Pomalidomide for Symptomatic Kaposi's Sarcoma in People With and Without HIV Infection: A Phase I/II Study

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ABSTRACT

Purpose

Kaposi's sarcoma (KS) is a multicentric tumor caused by Kaposi's sarcoma-associated herpesvirus. Unmet needs include therapies that are oral, anthracycline sparing, and deliverable in resource-limited settings. We evaluated pomalidomide, an oral immune modulatory agent, in patients with symptomatic KS.

Methods

The primary objectives were to assess tolerability, pharmacokinetics, and activity. Initial dosage level was 5 mg once per day for 21 days per 28-day cycle, with a de-escalated level of 3 mg if not tolerable, and aspirin 81 mg once per day thromboprophylaxis. HIV-infected patients required controlled viremia with either persistent KS despite 3 months of antiretroviral therapy (ART) or progressive KS despite 2 months of ART. Evaluations included tumor response and health-related quality of life (HRQL).

Results

Twenty-two patients were treated; 15 (68%) were HIV infected, 17 (77%) had advanced (T1) disease, and 19 (86%) previous KS therapy excluding ART. All were treated with 5 mg because no dose-limiting toxicities occurred. Over 156 cycles, the grade 3/4 adverse events possibly attributable to therapy were neutropenia (23 cycles, 10 patients), infection (1 cycle), and edema (1 cycle). Sixteen patients responded (73%; 95% CI, 50% to 89%); nine of 15 HIV-infected patients (60%; 95% CI, 32% to 84%) and all seven HIV-uninfected patients (100%; 95% CI, 59% to 100%). Median time to response was 4 weeks (range, 4 to 36 weeks). HRQL showed no impairment during therapy and improved satisfaction with appearance at end therapy ($P = .03$). Significant increases in CD4⁺ and CD8⁺ cells were seen in patients with and without HIV, together with a transient increase in Kaposi's sarcoma-associated herpesvirus viral load at week 4 ($P = .05$).

Conclusion

Pomalidomide is well tolerated and active in KS regardless of HIV status. Responses were rapid, with improved self-reported outcomes, and occurred in advanced and heavily pretreated disease. Correlative studies support, at least in part, an immunologic mechanism of activity.

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INTRODUCTION

Kaposi's sarcoma (KS) is a multicentric tumor caused by Kaposi's sarcoma-associated herpesvirus (KSHV, or human herpesvirus 8).¹ It is characterized by proliferation of KSHV-infected spindle cells and abnormal neovasculation.² KS involves the skin most frequently but may also involve the oral mucosa, lymph nodes, and viscera.² There is a particularly high incidence of KS in sub-Saharan Africa, where HIV and KSHV infection are endemic.^{2,3}

KS is remarkable for its interrelationship with host immunity. It is most common in individuals with altered cellular immunity, including those with HIV, transplant recipients, and the elderly.^{4,5} A decreasing CD4 count is associated with increasing risk of KS in people with and without HIV, and treatment of HIV with antiretroviral therapy (ART) decreases the risk of KS. Patients with KS have decreased KSHV-specific T-cell responses when compared with KSHV-infected individuals without KS.⁶ Increases in KSHV-specific T-cell responses have been observed in patients with HIV-associated KS treated

with ART⁷ and in transplant recipients whose KS regressed with reduced immunosuppression.⁸

In patients with HIV-associated KS, ART is the foundation of therapy^{2,9}; HIV control allows restoration of KSHV-directed cellular immunity, and institution of ART alone can lead to regression of KS in a minority of patients.^{7,10} For patients with HIV-associated KS whose response to ART is incomplete, the most commonly added KS-specific therapies are liposomal anthracyclines and paclitaxel; each is approved by the United States Food and Drug Administration for HIV-associated KS, with response rates ranging from 46% to 76%.¹¹⁻¹³ Therapy in HIV-uninfected patients is less established, but cytotoxics remain a mainstay of therapy. Immune modulatory agents including interferon- α and thalidomide have also been studied in KS, with response rates reported at 35% to 47%^{14,15}; the former is especially used in HIV-uninfected patients, but both are limited by constitutional adverse effects. Limited disease may also respond to local therapies.²

There is a substantial unmet need for novel KS therapies. There exists a lack of effective oral agents; chronic administration of cytotoxic agents is poorly tolerated, in part because of hematotoxicity; and cumulative anthracyclines increase cardiotoxicity risk. The latter considerations are significant because KS commonly recurs and patients often require treatment, at least intermittently, for years.^{2,12} In addition, with the exception of ART, no effective treatment is readily deliverable in resource-limited areas such as sub-Saharan Africa, where the KS burden is the greatest.³

Pomalidomide is an orally available small molecule derivative of thalidomide, with immune modulatory, antiangiogenic, and antiproliferative activities.¹⁶ Thalidomide derivatives were developed with the aim of reducing neurotoxicity and sedation and increasing potency, especially immunomodulation. They act by targeting cereblon, an E3 ubiquitin ligase, leading to degradation of ikaros (IKZF1) and aiolos (IKZF3).^{17,18} Downstream effects include modulation of tumor necrosis factor- α , interleukin-6, and vascular epithelial growth factor (VEGF), and enhancement of CD4⁺ and CD8⁺ T-cell costimulation.

Given the immune modulatory effects of pomalidomide and its lack of predicted interactions with ART and oral availability, together with the activity of thalidomide in KS, we hypothesized that pomalidomide could be safe and useful in treating KS. We therefore conducted a phase I/II study in patients with symptomatic KS regardless of HIV status to explore its tolerability and efficacy.

METHODS

Eligibility

Patients were adults with pathologically confirmed symptomatic KS and at least five evaluable cutaneous lesions. HIV-positive patients had to have been receiving ART with controlled HIV viral load (VL) for ≥ 2 months with progressive KS, or ≥ 3 months without regression, to ensure tolerability of ART and to exclude patients responding to ART alone. Additional requirements included Eastern Cooperative Oncology Group performance status ≤ 2 , life expectancy ≥ 6 months, absolute neutrophil count (ANC) $\geq 1,000$ cells/ μ L, hemoglobin ≥ 10 g/dL, platelets $\geq 75,000$ cells/ μ L, and creatinine clearance > 60 mL/min. There was no CD4⁺ count

criterion. Patients with symptomatic visceral KS, concurrent malignancies not in remission for ≥ 1 year, previous thromboembolic disease, or procoagulant disorders were ineligible.

Design

This was a single-center phase I/II study. Patients received pomalidomide orally for 21 days of a 28-cycle, with aspirin 81 mg once per day as thromboprophylaxis. The phase I portion was designed with an initial dosage level of pomalidomide 5 mg once per day, with a de-escalated level of 3 mg should this not prove tolerable. Because no dose-limiting toxicities occurred at 5 mg, this dose was taken to phase II and therefore, all patients were treated with 5 mg once per day 21 of 28 days.

Subsequent cycles commenced on day 29 as long as ANC was $\geq 1,000$ cells/ μ L, hemoglobin ≥ 10 g/dL, and platelets $\geq 50,000$ cells/ μ L or otherwise held until these thresholds were met. Pomalidomide was held for ANC < 500 cells/ μ L, platelets $< 25,000$ μ L, or severe infection. HIV-infected patients continued baseline ART without adjustment. Prophylaxis for opportunistic infections including *Pneumocystis jiroveci* was administered following current guidelines. Pomalidomide was continued for a maximum of 12 months or was stopped earlier for complete response (CR), progressive disease (PD), unacceptable adverse events (AEs), non-adherence, or patient preference.

Response Assessment

KS responses were evaluated every cycle and were categorized as CR, partial response (PR), stable disease, or PD using modified AIDS Clinical Trials Groups criteria as described previously.¹⁹ To be evaluable for response, completion of two cycles of therapy was required. Evaluations included lesion counts, measurement of the sum product of the diameters of five indicator lesions, assessment of number of nodular lesions, and measurement of limb circumference if tumor-associated edema was present. PR required a $\geq 50\%$ decrease in the number of lesions and/or sum product of the diameters of marker lesions and/or nodularity of lesions, and no new lesions in previously uninvolved areas or criteria for PD. CR required clinical resolution of all lesions and tumor-associated phenomenon, with biopsy confirmation. Both CR and PR had to be sustained for 4 weeks. Best response was evaluated for each patient.

Patient-reported health-related quality of life (HRQL) was evaluated at baseline, after 3 months of therapy, and 1 month after completion of therapy using the Functional Assessment of HIV Instrument (FAHI) supplemented with the three KS-specific questions described previously.^{12,20}

AE Assessment

AEs were monitored during each cycle and 4 weeks after completing therapy, with any continuing AEs observed until resolution. Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.²¹ Lymphocyte subsets, and HIV VL in HIV-infected patients, were evaluated at the end of each cycle.

Pharmacokinetic Assays

Plasma concentrations of pomalidomide were assayed using high-performance liquid chromatography with fluorescence detection, with a lower limit of quantitation of 1 ng/mL, as described.²² A non-compartmental analysis was used to calculate plasma pharmacokinetic parameters (Pharsight, Mountain View, CA). The maximal plasma concentration (C_{MAX}) and time to C_{MAX} were recorded as observed values; the area under the plasma concentration versus time curve (AUC) was calculated using the log-linear trapezoidal method. For day 1 of cycle 1 (C1D1), the AUC extrapolated to infinity was used, unless the percent extrapolated exceeded 25%, in which case AUC to the last quantifiable time point (AUC_{LAST}) was used. The steady-state exposure on day 15 of cycle 1 (C1D15) was calculated using AUC_{LAST}.

Laboratory Assays

Lymphocyte subsets were assessed by fluorescent-activated cell sorting using the BlueOcean platform (Beckman Coulter, Carlsbad, CA). Plasma HIV-1 mRNA was evaluated using an ultrasensitive assay whose sensitivity was 1 viral copy per plasma volume. Briefly, we used a triplex polymerase chain reaction using a modification of a previously reported assay²³ with three primers: one spanning the start codon of *gag*, one in the *gag* coding region, and one internal control. Samples were tested from 6-mL plasma aliquots, with 12 replicants per sample. KSHV VL in peripheral blood mononuclear cells was assessed by quantitative real-time polymerase chain reaction, as described.²⁴

Statistical Considerations

The primary objectives were to determine the safety, tolerability, and pharmacokinetics of pomalidomide in patients with KS. For the phase II component, the primary objective was to determine the overall response rate (ORR, comprising CRs and PRs) for patients treated with pomalidomide at 5 mg 21/28 days. HIV-infected and HIV-uninfected cohorts were evaluated separately and combined. We defined the unacceptable ORR for further development as 10% and a desirable (targeted) ORR as 40%. Up to 10 HIV-negative patients were to be enrolled, with the goal of obtaining at least three responses in those 10 patients; this would have an 83.3% probability of occurring if the true ORR were 40% and a 7.0% probability of occurring if the true ORR were 10%. Up to 15 HIV-positive patients were to be enrolled, with the goal of obtaining at least four responses in those 15 patients; this would have a 90.9% probability of occurring if the true ORR were 40% and a 5.6% probability of occurring if the true ORR were 10%. Progression-free survival, defined as time from day 1 of pomalidomide therapy until progression requiring a change in therapy, was estimated using the Kaplan-Meier method.

Changes in immunologic and virologic parameters were evaluated by a Wilcoxon signed rank test. Exact Wilcoxon rank sum tests were used to compare pharmacokinetic parameters at each time point and differences from baseline. All *P* values were two-tailed and are reported without adjustment for multiple comparisons. HRQL was analyzed using a mixed-model repeated-measures analysis for FAHI and the marginal homogeneity test for KS-specific questions.

RESULTS

Patients

Between January 2012 and September 2014, 22 patients with symptomatic KS were enrolled: 15 (68%) were HIV infected and seven (32%) were uninfected. Clinical characteristics are summarized in Table 1. All were genetically male (one transgender female). For HIV-infected patients at entry, median time receiving ART was 48 months (range, 7 to 227 months); HIV VL < 50 copies/mL (all); and median CD4⁺ count was 378 cells/μL (range, 135 to 732 cells/μL). The cohort was heavily pretreated, with 19 patients (86%) having at least one prior therapy (not counting ART). Advanced (T1) disease by AIDS Clinical Trials Groups criteria²⁵ was also common, being present in 17 patients (77%); this consisted of tumor-associated edema in all. Patients received a median of seven cycles of pomalidomide (range, two to 12 cycles). All were evaluable for response.

Activity

Across all 22 patients, 16 achieved objective tumor responses, for an ORR of 73% (95% CI, 50% to 89%), including four (18%) who achieved CRs (Table 2). Among the 15 HIV-infected patients, nine achieved objective responses (ORR, 60%; 95% CI, 32% to 84%), whereas all seven HIV-uninfected patients achieved objective responses (ORR, 100%; 95% CI, 59% to 100%). Three patients, all HIV infected, had PD on study, including one who became nonadherent to both ART and protocol therapy, progressed, and then was lost to follow-up.

Patients who responded had a decrease in the number of nodular lesions, a decrease in the number of lesions, or both (Figs 1 and 2). Responses were generally rapid, with a median time to first response of 4 weeks (range, 4 to 36 weeks); this is the earliest time point at which response evaluation was performed. Responses occurred in patients who had received previous

Table 1. Patient and Disease Characteristics

Characteristic	All Patients (N = 22)	HIV-Positive Patients (n = 15)	HIV-Negative Patients (n = 7)
Male sex	22 (100)*	15 (100)	7 (100)*
Age, median (range), years	52 (32-74)	49 (32-65)	61 (38-74)
Self-reported ethnicity			
White	17 (77)	10 (66)	7 (100)
African-American	3 (17)	3 (20)	—
Hispanic	2 (9)	2 (13)	—
Advanced (T1) disease	17 (77)	10 (67)	7 (100)
> 50 KS lesions	13 (59)	8 (53)	5 (71)
Prior KS therapy†	19 (86)	13 (87)	6 (86)
Chemotherapy	10 (45)	8 (53)	2 (29)
Radiation therapy	7 (32)	3 (20)	4 (57)
Thalidomide and/or lenalidomide	2 (9)	1 (7)	1 (14)
Interferon	1 (5)	—	1 (14)
Local therapy‡	7 (32)	2 (13)	5 (71)
Time since last KS therapy,§ median (range), months	8 (1-30)	11 (1-30)	7 (1-27)

NOTE. Data are presented as No. (%) unless indicated otherwise. Abbreviation: KS, Kaposi's sarcoma.

*Includes one HIV negative transgender female, genetically male.

†Some patients had multiple prior therapies; antiretroviral therapy is not counted as a prior therapy for HIV-infected patients.

‡Local therapies included topical panretin and local laser therapy.

§For previously treated patients; antiretroviral therapy is not counted as a prior therapy for HIV-infected patients.

Table 2. Objective Responses and Timing of Responses

Group	Patients Enrolled (assessable)	Overall Response (CR + PR), No. (%)	CR, No. (%)	PR, No. (%)	SD, No. (%)	PD, No. (%)	Time to Response, Median (range), Weeks
All patients	22 (22)	16 (73)	4 (18)	12 (55)	3 (14)	3 (14)	4 (4–36)
HIV-positive patients	15 (15)	9 (60)	3 (20)	6 (40)	3 (20)	3 (20)*	8 (4–32)
HIV-negative patients	7 (7)	7 (100)	1 (14)	6 (86)	0	0	4 (4–36)

NOTE. Complete and partial responses are objective tumor responses by modified AIDS Clinical Trial Group Criteria for Kaposi's sarcoma; CR requires pathologic confirmation.

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

*Includes one patient who became nonadherent to antiretroviral therapy and protocol therapy.

KS therapy, including thalidomide or lenalidomide, as well as in patients with advanced disease. Several patients with PRs had substantial disease improvement with complete flattening of lesions (Fig 1). Median progression-free survival was 16.6 months.

Patients receiving pomalidomide also showed a decrease in tumor-associated edema: 10 of 17 patients with edema (59%) had evidence of improvement. In eight, measurements of limb circumference showed at least a 2-cm reduction with therapy. Two additional patients reported substantial subjective improvement: one had decreased pedal pain and one was able to resume wearing closed shoes.

Quality of Life

At baseline, HRQL by FAHI was comparable to recent reports in men with HIV,²⁰ whereas patients commonly reported KS-related edema (63.6%), dissatisfaction with appearance (54.6%), and KS-related pain interfering with work or activities (40.9%; Appendix Table A1, online only). HRQL by FAHI did not decrease during therapy and was stable after completion (all $P > .05$). There was a trend to improved satisfaction with appearance at the 3-month questionnaire (during therapy; $P = .07$) and a significant increase at the end-therapy questionnaire ($P = .03$), with the number of patients reporting little to no satisfaction decreasing from 12 (54.6%) to five (26.3%). Other parameters did not change significantly (Appendix Table A2, online only).

AEs

Pomalidomide was well tolerated, and AEs in both cohorts were consistent with those found in previous studies (Table 3). Common AEs were neutropenia, constipation, anemia not requiring transfusion, fatigue, and rash. These were generally mild and self-limited or resolved after cessation of therapy. There were no unplanned hospitalizations, no episodes of febrile neutropenia, and no thromboembolic events. One patient ceased therapy because of intolerance (exacerbation of pre-existing anxiety).

Three patients developed malignancies after therapy: one HIV-uninfected patient with a poorly characterized immunodeficiency developed an Epstein-Barr virus-associated Hodgkin lymphoma 12 months after therapy, one HIV-infected patient with a history of multicentric Castleman disease and KS developed primary effusion lymphoma 15 months after therapy, and one HIV-infected patient developed a squamous cell skin carcinoma. In addition, one HIV-infected patient manifested multicentric Castleman disease during therapy; review of previous KSHV VLs and C-reactive protein suggested this had been present but unrecognized at enrollment.

Pharmacokinetics

Pharmacokinetic studies were consistent with previous estimates for pomalidomide. Across all analyzed doses (C1D1 and C1D15), half-life was 7.10 ± 2.48 hours, C_{MAX} was 61.21 ± 29.30 ng/mL, and time to C_{MAX} was 2.71 ± 1.73 hours. There was

Fig 1. Individual patient responses to therapy by HIV status and disease characteristics. Waterfall plot showing responses at the individual patient level to pomalidomide therapy. Maximal change in lesion nodularity (left panel) and total number of lesions (right panel) are illustrated; the HIV status and Kaposi's sarcoma characteristics and denoted by the bar color and diamond symbol, respectively

Fig 2. Representative tumor response in a treated patient. Representative response of a left great toe lesion (one of a number present on this patient) to pomalidomide therapy. (A) The nodular lesion is seen at baseline. (B) Complete flattening is seen at the end of 4 weeks (one cycle) of therapy; all lesions had flattening at this time point and the patient was confirmed as a partial response. (C) Complete resolution of the lesion is seen at the end of 24 weeks (six cycles) of therapy; at this time, a biopsy at the site of another lesion showed only residual hemosiderin pigmentation and confirmed a complete pathologic response. PD, progressive disease; PR, partial response.

no evidence of accumulation between day 1 and day 15. We observed no significant difference in parameters by HIV status or specific antiretroviral drugs. Comparing HIV-infected with HIV-uninfected patients, for C_{MAX} at C1D1, $P = .45$; at C1D15, $P = .80$; at C1D15 and comparing changes from baseline, $P = .91$; for AUC_{LAST} at C1D1, $P = .63$; at C1D15, $P = .97$; and comparing changes from baseline, $P = .91$.

Immunologic and Virologic Parameters

We observed significant increases in $CD4^+$ and $CD8^+$ cells during pomalidomide therapy (Table 4). These were seen beginning in week 4, were sustained at week 8, and had returned to baseline at completion of therapy. By contrast, there was no significant change in natural killer cells and a reversible decrease in $CD19^+$ B cells. There was no significant change in plasma HIV VL

by ultrasensitive single-copy assay. There was a significant increase in KSHV VL at week 4 ($P = .05$): 10 patients (45%) showed an increase in KSHV VL, including eight (35%) who became detectable from undetectable. This resolved at subsequent time points.

DISCUSSION

This study demonstrates that the immune modulatory agent pomalidomide at a dosage of 5 mg for 21 of 28 days is tolerable and active in patients with symptomatic KS regardless of HIV status. The ORR was 73%, and it is particularly striking that all HIV-uninfected patients responded. Responses were generally rapid and occurred in advanced KS and in patients who had received cytotoxic therapy, thalidomide, and/or lenalidomide, including

Table 3. Common and Serious Adverse Events Possibly Attributable to Therapy

Adverse Event	Grade 1			Grade 2			Grade 3			Grade 4		
	Patients (No.)	Cycles		Patients (No.)	Cycles		Patients (No.)	Cycles		Patients (No.)	Cycles	
		No.	%		No.	%		No.	%		No.	%
Neutropenia*	13	22	14	17	65	42	10	21	13	2	2	1
Constipation	16	73	47	1	3	2	0	0	0	0	0	0
Anemia	11	59	38	2	2	1	0	0	0	0	0	0
Fatigue	9	46	29	2	7	4	0	0	0	0	0	0
Rash	14	34	22	5	6	4	0	0	0	0	0	0
Thrombocytopenia	13	28	18	0	0	0	0	0	0	0	0	0
Lymphocytopenia	10	27	17	1	1	1	0	0	0	0	0	0
Hypothyroidism	1	11	7	3	12	8	0	0	0	0	0	0
Elevated ALT	7	17	11	0	0	0	0	0	0	0	0	0
Impaired concentration	3	15	10	0	0	0	0	0	0	0	0	0
Infection†	0	0	0	2	5	3	1	1	< 1	0	0	0
Fever‡	2	3	2	1	1	< 1	0	0	0	0	0	0
Edema§	2	9	6	1	2	1	1	1	< 1	0	0	0
Depression	0	0	0	1	1	< 1	0	0	0	0	0	0
Anxiety	0	0	0	1	1	< 1	0	0	0	0	0	0

NOTE. Adverse events across 156 cycles of therapy. All adverse events potentially attributable to therapy and graded CTCAE grade 2 or higher are included, together with adverse events potentially attributable to therapy graded CTCAE grade 1 that occurred in $\geq 10\%$ of cycles.

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

*Includes neutropenia occurring in two patients with benign ethnic neutropenia, whose neutrophil counts would have been graded as CTCAE grade 2 at baseline. Both episodes of grade 4 neutropenia occurred in patients with benign ethnic neutropenia and resolved before day 28.

†Infections included three respiratory tract infections and three soft tissue infections; the grade 3 infection was a lower respiratory tract infection requiring intravenous antibiotics.

‡Noninfectious fevers.

§The grade 3 edema was progressive tumor-associated lower-limb edema after commencement of therapy that was interfering with personal activities of daily living, in a patient whose Kaposi's sarcoma lesions were simultaneously improving with therapy

Table 4. Changes in Immunologic and Virologic Parameters

Parameter	Baseline	Change to Week 4	P	Change to Week 8	P	Change to End of Therapy	P
CD3, cells/ μ L	1,184 (525-3,325)	+275 (−506-1,524)	.0044	+190 (−972-1,455)	.0083	+11 (−1,368-903)	.93
CD4, cells/ μ L	440 (135-1,171)	+108 (−147-650)	< .001	+40 (−279-491)	.0099	−46 (−496-260)	.35
CD8, cells/ μ L	500 (259-2,385)	+101 (−444-915)	.017	+142 (−710-834)	.015	104 (−882-418)	.50
NK, cells/ μ L	178 (28-557)	+23 (−130-117)	.71	−6 (−174-127)	.72	10 (−279-94)	.53
CD19, cells/ μ L	141 (0-322)	−35 (−117-76)	.0031	−70 (−169-62)	< .001	−87 (−271-79)	< .001
KSHV VL, copies/PBMC*	0 (0-8,750)	0† (−238-5,250)	.05	0 (−238-20,850)	.56	0 (−238-160,674)	.63
Plasma HIV VL, copies/mL‡	1.5 (< 0.5-58)	+0.3 (−1.5-27)	.41	+0.75 (−35-40)	.16	−0.5 (−38-218.5)	.25

NOTE. Data are presented as median (range); at weeks 4 and 8 and at the end of therapy, the median change from baseline is given, with range of change in parentheses.

Abbreviations: KSHV, Kaposi's sarcoma-associated herpesvirus; NK, natural killer; PBMC, peripheral blood mononuclear cells; VL, viral load.

*Comparisons made with log₁₀ transformed KSHV VL and HIV VL.

†Ten patients (45%) showed an increase in KSHV VL in PBMCs at week 4, including eight (35%) who became detectable from undetectable.

‡Restricted to the 15 HIV-positive patients; paired data available for 10 to 13 patients.

a number who were refractory or poorly responsive to therapy. In addition to clearance of lesions, beneficial effects included improvement in tumor-associated edema and self-reported satisfaction with appearance. The latter is particularly important because visible KS is a major source of stigma.

The ORR reported here is comparable to that reported with standard cytotoxic agents in HIV-associated KS.¹² KS response rates are affected by patient immune status and disease bulk and can be confounded by ART initiation.^{9,25} The response estimate in this study is strengthened by the predominance of patients with advanced and previously treated disease. Importantly too, we controlled for any therapeutic effect of ART in two respects: first, by including HIV-uninfected patients in whom no such effect could be seen, and second, by excluding HIV-infected patients who had recently commenced ART. Indeed, the median time receiving ART among HIV-infected patients was 4 years, greatly exceeding common time estimates of maximal KS response to ART.⁹

Pomalidomide with aspirin thromboprophylaxis was well tolerated, with AEs consistent with those reported in previous studies and no impairment of self-reported HRQL during therapy.^{16,26} The occurrence of malignancies in three patients likely reflects their underlying immunodeficiency, which confers up to a 20-fold increase in the risk of lymphoma and increases in other cancers, including squamous cell skin cancer.^{4,5} No excess of lymphoid malignancies has been reported in larger and randomized trials using pomalidomide and related drugs.^{16,27} However, exploration of any role of therapy in their occurrence in this high-risk population is warranted and will require evaluation in the context of large randomized trials.

The study also provides the first evidence to guide the use of pomalidomide in HIV-infected patients, an important consideration given its activity in hematologic malignancies, which may develop in this population.¹⁶ Pharmacokinetic studies showed no differences in pomalidomide absorption or elimination in HIV-infected patients, and no evidence of accumulation even among patients receiving tenofovir. There were no excess or idiosyncratic AEs in HIV-infected patients. This supports the use of pomalidomide at standard doses in people with HIV.

The observed modulation of T-lymphocytes has not been reported previously and provides a window into the mechanism of

action of pomalidomide in KS. Increases in CD4⁺ and CD8⁺ cells occurred in patients with either stable HIV control or no HIV infection and were not explained by release from chemotherapy hematosuppression. Given the sensitivity of KS to cellular immunity, and the temporal association of T-lymphocyte modulation with responses, it is likely that these effects contributed to the observed responses. It is possible that the early transient increase in KSHV VL seen in some patients was from pomalidomide-induced suppression of interferon regulatory factor 4 (IRF4),¹⁷ a factor important in controlling KSHV reactivation from latency,²⁸ and that this reactivation and consequent expanded antigen expression could have further contributed to induced immune recognition of KSHV.

Other mechanisms of activity are also possible. Thalidomide and related drugs are known to modulate VEGF pathways, which are upregulated by KSHV and crucial to the pathogenesis of KS,²⁹ and have effects on several cytokines implicated in KS pathogenesis, including interleukin-6.³⁰ The response rate observed here is substantially higher than that reported with VEGF-specific therapies in KS,¹⁹ suggesting that VEGF alone is not the primary target of pomalidomide in KS, but that it or other cytokine pathways could be additional contributors to activity.

In summary, this study provides formative evidence that pomalidomide can address key unmet clinical needs for people with KS. In resource-rich regions, pomalidomide may be of particular use in HIV-uninfected patients, in patients who have received substantial cumulative doses of anthracyclines, and in patients with less extensive but symptomatic disease for whom avoidance of cytotoxic chemotherapy would be beneficial. In resource-limited regions, there is an urgent need for effective and tolerable oral agents³; with appropriate safeguards and monitoring, pomalidomide could address this. Confirmatory studies of pomalidomide alone and in combination with cytotoxic chemotherapy are planned, including in sub-Saharan Africa.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pomalidomide for Symptomatic Kaposi's Sarcoma in People With and Without HIV Infection: A Phase I/II Study

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Appendix

Table A1. Self-Reported Health-Related Quality of Life Instrument: FAHI

Quality of Life Measurement	Baseline (n = 22)	After 3 Months of Therapy (n = 19)	After Completion of Therapy (n = 19)
FAHI total	123.0 (30.2)* 127 (53-163)	123.4 (28.4) 131 (71-163)	118. (29.0)† 126 (62-160)
FAHI categories			
Physical well-being	30.8 (8.7) 32 (10-40)	31.3 (8.2) 34 (14-40)	31.3 (9.1) 35 (11-40)
Emotional well-being	25.1 (7.6) 26 (8-35)	27.7 (7.5) 28 (13-39)	26.2 (7.7) 27 (10-40)
Functional and global well-being	34.4 (10.3) 36.5 (13-48)	34.5 (10.1) 33 (18-51)	32.9 (9.6) 33 (19-50)
Social well-being	22.1 (6.6) 23 (2-32)	21.5 (7.8) 25 (4-29)	20.9 (6.8) 23 (5-31)
Cognitive functioning	9.1 (2.7) 10 (3-12)	8.5 (2.7) 9 (2-12)	8.7 (2.3) 9 (5-12)

NOTE. Data are presented as mean (SD) and median (range).
Abbreviation: FAHI, Functional Assessment of HIV Instrument.
*Missing responses within questionnaire (n = 21).
†Missing responses within questionnaire (n = 17).

Table A2. Self-Reported Health-Related Quality of Life: KS-Specific Questions

KS-Specific Question and Time Point	Not At All	A Little Bit	Little or None*	Somewhat	Quite a Bit	Very Much	Somewhat or More†
Pain has interfered with my normal work or activities							
Baseline	10 (45.5)	3 (13.6)	13 (59.1)	2 (9.1)	5 (22.7)	2 (9.1)	9(40.9)
TP2	7 (36.8)	5 (26.3)	12(63.2)	5 (26.3)	1 (5.3)	1 (5.3)	7(36.8)
TP3	7 (36.8)	5 (26.3)	12(63.2)	4 (21.1)	1 (5.3)	2 (10.5)	7(36.8)
I am satisfied with my physical appearance							
Baseline	6 (27.3)	6 (27.3)	12 (54.6)	6 (27.3)	3 (13.6)	1 (4.5)	10 (45.4)
TP2	6 (31.6)	1 (4.5)	7 (36.8)	5 (26.3)	5 (26.3)	2 (10.5)	12 (63.2)
TP3	3 (15.8)	2 (10.5)	5 (26.3)	5 (26.3)	8 (42.1)	1 (5.3)	14 (73.7)
I have had swelling in my face, arms, or legs							
Baseline	6 (27.3)	2 (9.1)	8 (36)	5 (22.7)	4 (18.2)	5 (22.7)	14 (63.6)
TP2	7 (36.8)	2 (10.5)	9 (47)	4 (21.1)	4 (21.1)	2 (10.5)	10 (52.6)
TP3	6 (31.6)	3 (15.8)	9 (47)	4 (21.1)	5 (26.3)	1 (5.3)	10 (52.6)

NOTE. Data are presented as No. (%). Baseline (n = 22); TP2 (n = 19); TP3 (n = 19).
Abbreviations: KS, Kaposi's sarcoma, TP, time point.
*Sum of two preceding columns.
†Sum of three preceding columns.