the diameters of the five indicator lesions, no new lesions in uninvolved regions, and not meeting criteria for PD. PD involved a 25% or greater increase in total lesions, nodular lesions, or area of the five indicator lesions; stable disease (SD) was assessed for patients who did not meet criteria for CR, PR, or PD. Best response was captured for each participant. AEs were monitored during each cycle and 4 weeks beyond completing therapy and assessed using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Correlative assays

Correlative assays evaluating select cytokines and growth factors that are either important in KS pathogenesis or potentially affected by treatment were performed on stored specimens at baseline, after 4 and 8 weeks of treatment, at the time of best response, and at end of treatment. Cytokines were evaluated using MSD 96-Well Multiarray Proinflammatory 7-plex assay (MesoScale Discovery). KSHV viral load (VL) in peripheral blood mononuclear cells was assessed by quantitative real-time polymerase chain reaction (PCR) as previously described (29).

Statistical considerations

The primary objective for the study was to assess the safety, tolerability, and pharmacokinetics of pomalidomide for patients with KS. For the phase II component of the study, the objective

Table 1. Baseline characteristics: participant demographics at baseline for all participants and by HIV status.

Baseline characteristics	All patients $N = 28$, (%)	HIV positive $N = 18$, (%)	HIV negative $N = 10$, (%)
Age, median (IQR), years	52.5 (44.9–61.3)	50.8 (42.4–57.1)	61.3 (51.4–66.4)
Sex			
Cisgender male	27 (96)	18 (100)	9 (90)
Transgender female	1 (4)	—	1 (10)
Race			
White	20 (71)	12 (67)	8 (80)
Black	4 (14)	4 (22)	0
Asian	1 (4)	0	1 (10)
Unknown	3 (11)	2 (11)	1 (10)
Ethnicity			
Hispanic/Latino	4 (14)	3 (17)	1 (10)
Not Hispanic/Latino	24 (86)	15 (83)	9 (90)
ECOG			
0	14 (50)	9 (50)	5 (50)
1	14 (50)	9 (50)	5 (50)
KS characteristics			
Time from KS diagnosis, median (range), years	4.5 (1–27)	4.3 (1–20)	5.1 (1–27)
KS staging			
T0	7 (25)	6 (33)	1 (10)
T1	21 (75)	12 (67)	9 (90)
>50 KS lesions, *n* (%)	3 (11)	2 (11)	1 (10)
Time since last KS therapy[a], median (range), months	4.7 (1–30)	1.5 (1–30)	5.9 (4.7–19.3)
Prior KS therapy			
Prior systemic therapy	22 (79)	15 (83)	7 (70)
Liposomal doxorubicin	14 (50)	11 (61)	3 (30)
Paclitaxel	8 (28)	5 (28)	3 (30)
Radiotherapy	9 (32)	5 (28)	4 (40)
Immunomodulatory therapy	3 (11)	2 (11)	1 (10)
Interferon alpha	5 (18)	3 (17)	2 (20)
Local therapy	10 (36)	6 (33)	4 (40)
CD4 T-cell count and HIV characteristics			
Time from HIV diagnosis, median (range), years	7.4 (0.8–24.8)	7.4 (0.8–24.8)	—
CD4 T-cell count, cells/μL (median, IQR)	492 (349–730)	420 (306–488)	777 (720–996)
CD4 T-cell count < 200 cells/μL, *n* (%)	3 (11)	3 (17)	0 (0)
HIV viral load, copies/mL (median, IQR)	<50 (<50 to <50)	<50 (<50 to <50)	—
HIV viral load < 50 copies/mL, *n* (%)	16 (57)	16 (88)	—
On antiretroviral therapy (ART) (%)	18 (64)	18 (100)	—
Time on ART, median (range), years	3.9 (0.8–19)	3.9 (0.8–19)	—

[a]Time since prior therapy does not include antiretroviral therapy.

was to determine the overall response rate (ORR; comprising CRs and PRs) for all participants treated with pomalidomide at 5 mg 21/28 days. These response rates were assessed overall and separately evaluated by HIV status. The cohorts for participants with HIV and those who were HIV negative were intended to have 15 and 10 participants, respectively, and 3 additional participants were permitted to be enrolled, to have at least 80% power to rule out a 10% response rate and target a 40% response rate (Amendment B: 05/2012). Progression-free survival (PFS), defined as time from day 1 of pomalidomide therapy until progression from the best response on treatment, was estimated using the Kaplan–Meier method. Among responders, duration of response was defined as the time from response to progression from best response on treatment. Changes in immunologic and virologic parameters were evaluated by a Wilcoxon signed rank test, and values between responders and nonresponders were compared using a Wilcoxon rank sum test. Given the multiple comparisons undertaken, with varying degrees of dependence or independence of the parameters and the exploratory nature of the analyses, $P < 0.005$ was considered statistically significant while $0.005 < P < 0.05$ was considered evidence of a strong trend. All P values are two-tailed and reported without adjustment for multiple comparisons.

Results

Patient characteristics

Between 2012 and 2018, 28 participants (27 cisgender males and 1 transgender female) with symptomatic KS were enrolled (**Table 1**). Eighteen participants (64%) were HIV positive, and 10 participants (36%) were HIV negative. Twenty participants (71%) had T1 stage KS with tumor-associated edema. Among those with HIV infection, the median time from HIV diagnosis to study entry was 7.4 years [interquartile range (IQR): 0.8–24.8 years], and median duration of ART was 3.9 years (range, 0.8–19 years). The median $CD4^+$ T-cell count for participants with HIV was 420 cells/μL (IQR: 315–485 cells/μL), and 16 participants with HIV (88%) had an HIV VL of <50 copies/mL. Twenty-two participants (79%) received prior systemic therapy for KS: 83% in the HIV-positive group and 70% in the HIV-negative group. Three participants had received prior lenalidomide therapy (one received both thalidomide and lenalidomide). The median time from last KS treatment (excluding ART) to the initiation of study therapy for all participants was 4.7 months.

Treatment responses

Among all participants in the study, 20 participants had a CR, cCR, or PR; the ORR was 71%: [95% confidence interval (CI) 51%–87%; **Table 2**]. Twelve of 18 HIV-positive participants (67%; 95% CI, 41%–87%), and 8 of 10 HIV-negative patients (80%; 95% CI, 44%–97%) obtained a partial response or better. Three participants, all with HIV, had a CR, and one HIV-negative patient had a cCR. One of the participants assessed by study investigators to have a CR had a biopsy of a residual pigmented area demonstrating some KSHV latency-associated nuclear antigen (LANA)-positive endothelial cells; however, there were no malignant (spindle) cells, PCR was negative for KSHV, and after extensive review, this was classified as a CR. The participant with a cCR had resolution of disease except for residual pigmentation but declined a biopsy to confirm CR. Among the four CRs or cCR, the median time to achieve this response was 6.3 months. The median duration of response for all responses was 9.2 months; 11.3 months in those with HIV and 6.3 months in those without HIV (**Table 2**). Among 16 participants (9 of whom had HIV coinfection) who experienced a PR as a best response, this was seen within 2 months of initiation of therapy. One participant with a history of prior chemotherapy experienced a PR during study treatment and continued ART after study treatment cessation. In the follow-up period, this participant had no additional KS therapy and noted resolution of KS lesions that was confirmed with biopsy 2 years after initial treatment. In 5 participants who saw no change in their KS lesions and had SD or among those with progressive KS, this response failure to respond was seen early, within one month of treatment initiation, suggesting that participants whose KS did not initially respond did not have late responses with continued pomalidomide treatment. Of note, one participant with HIV who experienced SD KS response, fatigue, and sweats after three cycles of study therapy was diagnosed with KSHV-associated multicentric Castleman disease (MCD) on a lymph node biopsy. Treatment was discontinued and MCD-directed therapy was initiated with rituximab and liposomal doxorubicin.

Table 2. Responses by HIV status, time to response, and duration of response.

Group	Overall response (CR + PR), *n* (%)	CR/cCR, *n* (%)	PR, *n* (%)	SD, *n* (%)	PD, *n* (%)	Time to response[c], median (IQR), months	Median duration of response[d], months (95% CI)
First course of pomalidomide							
All participants ($N = 28$)	20 (71)	4[a] (14) (includes 1 CCR)	16[b] (57)	5 (18)	3 (11)	2.5 (1.1–4.2)	9.2 (5.0–49.8)
HIV positive ($N = 18$)	12 (67)	3[a] (17)	9[b] (50)	3 (17)	3 (17)	2.2 (1.0–3.7)	11.3 (3.9–not estimable)
HIV negative ($N = 10$)	8 (80)	1 (cCR) (10)	7 (70)	2 (20)	0 (0)	2.6 (1.5–4.2)	6.3 (3.9–21.4)
Second course of pomalidomide							
All participants ($N = 4$)	2 (50)	—	2 (50)	2 (50)	—	3.1 (NA)	25.9 (NA)
HIV positive ($N = 3$)	2 (67)	—	2 (67)	1 (33)	—	3.1 (NA)	25.9 (NA)
HIV negative ($N = 1$)	—	—	—	1 (100)	—		

[a]One participant assessed as having a CR had some residual pigmentation and a biopsy of a representative lesion that showed some residual cells with KSHV latency-associated nuclear antigen (LANA). PCR was negative for KSHV. Moreover, he had no spindle cells evident on biopsy, and thus met the criteria for a CR.
[b]One participant with HIV had a PR at the end of pomalidomide treatment and continued ART. This participant had no recurrence of KS in the follow-up period and a biopsy of a representative lesion 2 years after treatment cessation did not show any evidence of KS.
[c]Time to response was calculated from on-study date until date of response, among participants with a PR, CR, or cCR.
[d]Duration of response was calculated using the Kaplan–Meier method from date of response to date of progression, censoring at date last followed, among participants with a PR, CR, or cCR.

For all participants receiving the first course of therapy, median PFS was 10.2 months (95% CI, 7.6–15.7 months; Supplementary Fig. S1). The median PFS among participants with HIV was 10.3 months (95% CI, 4.8–21.9 months), and among those without HIV, it was 9.4 months (95% CI, 6.0–26.0 months); there was no difference in median PFS by HIV status (**Fig. 1A**; log-rank $P = 0.43$). Three participants with a PR and 2 with a CR had long-term responses with no further requirement for specific KS therapy after more than 3 years of follow-up (**Fig. 1B**).

Four participants (3 with HIV) received a second course of pomalidomide at the time of KS progression, within 12 months of treatment cessation. Two of these participants had a PR during the second course; one of these had a prior PR and one had a CR in the first course of treatment (**Table 2**; **Fig. 1B**). The other 2 participants had SD during the second course of therapy, of whom one had prior cCR and one had a PR in the first course.

Adverse events

Hematologic toxicities, such as leukopenia, neutropenia, and lymphocytopenia, were most common AEs seen in all participants within the study. Episodes of anemia did not require transfusions (**Table 3**). One participant had grade 2 neutropenia at baseline, and subsequently had grade 4 neutropenia during the study that resolved within 28 days. A second participant had grade 4 neutropenia during the second course of treatment with pomalidomide that resolved and did not recur during subsequent cycles. Another participant had grade 4 neutropenia within 2 weeks of initiating pomalidomide that investigators assessed as not attributable to pomalidomide. At cycle 7, this participant experienced febrile neutropenia requiring hospitalization that resolved with antibiotic therapy. One participant with HIV-negative KS experienced a widespread petechial rash and thrombocytopenia during cycle 6 of treatment. A skin biopsy confirmed leukocytoclastic vasculitis, and pomalidomide was discontinued. The participant received a tapering course of oral steroids for grade 3 vasculitis over 3 months, which led to resolution of these symptoms. However, due to evidence of PD following the course of steroids, this participant required additional chemotherapy treatment.

Other common toxicities included acneiform rash, fatigue, and constipation. Participants received topical hydrocortisone and antihistamines for the acneiform rash, with resolution in all cases during subsequent cycles. Four participants described intermittent memory impairment within the first six cycles of therapy. Two participants elected to stop study therapy due to neuropsychiatric effects (one with an exacerbation of preexisting anxiety and another due to his perception of memory impairment). Following treatment cessation, the participant with memory impairment did report improvement and

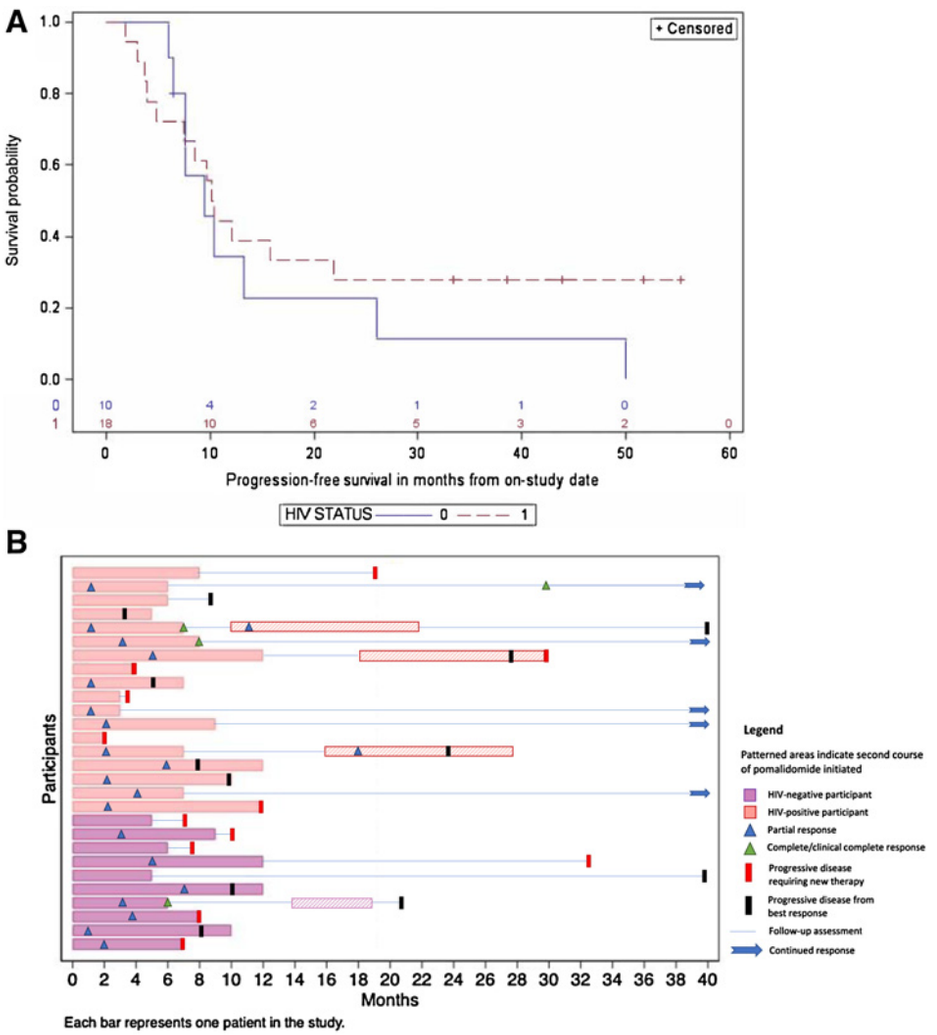

Figure 1

Patient outcomes on study. **A,** PFS by HIV status, log-rank $P = 0.43$. **B,** Swimmers' plot to represent treatment response in all participants. Areas of color denote periods of treatment with pomalidomide.

Table 3. Adverse events: selected adverse events that are possibly, probably, or definitely attributed to pomalidomide in 28 participants. Denominator for total number of events for a specific grade.

	Grade 1		Grade 2		Grade 3		Grade 4	
	Events = 406		Events = 141		Events = 43		Events = 4	
Toxicity among 28 patients	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Low white cell count								
Events	62	15	19	14	1	2		
Patients	21	75	10	36	1	4		
Febrile neutropenia								
Events					1	2		
Patients					1	4		
Neutropenia								
Events	51	13	71	50	31	72	4	100
Patients	24	86	26	93	14	50	3	11
Lymphocytopenia								
Events	21	5	2	1				
Patients	13	46	2	7				
Anemia								
Events	34	8	4	3				
Patients	16	57	4	14				
Thrombocytopenia								
Events	28	7						
Patients	16	57						
Fatigue								
Events	39	10	3	2				
Patients	17	60	2	7				
Infection								
Events			7	5	1	2		
Patients			7	25	1	4		
Constipation								
Events	31	8	3	1				
Patients	18	64	3	11				
Nausea								
Events	8	2						
Patients	10	36						
Elevated ALT								
Events	14	3						
Patients	7	25						
Impaired concentration								
Events	6	1	1	<1				
Patients	3	11	1	4				
Depression								
Events	1	<1	1	<1				
Patients	1	4	1	4				
Hypothyroidism								
Events	3	<1	3	2				
Patients	3	11	3	11				
Rash								
Events	39	10	6	4	2	5		
Patients	18	64	6	21	1	4		
Vasculitis								
Events					1	2		
Patients					1	4		

resolution during the follow-up period. There were no deaths on study attributable to pomalidomide.

Cytokine, viral, and immunologic correlatives

Among all participants, there was a net increase in IL4, IL8, and IL13 at week 4, following the first cycle of treatment (**Table 4**; **Fig. 2**; Supplementary Fig. S2). Additionally, there was evidence of trends toward increases in IL6, IL10, and TNFα within the same period. From baseline to 8 weeks, or two cycles of treatment, IL4, IL8, and IL13 remained elevated. At the end of treatment, there was an increase in IL4 from baseline and a trend toward increased IL6 and IL13 and decreased IFNγ from baseline. There were differences in the IL6 levels at baseline between responders as compared with nonresponders. IL6 levels were higher among nonresponders at baseline as compared with responders (median 2.7 pg/mL vs. 1.5 pg/mL, $P = 0.004$; Supplementary Table S1). At the time of a best response, among nonresponders (who experienced SD or PD), there was also a trend toward higher IL6 as compared with responders (median

Table 4. Cytokines $CD4^+$, $CD8^+$, $CD19^+$, and viral load changes: Change in cytokines and immunologic and viral markers from baseline to 4 weeks, 8 weeks, and at the end of treatment.

	Baseline	Change from baseline to 4 weeks			Change from baseline to 8 weeks			Change from baseline to end of treatment		
	Median (IQR)	Median	IQR	*P* value	Median	IQR	*P* value	Median	IQR	*P* value
Cytokines pg/mL										
IFNγ	10.4 (7.9–16.1)	−0.3	(−4.7 to 1.4)	0.19	−0.4	(−7.4 to 4.5)	0.72	−2.4	(−5.3 to 55.1)	0.03
IL4	0.06 (0.06–0.06)	0.07	(0.02–0.1)	<0.0001	0.1	(0.04–0.2)	<0.0001	0.06	(0.001–0.1)	<0.0001
IL6	2.7 (1.7–3.4)	0.4	(−0.04 to 1.8)	0.005	0.3	(−0.3 to 1.1)	0.06	0.6	(−0.3 to 5.8)	0.007
IL8	42.5 (26.4–100.1)	71.9	(5.3–163.1)	0.0003	64.8	(−0.2 to 233.1)	0.0002	47.5	(−9.1 to 121.1)	0.01
IL10	0.7 (0.7–1.9)	0.1	(−0.1 to 1.4)	0.03	−0.03	(−0.2 to 0.4)	0.91	−0.05	(−0.3 to 0.2)	0.64
IL12	0.2 (0.1–0.4)	0.02	(−0.08 to 0.09)	0.70	0.00	(−0.07 to 0.09)	0.59	0.03	(−0.07 to 0.14)	0.26
IL13	0.1 (0.1–0.7)	0.7	(0.03–1.9)	0.0008	0.9	(0.0–1.7)	<0.0001	0.6	(−0.02 to 1.3)	0.007
TNFα	2.1 (2.1–2.9)	0.3	(−0.09 to 0.8)	0.005	0.5	(0.1–0.8)	0.007	0.06	(−0.3 to 0.4)	0.46
IP-10	1,169.1 (716.9–1,597.1)	76.5	(−214.5 to 239.3)	0.42	18.4	(−271.7 to 216.6)	0.85	−73.3	(−335.7 to 127.8)	0.16
Immune and viral markers										
$CD4^+$, cells/μL	376.5 (290.5–648.5)	66.5	(−77.5 to 221)	0.07	37	(−57.0 to 176.0)	0.13	−54	(−178.5 to 91.5)	0.15
$CD4^+$, cells/μL among HIV^+ participants	420.5 (306–488)	72	(−29 to 257)	0.03	37	(−15 to 291)	0.06	−14	(−79 to 132)	0.79
$CD8^+$, cells/μL	423 (336.5–701.5)	104.5	(−76.5 to 257)	0.03	115	(−19 to 288)	0.008	73	(−38.5 to 194.5)	0.12
$CD8^+$, cells/μL among HIV^+ participants	738.5 (431–1,008)	198	(−20 to 414)	0.02	129	(1 to 430)	0.02	75	(−102 to 295)	0.36
$CD19^+$, cells/μL	100 (82–139.5)	−40	(−73 to −3.5)	0.002	−55	(−123 to 5)	0.0002	−75	(−124.5 to −49.5)	<0.0001
KSHV viral load, copies/PBMC	0 (0–81.5)	0	(0–136)	0.13	0	(0–0)	0.65	0	(0–0)	0.32
HIV VL[a], copies/mL	<50 (<50 to <50)	0	(0–0)	0.56	0	(0–0)	0.65	0	(0–0)	0.56

[a]The lower limit of detection for HIV VL is <50 copies/mL.

13.8 vs. 1.8 pg/mL, $P = 0.02$). There was also a trend toward higher IL10 levels among nonresponders as compared with responders both at baseline and at best response (Supplementary Table S1; Supplementary Fig. S2). There were no differences between HIV-infected or uninfected patients in cytokine levels at baseline or changes from baseline to either cycle 2 or end of treatment.

Over the course of the study, in the full cohort of 28 patients, we did not see a significant increase in the $CD4^+$ T-cell count from baseline to 4 weeks, 8 weeks, or end of treatment among all participants (**Table 4**). However, among participants with HIV, there was a trend to increased $CD4^+$ T-cell count from baseline to 4 weeks ($P = 0.03$), which was not evident 8 weeks after initiation of treatment. There was a trend toward increased $CD8^+$ T-cell counts from baseline to 4 weeks and 8 weeks for all participants and in those with HIV; however, this change did not persist at the end of treatment. KSHV and HIV VLs were unchanged throughout the course of the study. Furthermore, both the immune and viral markers were not different among those with and without a response to therapy.

Long-term outcomes in follow-up period

In the follow-up period, among all participants, 11 participants (5 with HIV) were administered additional chemotherapy for progressive KS (**Fig. 1B**). In addition to one participant who had a diagnosis of MCD after three cycles of study treatment, 3 other participants with HIV were diagnosed with other KSHV-associated disorders in the follow-up period. This included a participant diagnosed with primary effusion lymphoma (PEL) 15 months after the study. Despite multiple therapies, this patient died of PEL. Two participants had worsening KS with signs and symptoms of excess inflammatory cytokines. In one case, neither MCD nor PEL was diagnosed, and this participant was assessed as having KSHV-inflammatory cytokine syndrome (KICS; refs. 29, 30), which led to his death. The other patient died during subsequent treatment with pembrolizumab from KSHV-associated polyclonal B-cell lymphoproliferation, as was previously reported (31).

Four participants were diagnosed with other malignancies not related to KSHV in the follow-up period. One HIV-negative participant with idiopathic $CD4^+$ T-cell lymphocytopenia was diagnosed with Hodgkin lymphoma 12 months after therapy with a favorable outcome following combination chemotherapy. Three participants with HIV were diagnosed with squamous cell carcinoma (involving the bladder, anus, or skin). The participant diagnosed with anal cancer subsequently died of metastatic disease.

Discussion

In this study, we have shown that pomalidomide administered at 5 mg orally per day is safe and active against KS in participants with or without HIV. We previously described the activity of pomalidomide in the first 22 patients on this trial (22). Among all 28 participants, the response rate was 71% and the median PFS was 10.2 months. Four participants received a second course of therapy, yielding a PR in 2 participants. Based on the results of this study, the FDA approved pomalidomide as first-line therapy for patients with KS without HIV infection and as initial KS-specific therapy for patients with HIV whose KS did not respond to ART alone (32).

This clinical trial builds on previous work demonstrating the activity of cereblon-binding immunomodulatory agents on KS (21, 33). The original impetus was an *in vitro* study showing that thalidomide had antiangiogenic activity; this was proposed as the mechanism for its teratogenic effects (20). In a clinical trial done before the widespread

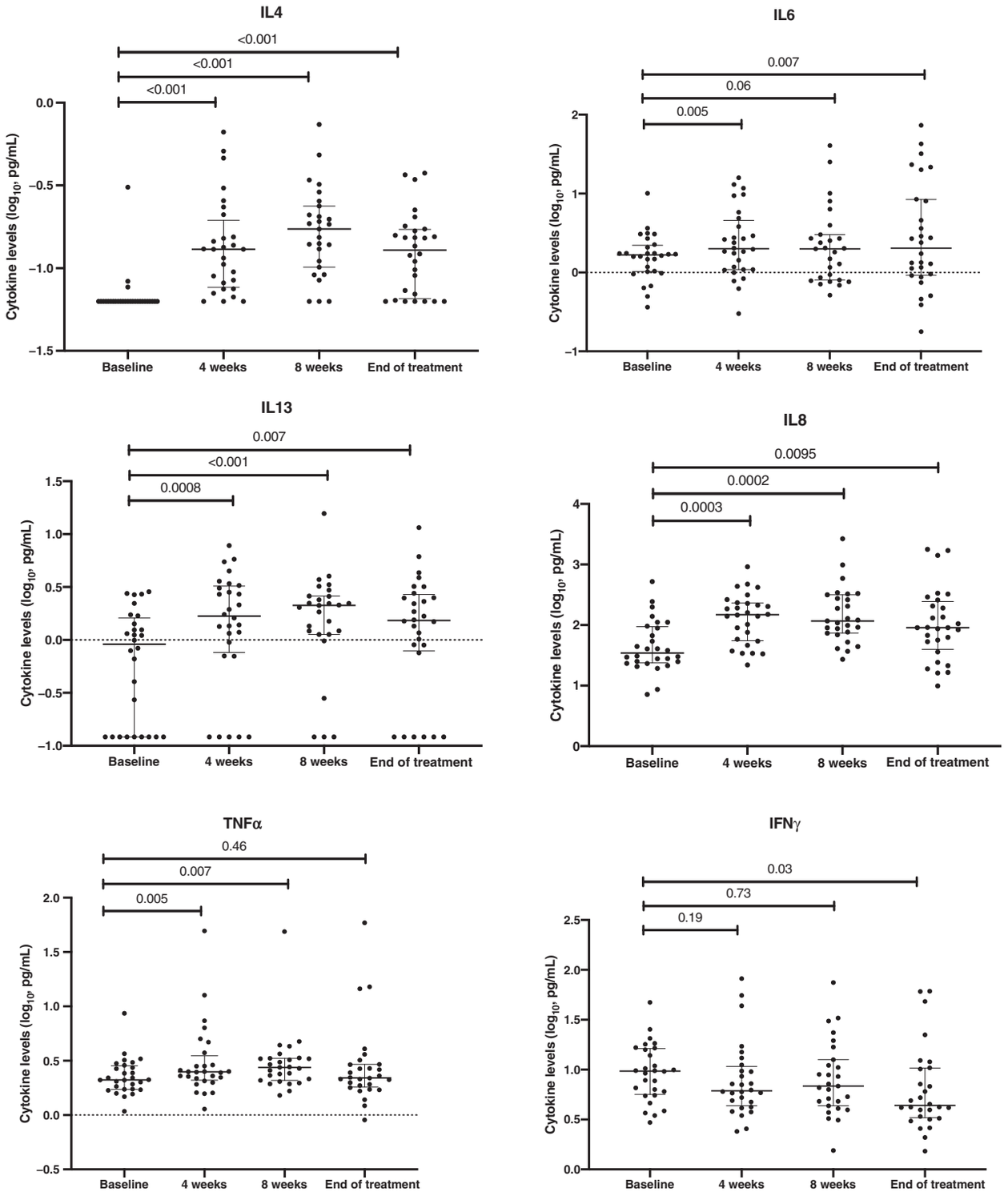

Figure 2
Changes in selected inflammatory cytokines over time in all participants.

use of three-drug combination ART, a high dose of thalidomide was shown to yield a response rate of 47%; however, the toxicity profile limited its use. Pomalidomide is an analogue of thalidomide developed to have a greater activity and less systemic toxicity, and as seen in the present study, it is effective against KS at doses that are generally well tolerated. Another cereblon-binding immunomodulatory drug, lenalidomide, demonstrated activity against KS with a response rate of 40% at 48 weeks using the ACTG criteria (34).

In the current study, the response rates did not differ by HIV status, with 67% response rates among participants with HIV and 80% among those without HIV. Among participants with HIV, the median time on antiretroviral therapy at entry was 3.9 years, highlighting the persistence of KS despite ongoing well-controlled HIV infection. It is noteworthy that 22 of the participants (79%) had had prior systemic therapy, and 20 of the participants (71%) had poor risk (T1) KS. The response rate of 67% among participants with HIV is comparable with that seen in previous studies of paclitaxel and liposomal doxorubicin in HIV-associated KS during the early ART period (16, 18, 35, 36). It is also similar to the response rate of 58% observed in a recent study of paclitaxel and ART (A5263/AMC-066) conducted in resource-limited settings (37). The median PFS among participants with HIV, which was determined from entry to progression from best response, was 10.3 months. This is slightly less than the 64% PFS seen at 48 weeks in patients on paclitaxel in the A5263/AMC-066 trial; however, comparisons between HIV-associated KS studies are difficult due to differences in stage, prior therapy (the A5263/AMC-066 trial was in treatment-naïve participants), and ART regimens. It is noteworthy that 60% of all participants in the follow-up period in this study did not require additional systemic therapy for KS.

The majority of participants experienced hematologic toxicities; in addition, gastrointestinal symptoms, fatigue, and rash were also commonly seen. One participant experienced severe rash and vasculitis that was possibly attributable to pomalidomide and responded to a long course of steroid therapy. Study participants experiencing maculopapular rashes were successfully treated with hydrocortisone and improved over time with subsequent cycles. No thrombotic events or complications were noted from daily thromboprophylaxis. Though there were no cisgender female participants in the study, all participants received counseling at every visit about the teratogenic effects of pomalidomide. The toxicity profile and mechanism of action of pomalidomide is substantially different from that of liposomal doxorubicin, which is commonly used in KS, and our group is exploring a study of the two agents used in combination in severe KS (NCT02659930). With regard to secondary malignancies, none of the participants developed myelodysplastic syndromes or myelogenous leukemia, as was previously observed in some individuals treated with pomalidomide for multiple myeloma (38). However, 4 participants in this study did develop new malignancies, three of which are a part of the spectrum of cancers impacting PLWH or other forms of immunosuppression; none were assessed as being likely to be related to pomalidomide (2, 39).

There are several mechanisms by which pomalidomide may work in KS, but the principal mechanism of action remains elusive. Pomalidomide has been shown to have multiple biological activities that largely derive from its binding to cereblon, and one or more of these could be responsible for the observed activity against KS. In addition to its antiangiogenic effects, pomalidomide has been reported to enhance T-cell responses, and increased cytotoxic T-cell activity may account for some of its activity. We noted a trend toward increases in $CD8^+$ T cells from baseline to 4 and 8 weeks among all participants, and among participants with HIV, we observed a trend toward increased $CD4^+$ and $CD8^+$ T-cell counts from baseline to 4 weeks. Also, pomalidomide has been shown to enhance NK activity, which is believed to play an important role in the control of herpesvirus-infected cells. Our group has shown that in PEL cell lines, pomalidomide prevents KSHV-induced downregulation of immune surface markers that are essential for immune recognition, including MHC-1, ICAM-1, and B7-2 (CD86; refs. 25, 26). However, it is unclear at this time if this occurs in KS.

With regard to cytokine changes, it is not obvious how the changes observed would promote an anti-KS response. One of the most substantial changes was an increase in levels of IL8. IL8 is associated with several cancer subtypes, and increases in IL8 are often associated with worse cancer outcomes. KSHV encodes a latently expressed gene, K13, which transcriptionally upregulates IL8, and this may have a role in angiogenesis and KS pathogenesis (40–42). There is evidence that IL6 is involved in KS pathogenesis (43, 44) and is often elevated in other KSHV-associated disorders that occur in tandem with KS (45, 46). In this study, IL6 levels increased during pomalidomide treatment. However, the higher IL6 levels at baseline among participants who did not respond suggest that this may be used as a predictive marker in future studies. Interestingly, serum IL6 levels also increased more in participants who did not respond as compared with those who responded, it is unclear if this increase is simply a result of the failure of KS to respond or is involved in the varying drug effect causing the difference in response. Additional studies will be needed to further unravel the mechanisms by which pomalidomide works against KS.

In summary, this study of pomalidomide demonstrates its activity in both PLWH and those without HIV, and based on this study pomalidomide received accelerated approval by the FDA for the treatment of HIV^+ and HIV^- KS. Pomalidomide is an oral agent requiring fewer resources than infusional chemotherapy agents and may be useful in resource-limited settings with a high incidence of KS, although risk mitigation is required to avoid teratogenicity. The NCI-funded AIDS Malignancy Consortium has initiated a trial of pomalidomide to assess its feasibility in this region (NCT03601806) and is also planning a confirmatory study within the United States to determine the activity and safety in a larger cohort of participants.

Authors' Disclosures

R. Ramaswami reports non-financial support from Celgene/BMS during the conduct of the study, as well as non-financial support from Merck/EMD-Serono, Eli Lilly, CTI BioPharma, and Janssen Pharmaceuticals outside the submitted work. M.N. Polizzotto reports a patent for Immunomodulatory Compounds for KSHV-Associated Malignancies issued to US Federal Government. K. Lurain reports other support from BMS-Celgene during the conduct of the study; K. Lurain also reports other support from EMD-Serono, as well as non-financial support from Merck, CTI BioPharma, Janssen, Miltenyi-Lentigen, and Eli Lilly outside the submitted work. K.M. Wyvill reports non-financial support from Celgene during the conduct of the study; in addition, K.M. Wyvill has US patent 6,423,308: Treatment of Kaposi's sarcoma with IL12 issued and US patent 6,509,321: Treatment of Kaposi's sarcoma with IL12 issued. P. Goncalves reports other support from Regeneron Pharmaceuticals Inc outside the submitted work. D. Whitby reports patent 10,001,483 555 issued to Celgene Corp. T.S. Uldrick reports non-financial support and other support from Celgene during the conduct of the study; T.S. Uldrick also reports other support from Roche, Merck, and Regeneron, as well as personal fees from Seattle Genetics and AbbVie outside the submitted work. In addition, T.S. Uldrick has patent 10,001,483 issued to Celgene. R. Yarchoan reports other support from Celgene/Bristol Myers Squibb during the conduct of the study, as well as other support from EMD Serono, Eli Lilly, CTI BioPharma, and Janssen Pharmaceuticals outside the submitted work. R. Yarchoan has a patent for use of pomalidomide to treat KSHV-induced B-cell tumors issued and a patent for use of IL12 to treat KS issued; in addition, R. Yarchoan's

spouse is coinventor on patents related to internalization of target receptors, on KSHV viral IL6, and on the use of calreticulin and calreticulin fragments to inhibit angiogenesis; all are assigned to DHHS. No disclosures were reported by the other authors.

Authors' Contributions

R. Ramaswami: Data curation, formal analysis, visualization, writing–original draft, writing–review and editing, caring for patient participants. **M.N. Polizzotto:** Conceptualization, data curation, writing–review and editing, caring for patient participants. **K. Lurain:** writing–review and editing, caring for patient participants. **K.M. Wyvill:** Data curation, project administration, writing–review and editing, caring for patient participants. **A. Widell:** Data curation, project administration, writing–review and editing, caring for patient participants. **J. George:** Formal analysis, writing–review and editing, caring for patient participants. **P. Goncalves:** Writing–review and editing, caring for patient participants. **S.M. Steinberg:** Formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **D. Whitby:** Data curation, formal analysis, investigation, writing–review and editing. **T.S. Uldrick:** Conceptualization, resources, data curation, writing–review and editing, caring for patient participants. **R. Yarchoan:** Conceptualization, resources, data curation, formal analysis, supervision, investigation, visualization, methodology, writing–original draft, writing–review and editing, caring for patient participants.

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