SUMMARY OF CHANGES

A Phase II Multicenter Study of Pomalidomide Monotherapy in HIV-Positive Individuals with Kaposi Sarcoma (KS) in Sub-Saharan Africa (SSA)

Version 10.0

NCI Protocol #: AMC-100
Local Protocol #: AMC-100

NCI Version Date: 04DEC2023
Protocol Date: 04DEC2023

I. Scientific and Substantive Changes

#	Section	Comments
1.	Protocol Synopsis 2.3 3.3 Table 12-1	The accrual targets (overall and by ethnic category), study design and rationale, and sample size were updated to reflect the expected enrollment of 26 participants instead of the originally planned 30 participants. The number of participants to be entered has been reduced from the originally planned 30 to 26 because Celgene, the donor of the study drug, requires that the last participant begin on study treatment no later than December 1, 2023. The revised sample size will provide only a slightly reduced statistical power (87.5% vs 90%) to test the null hypothesis that the ORR = 10% against the alternative that it is 30% with pomalidomide monotherapy at the one-sided 10% significance level.
2.	10.1.2	The statistical power calculation was updated to reflect the expected enrollment of 26 participants instead of the originally planned 30 participants.
3.	Table 4-1 10.1.3 Table 10-1 Table 10-2	Due to the expected enrollment of 26 participants instead of the originally planned 30 participants, the table describing the criteria for dose reduction, the table describing stopping rules for dose-limiting toxicity, and the table describing stopping rules for hematologic and non-hematologic toxicity were updated to remove the stopping rules for 28-30 participants. In addition, the stopping rule for dose-limiting toxicities for 21-27 participants was adjusted to 21-26, and the stopping rule for hematologic and non-hematologic toxicity for 27 participants was removed.

II. Administrative and Editorial Changes

#	Section	Description of Change
4.	Protocol Roster	The study statistician was updated from Jeannette Y. Lee, PhD, to Deukwoo Kwon, PhD.
5.	10.1.1	The overall response rate meeting the efficacy criteria to merit consideration of further clinical development of pomalidomide in this clinical setting was converted from 0.3 to 30%.
6.	Global	The version number and date have been updated to version 10.0, dated 04DEC2023.

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL #100:

A Phase II Multicenter Study of Pomalidomide Monotherapy in HIV-Positive Individuals with Kaposi Sarcoma (KS) in Sub-Saharan Africa (SSA)

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT03601806
Pharmaceutical Support Provided by:	Celgene Corporation Pomalidomide (NSC 767909)
Regulatory Status:	Pursuant to national requirements for each participating site
Protocol Chair:	Susan E. Krown, MD
Protocol Co-Chair:	Samantha Vogt, MD, MPH

Version 10.0, 04DEC2023
NCI Version Date 04DEC2023

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol # 100 – A Phase II Multicenter Study of Pomalidomide Monotherapy in HIV-Positive Individuals with Kaposi Sarcoma (KS) in Sub-Saharan Africa (SSA) (Version 10.0, 04DEC2023),** as written according to AMC, NCI, and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (DDMMMYYYY)

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SITES PARTICIPATING IN THE STUDY

This protocol will be open for participant enrollment at the AMC core sites in Africa named in the protocol roster, as approved by the AMC Executive Committee and the protocol leadership for participation.

PROTOCOL ROSTER

AMC Protocol # 100
A Phase II Multicenter Study of Pomalidomide Monotherapy in HIV-Positive Individuals with Kaposi Sarcoma (KS) in Sub-Saharan Africa (SSA)

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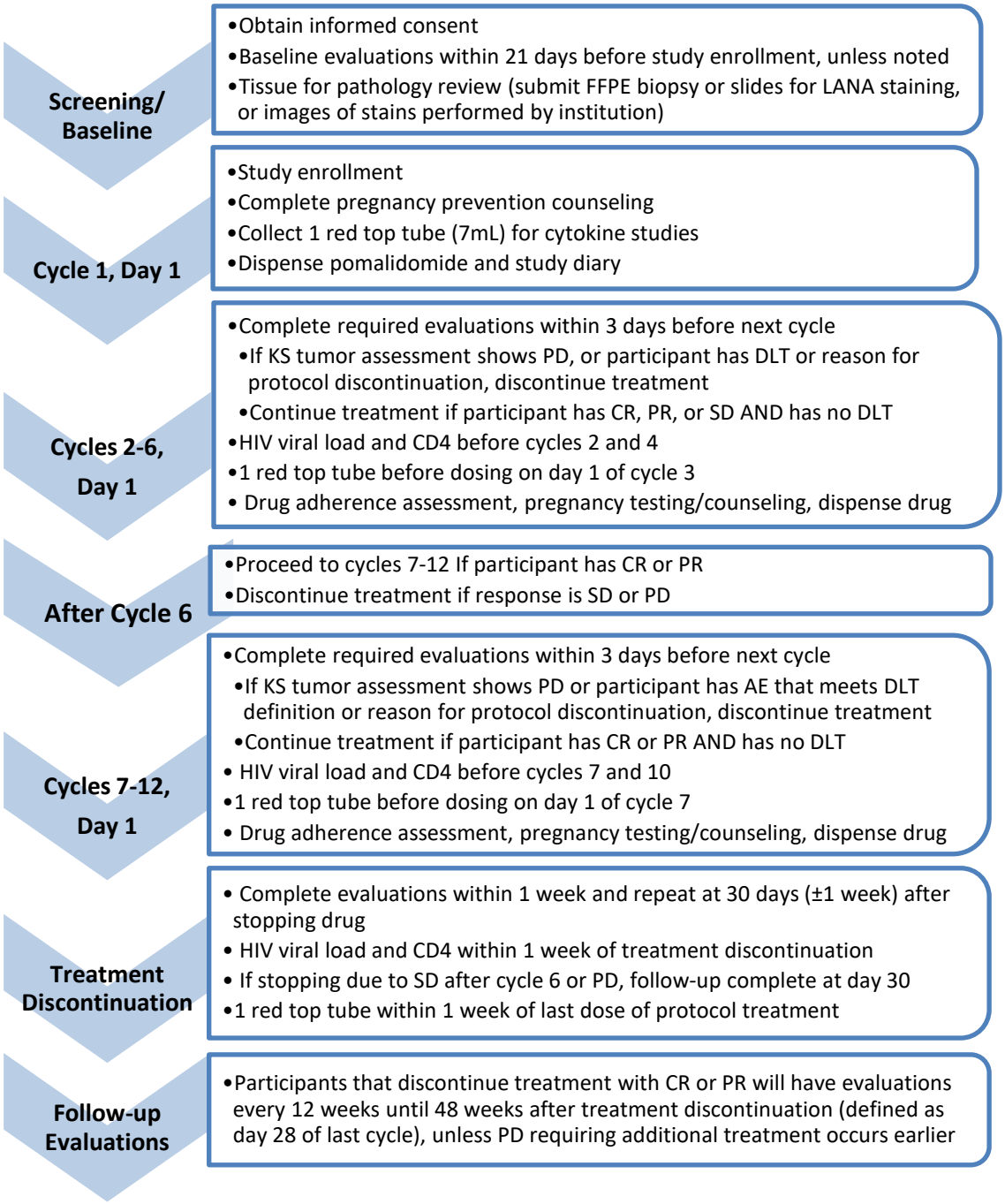
PROTOCOL SYNOPSIS

Title:	A Phase II Multicenter Study of Pomalidomide Monotherapy in HIV-Positive Individuals with Kaposi Sarcoma (KS) in Sub-Saharan Africa (SSA)
Phase of Study:	Phase II
Participating Institutions:	This protocol will be open to all AMC international member sites in sub-Saharan Africa. Participating institutions will also be required to complete Celgene's pregnancy prevention counseling training before activating this trial.
Accrual Target:	26 participants
Population:	Participants with KS and HIV infection. See Section 3.0 for eligibility criteria.
Regimen:	Each cycle of treatment includes administration of 21 doses of pomalidomide during a 4-week period, administered on Days 1-21 of a 28-day cycle. Eligible participants will begin pomalidomide therapy at Dose Level 1, 4 mg/day on Days 1-21 of each 28-day cycle. Dose level -1, 3 mg/day on Days 1-21 of each 28-day cycle, is provided for participants entered on Dose Level 1 who require dose reduction. Safety and the need for dose reduction will be continuously monitored by the protocol team. Antitumor effects will be assessed immediately prior to the start of each 28-day treatment cycle in all participants and every 12 weeks after completion of pomalidomide therapy in participants showing complete or partial response.
Duration:	The maximum duration of treatment is 12, 4-week cycles.
Primary Objective:	To determine if pomalidomide monotherapy induces a minimal level of antitumor efficacy to justify its further development for HIV-associated KS in sub-Saharan Africa and is safe and tolerable.
Secondary Objectives:	To evaluate the effects of pomalidomide monotherapy on standard measures of HIV control, i.e., CD4 counts and HIV viral loads, in this participant population.

Exploratory Objectives:

1. To assess the effect of pomalidomide treatment on serum cytokine levels.
2. To evaluate if changes in serum cytokine levels correlate with clinical response.

PROTOCOL SCHEMA



ABBREVIATIONS LIST

Abbreviation	Definition
ABV	doxorubicin, bleomycin, and vincristine
ACTG	AIDS Clinical Trials Group
AE	adverse event
AERS	Adverse Event Reporting System
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AMC	AIDS Malignancy Consortium
AML	acute myelocytic leukemia
ANC	absolute neutrophil count
ART	antiretroviral therapy
AST	aspartate aminotransferase
AZT	zidovudine
bFGF	basic fibroblast growth factor
b-HCG	beta human chorionic gonadotropin
BV	bleomycin and vincristine
CAEPR	Comprehensive Adverse Events and Potential Risks List
cART	combined antiretroviral therapy
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
CR	complete response
CRBN	cereblon
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Monitoring Service
CXR	chest X-ray

DARF	Drug Accountability Record Form
DHHS	Department of Health and Human Services
DLT	dose-limiting toxicity
E/CIA	enzyme or chemiluminescence immunoassay
ECOG	Eastern Cooperative Oncology Group
FCBP	female of child bearing potential
FDA	Food and Drug Administration
GEE	general estimating equations
HDPE	high-density polyethylene
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus
IDB	Investigational Drug Branch
IDE	investigational device exemption
IEC	institutional ethics committee
IME	important medical event
IMiD	immunomodulatory imide drugs
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
KPS	Karnofsky performance status
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated herpesvirus
LANA	latency-associated nuclear antigen
MCD	multicentric Castleman disease
MDS	myelodysplastic syndrome
MOP	manual of procedures
NCI	National Cancer Institute
ODMC	Operations and Data Management Center
OHAM	Office of HIV and AIDS Malignancy
ORR	Overall response rate
PCR	polymerase chain reaction

PD	progressive disease
P-gp	P-glycoprotein
PFS	progression-free survival
PI	principal investigator
PIO	Protocol Information Office
PR	partial response
REMS	Risk Evaluation and Mitigation Strategy
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SPEER	Specific Protocol Exceptions to Expedited Reporting
SSA	Sub-Saharan Africa
Th	T-helper [cell]
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WHO	World Health Organization
ZDV	zidovudine

1.0 OBJECTIVES

1.1 Hypotheses

1.1.1 Pomalidomide will induce an overall response rate of at least 30% in HIV-positive individuals with Kaposi sarcoma in sub-Saharan Africa.

1.1.2 Pomalidomide will be safe and well tolerated at the dose(s) tested in individuals with Kaposi sarcoma in sub-Saharan Africa.

1.1.3 Pomalidomide will not adversely affect CD4 counts and HIV control in HIV-positive individuals with Kaposi sarcoma in sub-Saharan Africa.

1.2 Primary Objective

To determine if pomalidomide monotherapy induces a minimal level of antitumor efficacy to justify its further development for HIV-associated KS in sub-Saharan Africa and is safe and tolerable.

1.3 Secondary Objectives

To evaluate the effects of pomalidomide monotherapy on standard measures of HIV control, i.e., CD4 counts and HIV viral loads, in this participant population.

1.4 Exploratory Objectives

1.4.1 To assess the effect of pomalidomide treatment on serum cytokine levels.

1.4.2 To evaluate if changes in serum cytokine levels correlate with clinical response.

2.0 BACKGROUND

2.1 Study Disease

2.1.1 Kaposi sarcoma in sub-Saharan Africa and clinical presentation

Kaposi sarcoma (KS) is a vascular tumor caused by Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8). Historically, it has been classified into four major types: classic KS, occurring most often in elderly males of Mediterranean or Ashkenazi Jewish heritage; endemic KS, occurring in both male and female adults and children in Africa; epidemic KS, occurring in individuals co-infected with HIV; and, iatrogenic KS, occurring mostly in solid organ allograft recipients undergoing immunosuppressive therapy to prevent graft rejection.

In sub-Saharan Africa (SSA), it is estimated that between 35-80% of HIV-infected individuals are co-infected with HHV-8 (Campbell 2009, Nguyen 2010, Maskew 2011). This high co-infection rate in the setting of HIV-induced immunosuppression helps to explain why KS is the most common malignancy associated with HIV infection in the region and a cause of significant morbidity and mortality.

The clinical manifestations of KS range from the classic pigmented cutaneous lesions that can be associated with bleeding and ulceration, to lymphadenopathy, oral mucosal lesions, visceral involvement, and lymphedema. Tumor-associated edema, which can be a particularly devastating clinical presentation, was reported in roughly a third of cases in a cohort of patients in Uganda (Phipps 2010).

A basic understanding of the mechanism by which KSHV promotes angiogenesis and edema can help shed light on possible targets for treatment strategies. KSHV is a double-stranded DNA virus that results in either latent or lytic infection of host cells. In KS, latent infection of host cells dominates the clinical picture, with only 5% of cells undergoing lytic replication (Stakus 1997). The differential viral gene expression in both the latent and lytic replication states are responsible for the up-regulation of various inflammatory cytokines including TNF-α, IL-1β, PDGF-B, and IL-6 (Naranatt 2004) that can induce production of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). VEGF and bFGF have subsequently been shown to promote angiogenesis and edema in animal models (Samaniego 1998).

2.1.2 Current treatment strategies in sub-Saharan Africa

With the advent of widespread availability of combination antiretroviral therapy in Africa, there has been a decline in incident cases of KS (Semeere 2012, Bohlius 2014, Mutyaba 2015), which is an encouraging finding that helps explain why ART remains the backbone of therapy for KS. However, ART has proven to be insufficient by itself to prevent KS progression and development of new incident cases (Rohner 2014, Bower 2014). Furthermore, a diagnosis of KS in HIV-infected individuals starting ART in Uganda was associated with a marked increase in mortality as compared to those without KS (Asiimwe 2013) and KS was the leading cause of early death after initiation of ART in SSA (Lawn 2008, Zachariah 2006,

Castelnuovo 2009).

Current treatment strategies for KS have often been based on an individual's stage at presentation. Patients with Stage T0 disease (KS limited to the skin and lymph nodes with no more than minimal oral disease) are often managed with ART alone, while patients with Stage T1 disease (KS with tumor-associated edema or ulceration, extensive oral disease, and/or visceral disease) are usually considered to require systemic chemotherapy in addition to ART. Among patients with T0 disease, it is not known whether some patients may also benefit from the early addition of chemotherapy to ART.

In SSA, several chemotherapy options have been used including the ABV regimen (doxorubicin, bleomycin and vincristine) (Bihl 2007), BV (bleomycin and vincristine) or single agent paclitaxel (Herce 2015), and gemcitabine (Strother 2010). However, there is limited data from prospective randomized clinical trials in Africa and no overall survival benefit was seen in the trial conducted by Mosam et al. comparing mostly patients with T1 disease receiving either ART alone or ART plus chemotherapy (ABV or, in some cases, oral etoposide) (Mosam 2012), suggesting that further research is desperately needed to help establish the standard of care for patients with KS in SSA. Currently, large randomized trials are in progress to evaluate optimal treatment strategies for management of both limited-stage and advanced KS in resource-limited settings (NCT01352117, NCT01435018), including SSA, but the results of these studies, which utilize ART, either alone or combined with different chemotherapeutic regimens, will not be available for several years.

2.1.3 Rationale for treatment of KS with IMiDs

In recent years, a class of medications called IMiDs (immunomodulatory imide drugs) has gained traction in the management of several malignancies, including KS, based on their anti-inflammatory, anti-angiogenic, and immunomodulatory properties. Case reports describing improvement in KS lesions and HHV-8 viral titers in KS patients treated with thalidomide (Soler 1996, Carlesimo 1995), set the stage for further research into this class of medications in KS treatment. Additionally, their oral bioavailability and limited side effect profile, particularly with the next generation IMiD, pomalidomide, are important factors supporting their attractiveness for KS treatment in resource-limited settings, including SSA.

Two Phase II trials of thalidomide (Little 2000, Fife 1998) reported partial response rates in AIDS-related KS ranging from 35-47%. Case reports have also described responses of advanced KS to lenalidomide (Martinez 2011, Steff 2013), a second-generation IMiD notable for its increased activity (compared to thalidomide) against TNF-α and IL-6 (Chaulet 2011). Lenalidomide was recently evaluated by the AIDS Malignancy Consortium (AMC) in a Phase I/II clinical trial in AIDS-associated KS (NCT01057121). Preliminary results indicate a response rate in excess of 40% (K. Shimabukuro, E. Reid, unpublished results).

2.2 Study Agents

2.2.1 Pomalidomide

Pomalidomide, a next generation IMiD, was designed to further increase the anti-angiogenic and immunomodulatory effects compared to the prior IMiD compounds. Pomalidomide promotes T helper cell (Th)-1differentiation in vitro (Xu 2008) and increased Th-1 cytokine production in animal models (Dredge 2002). In pre-clinical studies, pomalidomide was shown to be effective against myeloma and B-cell lymphoma cell lines (Lentzsch 2002) and have significant anti-angiogenic properties (Dredge 2002). It was initially postulated that the anti-angiogenic mechanism of action for both the parent compound thalidomide, and the subsequent IMiD derivatives was closely linked to their teratogenic potential. With the discovery of cereblon (CRBN) as the primary target of thalidomide teratogenicity (Ito 2010), the interaction between pomalidomide and CRBN has been further investigated. Not only does pomalidomide bind CRBN in vitro, but resistance to pomalidomide in myeloma cell lines is associated with a decrease in CRBN protein expression (Lopez-Girona 2012, Zhu 2011). Upon binding to CRBN, the IMiD-CRBN complex results in ubiquination and proteasome-dependent degradation of the transcription factors Ikaros and Ailos, which in turn are responsible for the downregulation of c-Myc and IRF4 (Gandhi 2014, Kronke 2014, Licht 2014, Lu 2010, Zhu 2014). These in vitro findings highlight the importance of the interaction of pomalidomide with CRBN, but the dynamics of this interaction and mechanism of resistance with clinical correlation require further investigation.

Clinically, in a phase 1 study evaluating pomalidomide treatment in 24 patients with relapsed or refractory multiple myeloma, pomalidomide was overall well tolerated, although three patients developed DVTs in the months following treatment (Schey 2004). Six patients developed Grade 4 neutropenia and eight patients developed Grade 3; Grade 4 thrombocytopenia was seen in three patients.

After promising results in several Phase II trials (Usmani 2014, Richardson 2014), a Phase III trial of pomalidomide combined with dexamethasone compared to dexamethasone alone in relapsed or refractory multiple myeloma showed an improved progression-free survival (PFS) of 4.0 months versus 1.9 months with a median follow-up of 10 months (San Miguel 2013). Taken together the results of various clinical trials ultimately led to Food and Drug Administration (FDA) approval of pomalidomide for relapsed or refractory multiple myeloma in February 2013.

Pomalidomide was evaluated in a phase I/II clinical trial (NCT01495598) for the treatment KS at the U.S. National Cancer Institute (NCI). Published results from the first 22 patients (15 HIV-infected and 7 HIV-uninfected) showed a 5 mg dose given daily for 21 days per 28-day cycle to be well tolerated (Polizzotto 2016). 16 patients (73%) had an objective response, including four patients showing complete response (CR) (18%) and 12 patients showing partial response (PR) (55%). An additional three patients showed stable disease (SD) (14%). Grade 3 or 4 adverse events included neutropenia (12 patients), infection (1 patient), and peripheral edema (1 patient), while other side effects such as cytopenias, constipation, rash, and fatigue were reported as mild.

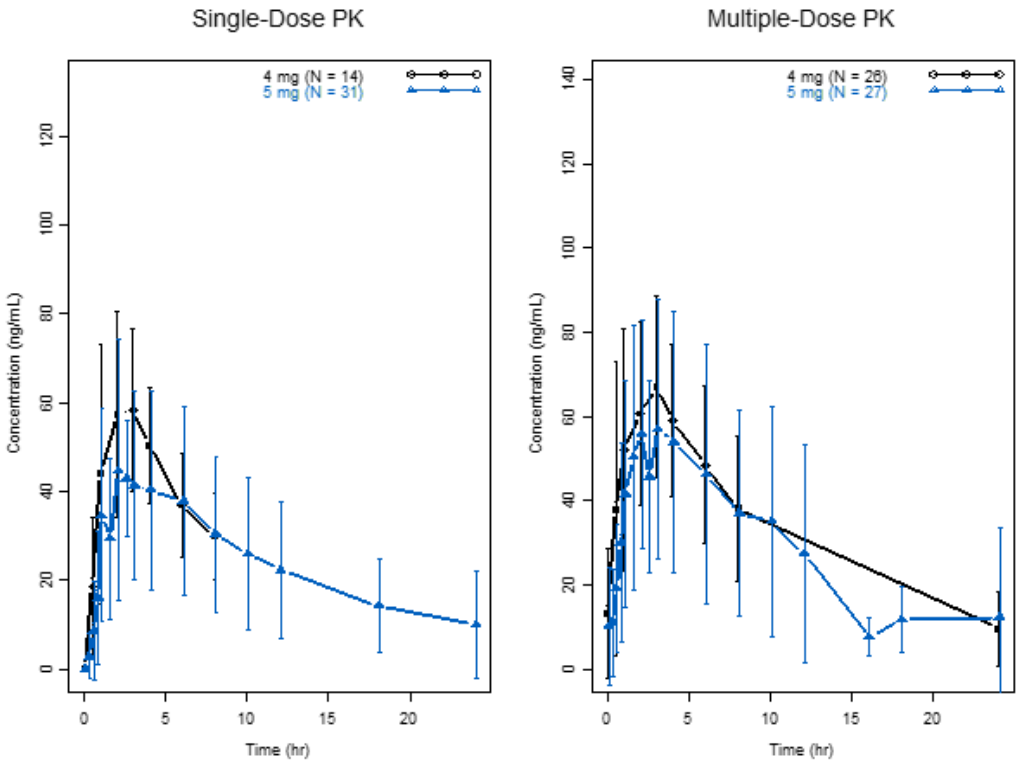
Duration of treatment ranged from 2-12 months of therapy, with two patients

currently remaining on pomalidomide. Reasons for variation in duration of treatment included patient and principal investigator (PI) discretion (i.e., need for surgery and bone pain from granulocyte-colony stimulating factor (GCSF)), and completion of planned number of cycles. While these results are encouraging there are several limitations including an inability to evaluate duration of unmaintained remission. Additionally, in at least three cases, progression occurred in the setting of a confounding factor (1 case occurred in a patient who developed KSHV-Multicentric Castleman Disease (MCD) after the patient received rituximab, a known iatrogenic cause of KS progression; one case occurred in the setting of cellulitis and KSHV-associated Inflammatory Cytokine Syndrome; one case occurred during a lapse in ART therapy).

A particularly interesting observation in this trial was the documented clinical improvement in tumor-associated limb edema with pomalidomide treatment (Mark Polizzotto, personal communication). Of 15 participants noted to have edema at the start of treatment, eight showed a decrease in limb circumference measurements of at least two centimeters (cm) with therapy and an additional two patients reported subjective improvement in limb edema (1 patient reported decreased pedal pain; one patient reported an ability to wear closed toe shoes again). Based on the data from this study, which eventually included 28 participants (18 HIV-postive and 10 HIV-negative), on May 14, 2020 the U.S. Food and Drug Administration expanded the indication of pomalidomide to include treating adult patients with AIDS-related KS after failure of highly active antiretroviral therapy and KS in adult patients who are HIV-negative.

Individuals with HIV-associated KS in Africa often have a spectrum of co-morbidities (e.g., anemia, infections, and nutritional deficiencies) that differ from those of HIV-infected individuals in the U.S., and which may affect drug tolerance. Thus, it will be important to determine whether the same dose and schedule of pomalidomide tolerated in a study of KS patients in the U.S. will be equally well tolerated in SSA. Additionally, further PK analysis of pomalidomide dosing performed by Celgene (Fig. 2-1) suggests overlapped exposures for 4 mg and 5 mg doses, indicating that there is no clinically meaningful exposure differentiation between the 4 mg and 5 mg dose. For this reason, and because a 4 mg dose (but not a 5 mg dose) is commercially available, we will conduct this trial using the 4 mg starting dose.

Figure 2-1: Average Plasma Concentration Profiles by Dose (4mg versus 5mg) and Visit (Single-Dose PK versus Multiple-Dose PK)



Teratogenicity with the IMiD compounds has long been a concern since the early experience with thalidomide in the late 1950s and early 1960s and the subsequent development of birth defects. Upon approving pomalidomide, the FDA noted its teratogenic potential in both rats and rabbits when administered during organogenesis, garnering it Category X designation in pregnancy. This has required special precautions among both men and women receiving pomalidomide, and the requirement for enrollment in a Risk Evaluation and Mitigation Strategy (REMS) program to avoid embryo-fetal exposure. Mitigating these risks will be particularly important in AIDS-KS patients in SSA, where most affected individuals are heterosexual and a significant proportion are women of childbearing potential.

2.3 Study Design and Rationale

This is an open label, Phase II study of orally administered pomalidomide in participants with AIDS-associated KS in sub-Saharan Africa.

Pomalidomide monotherapy will be evaluated in 26 participants, who will be enrolled at a daily oral dose of 4 mg daily for 21 days of a 28-day cycle. This dosage may be de-escalated to 3 mg daily for 21 days of a 28-day cycle if ≥ Grade 2 toxicities are observed.

Pomalidomide will be considered for future development in this setting, either as a single agent or in combination with other anti-KS therapy, if the following conditions are met:

- An overall response rate of at least 30% is achieved; and,
- Either of the doses tested are tolerable, defined as no more than six participants showing ≥ Grade 3 toxicities.

2.4 Correlative Studies

Pomalidomide was designed to further increase the anti-angiogenic and immunomodulatory effects compared to the prior IMiD compounds. Pomalidomide promotes Th-1 differentiation in vitro (Xu 2008) and increased Th-1 cytokine production in animal models (Dredge 2002). Pomalidomide is known to be a potent immunomodulatory agent; pomalidomide and other IMiDs have anti-inflammatory, anti-angiogenic, and immunomodulatory properties. In patients with multiple myeloma, pomalidomide is known to decrease the production of inflammatory cytokines (IL1 and IL6), as well as VEGF, an angiogenesis-promoting factor, and to enhance immune responses, with increased T cell activity, decreased Treg activity and enhanced IFNγ production (Chanan-Khan 2013). Thalidomide and thalidomide-like drugs also are known to inhibit the production of pro-inflammatory cytokines, including TNFα, and in addition, can enhance T cell immunity (Corral 2008).

Since the pathogenesis of Kaposi's sarcoma (KS) is believed to involved the up-regulation of various inflammatory cytokines, including TNFα, IL1β, and IL6 (Naranatt 2004), which promote inflammation and induce production factors that promote angiogenesis (PDGF, VEGF), in the setting of deficient T cell immune responsiveness, it is important to better define the effects of pomalidomide therapy on serum levels of these pro-inflammatory and immunomodulatory molecules.

For this reason, the following cytokines will be measured at baseline, after cycles 2 and 6, and at treatment discontinuation: CRP and sTNFR2 as markers of systemic inflammation, VEGF as a marker of angiogenesis, IP10 (an IFN-inducible inflammation-associated chemokine), IL8, TNFα, IL17A/E, IL6 and IL10 (inflammation-associated cytokines), sCD27, IFNγ and sIL2Rα (immune activation biomarkers), and sCD14 and sCD163 (macrophage activation/inflammation-associated molecules). Multiple cytokines will be measured, as serum levels of these potent immunomodulatory molecules are near the limit of detection of conventional immunometric assays, even in persons who have inflammatory conditions. Therefore, measurement of several cytokines can provide a more complete picture of the inflammatory milieu in patients. Since these will be measured using Luminex multiplexed assays (Luminex, Austin, Texas, USA), a fluorescent bead-based assay which quantifies levels of several molecules simultaneously in one reaction volume, it is possible to do this without increasing the serum volume required, and with minimal added expense.

We hypothesize that pomalidomide will dampen the production of TH17 and inflammatory cytokines (decreased levels of IL17, IL6, IP10, IL8, TNF, IL10), resulting in decreased levels of inflammation (decreased CRP and sTNFR2), angiogenesis (decreased VEGF), and of soluble receptors that result from monocyte/macrophage activation (decreased sCD14, sCD163), and that it will enhance immune activation (increased levels of IFNγ,

sIL2Rα and sCD27). Additionally, it is expected that these anti-inflammation, anti-angiogenic and immune-enhancing responses will be associated with clinical responses to therapy.

Assays will be performed at the AMC Protein Biomarker Profiling Core Laboratory (See Appendix XII).

3.0 PARTICIPANT SELECTION

A rostered AMC investigator (CTEP-registered physician investigator) must document that each protocol participant meets all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

3.1 Eligibility Criteria

3.1.1 Participants must have measurable cutaneous KS that has been pathologically confirmed by an AMC-approved pathologist. Diagnostic tissue must be available to satisfy the tissue submission requirements at Appendix V for central pathology review.

3.1.2 Participants may not show evidence for ongoing improvement in KS lesions in the 4 weeks prior to enrollment.

3.1.3 HIV positive. Documentation of HIV-1 infection by means of any one of the following:

- HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating >1000 RNA copies/mL confirmed by a licensed screening antibody and/or HIV antibody antigen combination assay;
- Any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid multispot antibody differentiation assay.

  Note: The term "licensed" refers to a kit that has been certified or licensed by an oversight body within the participating country and validated internally.

  WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

3.1.4 Age ≥ 18 years.

Because no dosing or adverse event data are currently available on the use of Pomalidomide in participants <18 years of age, children are excluded from this study.

3.1.5 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (Karnofsky Performance Status (KPS) ≥ 50, see Appendix II).

3.1.6 Life expectancy ≥ 12 weeks.

3.1.7 Participants must have organ and marrow function within the following parameters, unsupported by hematopoietic growth factors within 7 days prior to enrollment:

- Hemoglobin ≥ 8 g/dL

- Absolute neutrophil count (ANC): ≥ 1,000 cells/mm^3 (1.0 x 10^9/L)
- Platelets: ≥ 75,000 cells/mm^3 (75.0 x 10^9/L)
- Total bilirubin: ≤ 1.5 times the upper limit of normal (ULN), unless the participant is receiving an antiretroviral drug known to be associated with increased bilirubin, in which case the direct fraction should be ≤ 2 times the ULN.
- Serum AST (SGOT) / ALT (SGPT): ≤ 2.5 x ULN
- Estimated or measured creatinine clearance ≥ 60 mL/minute (1.00 mL/s) (serum creatinine ≤ 2.0 mg/dL / 176.8 μmol/L)

3.1.8 Currently receiving local standard of care ART for ≥ 12 weeks, with HIV viral load ≤ 400 copies/mL within the preceding 12 weeks prior to enrollment.

Participants are required to be on antiretroviral regimens that are in accordance with the current International AIDS Society guidelines concurrently with chemotherapy. Excepting agents containing zidovudine, which is prohibited, the specific agents are at the discretion of the Investigator and the use of investigational ART agents currently available on an expanded access basis is allowed.

3.1.9 A FCBP is a female who has achieved menarche at some point, is < 60 years of age, and who meets one of the following criteria:

1) has not undergone a hysterectomy or bilateral oophorectomy, or

2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), or

3) does not have a serum or plasma FSH >40 mIU/mL and a history of amenorrhea x ≥ 1 year

FCBP must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 14 days prior to enrollment and again within 24 hours of starting pomalidomide and must either commit to continued abstinence from heterosexual intercourse or, if complete abstinence cannot be assured, they must begin TWO acceptable methods of birth control, including one of the following highly effective, long-acting methods, DepoProvera, an intrauterine device (IUD), an implant*, or bilateral tubal ligation, if it can be verified that the procedure was performed, and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking pomalidomide. FCBP must also agree to ongoing pregnancy testing.

* **NOTE:** Implants containing levonorgestrel and etonogestrel are prohibited in women receiving efavirenz, as drug interactions will render the implants ineffective.

Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy.

All participants must be counseled at a minimum of every 28 days about pregnancy

precautions and risks of fetal exposure. Serum or urine pregnancy testing will be repeated in FCBP, and must be negative, within 24 hours of starting each new cycle of pomalidomide. See Appendix VII: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix VIII: Pomalidomide Education and Counseling Guidance Document for further instructions.

3.1.10 Able to take aspirin daily as prophylactic anticoagulation as described in Section 4.3.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally, the presence of any of the following conditions will exclude a participant from study enrollment:

3.2.1 Participants who are receiving any other investigational agents (except as permitted in 3.1.8).

3.2.2 Any prior use of thalidomide, lenalidomide, or pomalidomide.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pomalidomide.

3.2.4 Participants who have visceral disease requiring cytotoxic chemotherapy (i.e., pulmonary KS, symptomatic gastrointestinal KS) or in whom the omission of conventional cytotoxic chemotherapy is not consistent with the local standard of care. KS-related lymphedema is permitted.

3.2.5 Use of agents containing zidovudine (including Combivir® and Trizivir®) are prohibited. In order to be eligible, participants taking zidovudine must change to a different regimen at least 7 days prior to therapy initiation. Changes to ART therapy during the study may be made if medically necessary (toxicity, failure of regimen, etc.).

Use of medications or substances that are strong inhibitors of CYP1A2, which include amiodarone, cimetidine, fluoroquinolones (e.g., ciprofloxacin, enoxacin), fluvoxamine, and ticlopidine is prohibited.

Co-administration of efavirenz, an inhibitor of CYP1A2, with strong inhibitors of CYP3A4 and P-glycoprotein (P-gp) is prohibited. See Appendix VI for a list of all prohibited medications on this trial.

Use of erythropoietin is prohibited.

Co-administration of corticosteroids greater than doses required for treatment of adrenal insufficiency is prohibited.

Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active

infection for which the participant has not completed at least 14 days of therapy prior to study enrollment and/or is not clinically stable; symptomatic congestive heart failure; unstable angina pectoris; cardiac arrhythmia; or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because pomalidomide is a thalidomide analog with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pomalidomide, breastfeeding should be discontinued if the mother is treated with pomalidomide.

3.2.8 Specific KS therapy, including cytotoxic chemotherapy but not including ART, within the past 4 weeks.

3.2.9 Use of other anticancer treatments or agents within the past 4 weeks.

3.2.10 History of malignant tumors other than KS, unless:

- In complete remission for ≥ 1 year, or
- Completely resected basal cell carcinoma, or
- In situ squamous cell carcinoma of the cervix or anus.

3.2.11 Grade > 1 peripheral neuropathy.

3.2.12 History of myocardial infarction (MI), cerebrovascular accident, or venous or arterial thromboembolism, unless line-related thrombosis without embolus occurring greater than 1 year prior to study entry.

3.2.13 Known procoagulant disorder including prothrombin gene mutation 20210, antithrombin III deficiency, protein C deficiency, protein S deficiency and antiphospholipid syndrome but not including heterozygosity for the Factor V Leiden mutation or the presence of a lupus anticoagulant in the absence of other criteria for the antiphospholipid syndrome.

3.2.14 Any condition, including the presence of current laboratory abnormalities or other factor that, in the opinion of the investigator, places the participant at unacceptable risk if they were to participate in the study or confounds the ability to interpret data from the study.

3.3 Number of Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll 26 participants.

3.3.2 Accrual rate

Approximately two participants per month.

3.4 Participant Enrollment Procedures

This study will be available for enrollment at the AMC African sites. Sites must have this protocol approved by their Institutional Review Boards (IRB), national regulatory authority (where required) and be registered with the AMC Operations and Data

Management Center (ODMC) before they may enroll participants. Protocol registration instructions and forms will be made available on the AMC Operations website (www.AIDSCancer.org). Participating sites may not order study drugs until protocol registration with the AMC ODMC is complete.

3.4.1 Registration for Screening

After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-100 Screening Segment) on-line via the AMC Advantage eClinical[SM] Internet Data Entry System. After successful registration into the screening segment, the participant will receive an eleven-digit participant ID and will then enter the screening process. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 42 days prior to the initiation of treatment. Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.

Please reference the AMC-100 MOP for additional details regarding the required tests prior to enrollment in the screening segment.

If the on-line system is inaccessible for Screening Registration (Screening Segment), the site should notify the AMC ODMC via email at amipm@emmes.com or via phone at 1-301-251-1161 for further instructions. Please refer to the AMC-100 MOP for additional instructions.

3.4.2 Treatment Segment Enrollment

After all required eligibility assessments are complete, the participating site will complete the protocol-specific eligibility checklist and enroll the participant into the AMC-100 Treatment Segment on-line via the AMC Advantage eClinical[SM] Internet Data Entry System. The participating site will ensure the participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.

If the on-line system is inaccessible for Treatment Enrollment Registration (Treatment Segment), the site should notify the AMC ODMC via email at amipm@emmes.com or via phone at 301-251-1161 for further instructions.

4.0 TREATMENT PLAN

4.1 Agent Administration

Pomalidomide will be administered on an outpatient basis. Reported adverse events and potential risks for pomalidomide are described in Section 6.0. Appropriate dose modifications for pomalidomide are described in Section 5.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

NOTES: At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with participants. The participant will be requested to maintain a medication diary of each dose of medication (Appendix IV). The medication diary will be returned to clinic staff at the end of each course.

The site will be required to document study agent return by participant in source documents. Non-compliance with study agent administration should be noted at the time of diary collection and the participant should be instructed again regarding dosing instructions.

4.1.1 Pomalidomide

Each cycle of treatment includes administration of 21 doses of pomalidomide during a 4-week period, administered on days 1-21 of a 28-day cycle (± 2 days). The maximum duration of treatment is twelve 4-week cycles. Pomalidomide will be administered on a daily schedule at approximately the same time each day. At each dose administration, the capsule number corresponding to the appropriate dose level of pomalidomide is to be swallowed whole with a glass of water (150-200 mL). Participants should be instructed not to bite or chew on the capsule. In case of breakage of the capsule in the oral cavity, an additional glass of water should be taken immediately. Participants will be instructed to fill out a medication diary to record medication administered each day.

Study medications will be dispensed at study entry (day 1) and at each subsequent study visit at the start of a new cycle. Participants will be instructed to return any unused study medication and medication containers at each study visit and bring their completed medication diary to each study visit. At each visit, medication diaries and returned medication counts will be performed and participants will undergo repeat counseling and medication adherence assessments. Participants will receive up to six cycles of pomalidomide if they have stable disease, or up to 12 cycles of pomalidomide if they show a complete or partial tumor response, unless they develop unacceptable toxicity or meet another protocol-defined reason for treatment discontinuation.

Only enough pomalidomide for one cycle of treatment will be provided to the participant at the start of each cycle.

If participants miss a dose, the dose may still be taken up to 12 hours after the time they normally would take it. If more than 12 hours have elapsed, the dose should be skipped. Take the next dose at the usual time. Participants should not take 2 doses to make up for the one they missed. Participants who take more than the prescribed

dose of pomalidomide should be instructed to contact the study staff immediately and to seek emergency medical care if needed.

4.1.2 Pomalidomide dosage levels

Eligible participants will begin pomalidomide therapy at dose level 1, 4 mg/day on days 1-21 of each 28-day cycle.

Dose level -1, 3 mg/day on days 1-21 of each 28-day cycle, is provided for participants entered on dose level 1 who require dose reduction.

Safety and the need for dose reduction will be continuously monitored by the protocol team.

The following table shows the number of participants who require dose reduction based on first cycle adverse events that are needed for the starting dosage level to be reduced to 3 mg/day in subsequent participants.

Table 4-1. Criteria for Dose Reduction

No. of participants enrolled	**More than X participants who required dosage reduction due to first cycle DLTs**
7-8	2
9-14	3
15-20	4
21-26	5

This table is based on the probability of observing ≥ x participants who require AE-related dosage reductions is < 0.05. if the underlying proportion of participants who require dosage reductions due to adverse events (AE) is 0.10.

4.2 Definition of Dose-Limiting Toxicity

Dose limiting toxicity (DLT) will be defined as the occurrence of any of the following during the first cycle of protocol treatment:

- Hematologic: Defined as neutropenia (ANC < 500/mm^3) or thrombocytopenia (platelets < 25,000/mm^3) lasting longer than seven days.
- Non-hematologic: Defined as any Grade 3 pomalidomide-related toxicity lasting seven days or longer or Grade 4 toxicity. Nausea, vomiting, and diarrhea are not DLTs if they can be managed with standard antiemetic and antidiarrheal medications. Incidental laboratory abnormalities that do not reflect underlying organ dysfunction are not DLTs.
    - Any instance of bullous erythema multiforme syndrome, toxic epidermal necrolysis syndrome (TENS), or Stevens-Johnson syndrome
- Failure to complete ≥ 80% of the planned 21 doses (i.e., ≥ 17 doses) of a pomalidomide treatment course due to pomalidomide-related toxicities.

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse

Events (CTCAE) Version 5.0 as outlined in Section 6.0. If multiple toxicities are seen, the presence of DLT will be based on the most severe toxicity experiences.

During the period for evaluating dose-limiting toxicity, participants who withdraw from the study or do not complete the required cycles of treatment owing to reasons other than drug-related adverse events can be replaced.

See Section 10.1.2 for early stopping rules based on the frequency of first-cycle DLT.

4.3 General Concomitant Medication and Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the participant, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate, are allowed.

The administration of any other therapies intended to treat KS including chemotherapy and biologic agents is **NOT** permitted. The use of other concurrent investigational drugs is not allowed.

All participants must be on stable antiretroviral therapy (ART) for a minimum of 12 weeks prior to study entry with an acceptable regimen that adheres to national guidelines for treatment of HIV infection. Participants are **not allowed** to receive zidovudine (AZT; ZDV) as part of the ART regimen, since it is myelosuppressive. Zidovudine may be discontinued and substituted as clinically indicated upon enrollment. If zidovudine is substituted, it must be at least 7 days prior to therapy initiation (see Section 3.2.5).

Strong inhibitors of CYP1A2, including: amiodarone, cimetidine, fluoroquinolones (e.g., ciprofloxacin, enoxacin), fluvoxamine; and ticlopidine are prohibited.

Co-administration of efavirenz, an inhibitor of CYP1A2, with strong inhibitors of CYP3A4 and P-glycoprotein (P-gp) is prohibited.

Use of erythropoietin is prohibited.

Because there is a potential for interaction of pomalidomide with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The protocol chairs should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix VI presents guidelines for identifying medications/substances that could potentially interact with the study agent.

Participants MUST receive medically appropriate care and treatment for HIV infection, including antiretroviral medications. Due to known cytochrome P450 inhibitory effects of protease inhibitors, particularly for ritonavir, the case report form will particularly note the use of ritonavir for HIV management.

Anticoagulation consideration

Pomalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis.

Participants must receive aspirin by mouth daily x 28 days for each cycle of pomalidomide

and for 30 days after the last pomalidomide dose. The recommended dose is 75-100mg daily, unless they are already receiving aspirin at an equal or higher daily dose for another indication. If the recommended dose of aspirin is not available, a dose of up to 325 mg daily may be administered.

Steroid considerations

Concurrent administration of corticosteroids greater than doses required for treatment of adrenal insufficiency is prohibited.

Estrogen-containing compounds

Concurrent administration of estrogen containing compounds, including estrogen containing contraceptives, may increase the risk of thrombosis. These compounds should be avoided during pomalidomide treatment.

Tobacco use

Concurrent tobacco use during pomalidomide therapy may increase the risk for thrombosis. Study staff will obtain information on participants' tobacco smoking history with participants at baseline. Participants who are current smokers will be provided guidance for smoking cessation per local policies.

Management of concurrent infections

The management of active tuberculosis (TB) or cryptococcal meningitis (CM) for participants will be per the local standard of care at the respective sites where the study is being carried out.

4.4 Duration of Therapy

Treatment may continue for up to 6 cycles for participants with stable disease, or up to 12 cycles if they have complete or partial response, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), as defined in Section 5.1
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unsuitable for further treatment in the judgment of the investigator, including but not limited to:
    - Pregnancy
    - Failure to return for scheduled follow up for more than 42 days

4.5 Duration of Follow Up

Participants with complete response (CR) or partial response (PR) will be followed for up to 48 weeks after their last dose of study treatment or until PD or death, whichever occurs first, for safety and response duration (Section 8.4). Participants with stable disease (SD) or progressive disease (PD) will be followed for 30 days after treatment discontinuation.

Participants removed from study treatment for unacceptable adverse event(s) will be followed at least weekly until resolution or stabilization of the adverse event, after which they will be followed according to their response status.

4.6 Criteria for Removal from Treatment

Participants will be removed from study treatment when any of the criteria listed in Section 4.4 applies. The reason for study treatment removal and the date the participant was removed must be documented in the Off Protocol Treatment Form in Advantage eClinical.

5.0 DOSING DELAYS/DOSE MODIFICATIONS

5.1 Dose Modifications for Pomalidomide

5.1.1 Dose reduction steps

Table 5-1. Pomalidomide Dose Reduction Steps

Dose Level	Dose and Schedule
Dose level 1 (starting dose)	4 mg daily on Days 1-21 every 28 days
Dose level -1	3 mg daily on Days 1-21 every 28 days

5.1.2 Instructions for initiation of a new cycle

A new course of treatment may begin on the scheduled day 1 of a new cycle if:

- The ANC is ≥ 1,000 cells/mm³ (1.0 x 10^9/L); The platelet count is ≥ 50,000 cells/mm³ (50.0 x 10^9/L);
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ Grade 1 severity;
- Any other drug related adverse events that may have occurred have resolved to ≤ Grade 2 severity.

If these conditions are not met on day 1 of a new cycle, the participant will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If pomalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the new cycle.

Unless otherwise specified in this section, if any Grade 3 or 4 toxicity persists for longer than two weeks after withholding pomalidomide, pomalidomide will be stopped permanently.

5.1.3 Instructions for dose modifications or interruption during a cycle

Note: If the site investigator has compelling evidence that the toxicity is NOT related to the study drugs or is not clinically significant (e.g., alopecia, electrolyte abnormalities that can be corrected with supplementation), then management of drug dosing is at the discretion of the site investigator after consultation with the study chair(s). Table 5-2. Dose Modifications For Non-Hematologic Toxicity

Toxicity	Dose Modification
Rash = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1).

Toxicity	Dose Modification
Rash = Grade 4 or bullous dermatitis (any grade)	Discontinue participant from pomalidomide treatment regimen.
Stevens-Johnson Syndrome (any Grade)	Discontinue participant from pomalidomide treatment regimen.
Anaphylaxis (any Grade)	Discontinue participant from pomalidomide treatment regimen.
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ Grade 2).
Thromboembolism event ≥ Grade 3	Hold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Peripheral neuropathy = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (neuropathy must resolve to ≤ Grade 1).
Peripheral neuropathy = Grade 4	Discontinue participant from pomalidomide treatment regimen.
Other ≥ Grade 3 pomalidomide-related adverse events	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (adverse event must resolve to ≤ Grade 2).

Dose modifications for non-hematologic toxicity

Grade 3 rash or peripheral neuropathy

If a participant experiences a new Grade 3 rash or peripheral neuropathy, pomalidomide must be withheld until the toxicity has resolved to ≤ Grade 1. If the participant is receiving 4 mg/day, the daily dose should be reduced by one dose level, to dose level -1 (3 mg/day). If Grade 3 toxicity recurs in a participant receiving 3 mg/day, pomalidomide treatment will be stopped.

If any participant experiences Steven-Johnson Syndrome, anaphylaxis, or Grade 4 peripheral neuropathy, pomalidomide must be discontinued.

All other Grade 3/4 non-hematologic toxicities

If a participant experiences Grade 3/4 non-hematologic toxicity, pomalidomide must be withheld until the toxicity has resolved to ≤ Grade 2. Participants receiving 4 mg/day may then have treatment resumed at dose level -1 (3 mg/day). If the Grade 3/4 toxicity occurs or recurs at dose level -1, pomalidomide treatment will be stopped.

Dose modifications for hematologic toxicity

Grade 1/2

There will be no dose interruptions or reductions for Grade 1 or 2 hematological toxicity.

Grade 3/4 thrombocytopenia

If the participant experiences Grade 3 or 4 thrombocytopenia (platelet count decrease), defined as a platelet count < 50 x 10^9/L, pomalidomide must be withheld until the toxicity has resolved to ≤ Grade 2. Participants receiving 4 mg/day may then have treatment resumed at dose level -1 (3 mg/day). If Grade 3 or 4 thrombocytopenia occurs or recurs at dose level -1, pomalidomide treatment will be stopped permanently. If, at any time, Grade 3 or 4 thrombocytopenia persists for longer than two weeks after withholding pomalidomide, pomalidomide will be stopped permanently.

Grade 3/4 neutropenia (see Figure 5-1)

If a participant experiences Grade 3 or 4 neutropenia (absolute neutrophil count decrease), defined as a calculated ANC < 1.0 x 10^9/L, treatment with pomalidomide must be withheld. If available, growth factor (filgrastim or pegfilgrastim) may be started at standard doses (see Manual of Procedures (MOP) for acceptable dosing regimens). NOTE: Growth factors will not be provided by the study. If the ANC returns to ≤ Grade 2 within 1 week without any additional toxicity (i.e., fever), treatment with pomalidomide may continue without dose modification with continued growth factor support in all subsequent treatment cycles. In participants receiving growth factor support, if the ANC fails to return to ≤ Grade 2 within one week, or if additional toxicity is seen (i.e., fever), or if ≥ Grade 3 neutropenia recurs in a participant on pomalidomide with growth factor support, participants receiving 4 mg/day may then have treatment resumed at dose level -1 (3 mg/day). If the Grade 3 or 4 neutropenia occurs or recurs at dose level -1, pomalidomide treatment will be stopped.

If growth factors are not available or cannot be provided on a sustained basis for all subsequent treatment cycles, pomalidomide must be withheld until the toxicity has resolved to ≤ Grade 2. Participants receiving 4 mg/day may then have treatment resumed at dose level -1 (3 mg/day). If the Grade 3 or 4 neutropenia occurs or recurs at dose level -1, pomalidomide treatment will be stopped permanently.

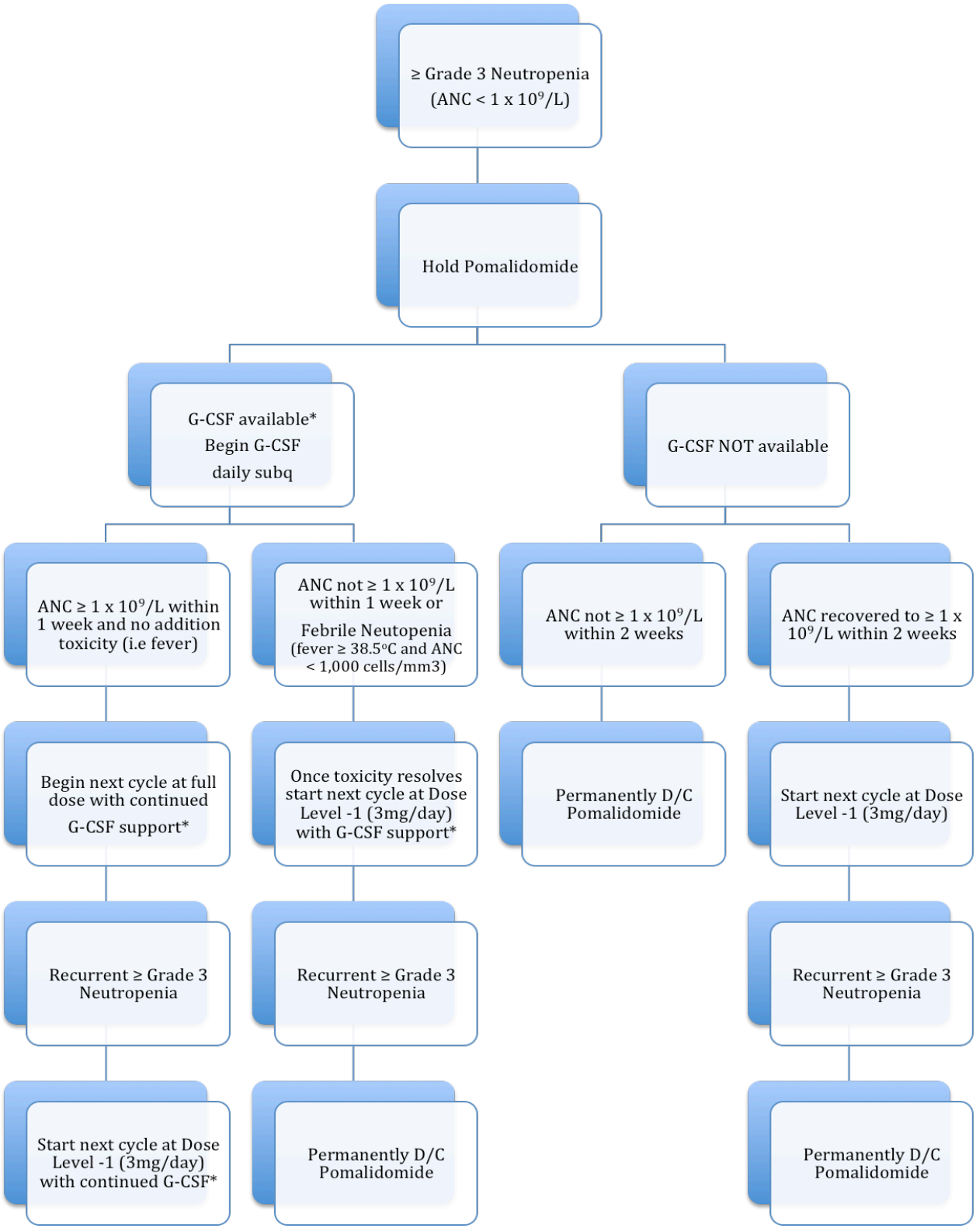
If, at any time, Grade 3 or 4 neutropenia persists for longer than two weeks after

withholding pomalidomide, pomalidomide will be stopped permanently.

Grade 1-4 anemia

No dose reductions will be performed for Grade 1-4 anemia. Participants who develop anemia may be transfused at the discretion of the investigator.

Figure 5-1. Dose Modification For and Management of Neutropenia With/Without G-CSF



* Available implies that sufficient supplies will be available to treat with G-CSF on all subsequent cycles using 300 mcg daily for five consecutive days during Days 22-28 of each cycle.

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting **in addition** to routine reporting (via Advantage eClinical). All adverse event reporting will be conducted via Advantage eClinical for this protocol.

The CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Version 5.0 of CTCAE.

6.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pomalidomide (CC-4047, NSC 767909)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2133 patients*. Below is the CAEPR for Pomalidomide (CC-4047).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, May 22, 2022[1]

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia[3]			***Anemia[3] (Gr 2)***
CARDIAC DISORDERS			
		Myocardial infarction[4]	
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
		Nausea	***Nausea (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
\INVESTIGATIONS			
	Alanine aminotransferase increased		
	Blood bilirubin increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
		Anorexia	***Anorexia (Gr 2)***
	Hyperkalemia		
	Hyponatremia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		
		Bone pain	***Bone pain (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies) [2]	
		Treatment related secondary malignancy[2]	
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		
		Dizziness	***Dizziness (Gr 2)***
		Dysesthesia	
		Paresthesia	
	Peripheral sensory neuropathy		
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
		Stroke[4]	
PSYCHIATRIC DISORDERS			
	Confusion		
		Hallucinations	
RENAL AND URINARY DISORDERS			

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Acute kidney injury		
	Urinary retention		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Cough	***Cough (Gr 2)***
		Dyspnea	***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Rash maculo-papular	***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (DRESS syndrome)	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
		Thromboembolic event[4]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]While not observed in human trials of pomalidomide, teratogenic effects (birth defects), thromboembolic events increases in secondary malignancy, tumor lysis syndrome, Stevens-Johnson syndrome, and thyroiditis/hypothyroidism are known events for this class of agents that include thalidomide and lenalidomide.

[3]Sickle cell crises in patients with SCD is a rare but serious event.

[4]Venous thromboembolic events (e.g., deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (e.g., myocardial infarction and stroke) have been observed to occur more frequently in multiple myeloma patients treated with pomalidomide and dexamethasone.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Pomalidomide (CC-4047) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pomalidomide (CC-4047) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (sickle cell anemia with crisis)[3]; Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Heart failure; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Vertigo

EYE DISORDERS - Blurred vision; Eye disorders - Other (eyelid swelling)

GASTROINTESTINAL DISORDERS - Abdominal pain; Colonic perforation; Dry mouth; Dyspepsia; Enterocolitis; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Disease progression; Malaise

IMMUNE SYSTEM DISORDERS - Allergic reaction

INVESTIGATIONS - CD4 lymphocytes decreased; CPK increased; Creatinine increased; Weight gain; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperuricemia; Hypocalcemia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Chest wall pain; Generalized muscle weakness; Muscle cramp; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (multiple myeloma, myelofibrosis, progression of MM); Tumor pain

NERVOUS SYSTEM DISORDERS - Dysphasia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Seizure; Syncope; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Depression; Insomnia

RENAL AND URINARY DISORDERS - Hematuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Nasal congestion; Oropharyngeal pain; Postnasal drip; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (sputum discolored)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythema multiforme; Hyperhidrosis; Pruritus

VASCULAR DISORDERS - Vascular disorders - Other (hyperviscosity syndrome)

Note: Pomalidomide (CC-4047) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.2 Classification of AEs by Severity and Relationship to Study Drug Administration

6.2.1 Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

This includes the following:

- AEs not previously observed in the participant that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with KS that were not present prior to study entry.
- Complications that occur as a result of protocol interventions.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency, or changed in character during the protocol-specified AE reporting period.

AEs will be followed for the participant's medical care until resolved to the baseline condition or protocol completion; for chronic conditions, resolution may occur when the AE is stable with appropriate medical management.

6.2.2 Life-threatening adverse event: Any AE that places the participant, in view of the Investigator, at immediate risk of death from the reaction.

6.2.3 Serious adverse event (SAE): Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.2.4 Hospitalization: hospitalization for expedited AE reporting purposes is defined as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the AE and should **ONLY** be used for situations where the AE truly fits this definition and **NOT** for hospitalizations associated with less serious events. (*e.g.*, a hospital visit where a patient is admitted for observation or minor treatment such as, hydration and released in less than 24 hours).

Prolongation of hospitalization is defined as an extension of current hospitalization equal to or greater than 24 hours.

Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

6.2.5 Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term 'toxicity' because of familiarity.

6.2.6 Unexpected adverse event: Any AE that is not listed in available sources including the package insert, the Investigator's Brochure, or the protocol, or is not consistent with the severity or specificity of the risk information described in the available sources, or is not consistent with the severity or specificity of the risk information described in the available sources.

6.2.7 CTEP Adverse Event Reporting System (CTEP-AERS): An electronic system for expedited submission of AE reports. A SAE reporting form in Advantage eClinical will be used in lieu of CTEP-AERS for this trial.

6.2.8 Attribution: An assessment of the relationship between the AE and the medical intervention. The CTCAE does not define an AE as necessarily "*caused by a therapeutic intervention."* After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Table 6-1: Attribution

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to	Unrelated	The AE *is clearly **NOT** related* to the

investigational agent/intervention		intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

NOTE: AEs listed as 'possibly, probably, or definitely' related to the investigational agent/intervention are considered to have a suspected 'reasonable causal relationship' to the investigational agent/intervention (ICH E2A). For routine adverse event reporting purposes on this protocol, "attribution" defines the relationship between the adverse event and the investigational agent(s)/intervention.

6.3 Expedited Adverse Event Reporting

6.3.1 Expedited AE reporting for this study must use Advantage eClinical. The reporting procedures to be followed are presented in this section and will align with the principles for SAE reporting in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 6.3.3).

A 24-hour notification is to be made to the AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into Advantage eClinical by the original submitter at the site.

6.3.2 Advantage eClinical is programmed for automatic electronic distribution of SAE reports to the following individuals: the AMC ODMC, AMC Medical Monitor, Protocol Chairs, and the Principal Investigator at the institution

6.3.3 Expedited reporting guidelines

Investigators must report ALL SAEs (as defined in Section 6.2.3) that occur from enrollment through 30 days following treatment discontinuation to the AMC and IRBs as required. The investigator's initial report to the AMC will be made using the Adverse Event form in Advantage eClinical within 24 hours of awareness of the event, followed by a completed SAE form as soon as possible, and in no more than 5 calendar days of awareness.

After 30 days following treatment discontinuation, SAEs will only be reported in the SAE form if determined by the investigator to have an attribution to the investigational agent of possible, probable, or definite.

Note: A death on study requires both routine and expedited reporting regardless of

causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions – Disease Progression."** Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

6.3.4 Expedited reporting for pregnancy

Female participants

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant or the partner of a male participant occurring while the participant is on pomalidomide or within 28 days after the participant's last dose, are considered immediately reportable events. Pomalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via Advantage eClinical and CTEP-AERS as a **Grade 4** event under: SOC pregnancy, puerperium and perinatal conditions; adverse event: **pregnancy, puerperium and perinatal conditions-other, fetal exposure.**

The female participant should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. Contact details of the healthcare provider who is following the pregnancy should be provided to the Investigator.

The Investigator will follow the female participant until completion of the pregnancy, and must make an amendment to the initial pregnancy report immediately regarding the outcome of the pregnancy and neonatal status (either normal or abnormal outcome). Infants must be followed through 1 year following birth, especially for developmental anomalies.

If the outcome of the pregnancy was abnormal (including spontaneous or therapeutic abortion, fetal demise and congenital abnormalities), the Investigator should report the abnormal outcome as an amendment to the initial pregnancy report as soon as the as the Investigator has knowledge of the outcome.

All neonatal deaths and neonatal complications that occur within 28 days of birth should be reported, without regard to causality, as an amendment to the initial pregnancy report. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the pomalidomide should also be reported as an amendment within 24 hours of the Investigator's knowledge of the event.

Male participants

If a female partner of a male participant taking investigational product becomes pregnant, the male participant taking pomalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

6.3.5 Expedited reporting to regulatory authorities

Each clinical center is responsible for ensuring that any AE or SAE that requires reporting to its IRB or respective national regulatory authority is completed in accordance with legal and regulatory timelines.

As this trial will not be conducted in the U.S. and will not support a marketing application or change in labeling or advertising for the drug, the trial is exempt from the requirement for an IND. No SAE reporting to FDA is required. In the event that any serious adverse events reported on this trial are determined to have a reasonable possibility of a causal relationship to the study drugs, the SAE will be reported to FDA using its voluntary reporting mechanism (MedWatch Online Voluntary Reporting Form). Voluntary SAE reporting will be performed by the AMC ODMC following the medical monitor's determination that the AE meets these criteria.

6.4 Routine Adverse Event Reporting

With the exception of the cases noted below, all adverse events that occur within timeframes defined in protocol Section 6.4.2 **must** be reported in routine study data submissions.

6.4.1 Additional protocol-specific routine adverse event reporting exclusions

All Grade 1 hematologic toxicities (Grade 1 thromboembolic events are excluded), all Grade 1 asymptomatic laboratory abnormalities, and Grade 2 anemia are not required to be reported in the Adverse Event Form in Advantage eClinical. These adverse events must be recorded in the source documents only.

6.4.2 Timeline for routine adverse event reporting

Adverse events that occur following the first dose of protocol treatment to 30 days post treatment discontinuation (Day 28 of the final cycle of treatment) must be recorded in the source documents and reported in an Adverse Event Form, unless specifically excluded in Section 6.4.1. AEs must be reported if the AE began any time within 30 days of completing study treatment. Additionally, if a site learns of any occurrence of death, cancer or fetal anomaly that is possibly, probably, or definitely related to the drug at any time after the study is closed, the event should be reported to the AMC through Advantage eClinical within 24 hours of when the investigator learns of the event.

6.5 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI Investigational New Drug (IND) or Investigational Device Exemption (IDE) application be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

6.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine adverse event reporting.

7.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 6.1.

7.1 Pomalidomide (NSC # 767909)

Pomalidomide is provided to the investigator via donation from Celgene. See the study Manual of Procedures for ordering information.

NOTE:

Before pomalidomide is dispensed, a patient must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Pomalidomide Counselor Program Site Counselor Identification Form in the protocol). Only a 21-day supply may be dispensed to a participant at one time.

7.1.1 Chemical name: 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

7.1.2 Other names: CC-4047, Pomalyst

7.1.3 Classification: immunomodulatory agent

7.1.4 CAS registry number: 19171-19-8

7.1.5 Molecular formula: C13H11N3O4, M.W.: 273.24

7.1.6 Mode of action: Pomalidomide induces cell cycle arrest and apoptosis. In vitro studies show immunomodulatory activity on T cell and NK cell mediated immunity and inhibition of certain pro-inflammatory cytokines. Pomalidomide can overcome some instances of lenalidomide resistance, which makes it an attractive agent for further drug development. Current investigations are underway to more precisely understand pomalidomide's multiple mechanisms of action.

7.1.7 Description: yellow solid with melting point of 319° C

7.1.8 How supplied: Celgene supplies and AMC distributes pomalidomide hard gelatin capsules in the following strengths, sizes and descriptions: 3 mg (size 2, dark blue and green) and 4 mg (dark blue and blue). Excipients include mannitol, pregelatinized starch, and sodium stearyl fumarate.

Pomalidomide capsules are supplied in high-density polyethylene (HDPE) containers fitted with induction seals and child-resistant plastic closures. Each bottle contains 21 capsules.

7.1.9 Storage: Store at 20°C-25°C (68°F-77°F) [USP Controlled Room Temperature]. Excursions are permitted to 15°C-30°C (59°F-86°F).

7.1.10 Stability: Celgene has run stability tests at 30°C/75% humidity (long term 3 years) and at 40°C/75% humidity conditions (accelerated for 6 months).

7.1.11 Route of administration: Take by mouth with or without food. Capsules should be swallowed whole and taken with water and not crushed, chewed or opened. If participants miss a dose, the dose may still be taken up to 12 hours after the time they normally would take it. If more than 12 hours have elapsed, the dose should

be skipped. Take the next dose at the usual time. Participants should not take 2 doses to make up for the one they missed.

7.1.12 Dispensing: Dispense up to a 21-day supply at one time. Sites may not mail pomalidomide to participants.

7.1.13 Patient care implications and counseling:

Risks associated with pregnancy

Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that pomalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Definition of female of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy, or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Before starting study drug

Female Participants: FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The participant may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Participants: Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Participants: Only enough pomalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

If pregnancy or a positive pregnancy test does occur in a study participant or the partner of a male study participant during study participation, pomalidomide must be immediately discontinued.

Counseling

Participants will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists, and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of participants. Refer to specific protocol sections for more information about training requirements.

Once trained, these healthcare staff will counsel participants prior to medication being dispensed to ensure that the participant has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the participant understands the risks associated with pomalidomide. This step will be documented with a completed Pomalidomide Education and Counseling Guidance Document (Appendix VIII) and no drug will be dispensed until this step occurs. Counseling includes verification with the participant that required pregnancy testing was performed and results were negative. A Pomalidomide Information Sheet (Appendix X) will be supplied with each medication dispense.

Tobacco use

Patients should be advised that smoking tobacco may reduce the efficacy of pomalidomide.

Overdose

Pomalidomide can be removed by hemodialysis.

7.1.14 Potential drug interactions: Pomalidomide is metabolized mostly by CYP 1A2 and 3A and is substrate for P-glycoprotein (P-gp). In vitro studies showed a significant plasma increase when strong CYP 1A2, 3A and P-gp inhibitors were given simultaneously. Avoid concomitant administration of strong inducers and inhibitors of CYP 1A2, 3A and P-gp in participants receiving pomalidomide. Closely monitor INR when participants receive concomitant warfarin and dexamethasone. Refer to the protocol for pomalidomide dose modifications. Pomalidomide does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5 in vitro. It is also not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. Pomalidomide does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4/5 in vitro.

7.1.15 Special handling: Pomalidomide should not be handled by non-patient FCBP or non-patient partners of FCBP unless gloves are worn. If any contact with a broken pomalidomide capsule or the medicine in the capsule occurs, the exposed area should be washed immediately and thoroughly with soap and water.

7.2 Drug Orders, Transfers, Returns, and Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Oral Drug Accountability Record Form (DARF) (available on the CTEP home page (http://ctep.cancer.gov)). The DARFs document the drug delivery date to the site, inventory at the site, use by each study participant. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol. The investigator will ensure that the drugs are used only in accordance with this protocol.

Drug will be shipped through a third party vendor. Instructions for drug ordering are available on the AMC website (www.AIDSCancer.org).

8.0 CLINICAL AND LABORATORY EVALUATIONS

Schedules shown in the Study Calendar below are provided in Appendix I.

8.1 Screening Evaluations

Screening evaluations are used to determine eligibility and are to be conducted within 21 days before treatment segment enrollment, unless otherwise specified. Participating sites must ensure a participant meets all eligibility criteria before completing the protocol-specific eligibility checklist in Advantage eClinical.

8.1.1 Informed consent must be collected prior to performing any screening evaluations.

8.1.2 Medical history, including history of AIDS-defining illnesses, history of smoking and current tobacco use, performance status, life expectancy, any prior receipt of thalidomide or its analogs, history of other malignancies, history of major cardiovasular events, history of coagulation disorders per Section 3.2.13, and participant demographic information.

8.1.3 Medication history, including all current ART and prior ART regimens. Per Section 3.1.8 the ART regimen must be stable for 12 weeks prior to study enrollment. All prescription and non-prescription medications, including over-the-counter medications, alternative therapies, herbal medicines/tea, and dietary supplements taken within 14 days prior to study enrollment must be recorded.

8.1.4 Complete physical examination including vital signs, height, weight, assessment of signs and symptoms,, neuropathy evaluation (i.e., pain, aching, or burning in hands or feet), and performance status.

8.1.5 Biopsy diagnostic of KS at any time prior to study enrollment. The biopsy specimen must be available for review (including performing or reviewing latency-associated nuclear antigen (LANA) stains) and confirmation by an AMC-approved pathologist. Specimens for this review must conform to the requirements listed in Appendix V.

8.1.6 Tumor assessment to determine that participant does not have visceral disease requiring cytotoxic chemotherapy.

8.1.7 HIV plasma quantitative RNA viral load via HIV quantitative polymerase chain reaction (PCR) within 12 weeks of enrollment.

8.1.8 Chest X-ray (CXR) to evaluate for pulmonary KS. If available and clinically indicated, computed tomography (CT) of the lung may be performed to verify chest X-ray findings.

8.1.9 Pregnancy testing if FCBP by beta-human chorionic gonadotropin (b-HCG) with a sensitivity of at least 25 mIU/mL within 14 days prior to enrollment.

8.1.10 Complete blood count (CBC) with differential and platelets within 7 days prior to enrollment.

8.1.11 Serum chemistries including sodium, potassium, chloride, bicarbonate, phosphate, glucose, creatinine, albumin, AST, ALT, alkaline phosphatase, and total bilirubin within 7 days prior to enrollment.

8.2 Baseline Evaluations

Baseline evaluations are to be conducted within 7 days prior to starting treatment, unless otherwise specified below. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the first cycle of therapy.

8.2.1 Enrollment into Advantage eClinical Treatment Segment once all eligibility criteria are confirmed.

8.2.2 Interim medical history, including HIV-related and AIDS-defining events.

8.2.3 Review of concurrent medications as defined in Section 8.1.3.

8.2.4 Complete physical examination including vital signs, weight, assessment of signs and symptoms, neuropathy evaluation (i.e., pain, aching, or burning in hands or feet), and performance status.

8.2.5 Tumor assessments with photographic record must be performed prior to initiating treatment. These may be performed on Day 1, but no earlier than 7 days before initiating study treatment. If the screening tumor assessments with photographic record are performed within 7 days before initiating study treatment, the screening tumor assessments can be used as a baseline assessment. Tumor assessments and photographs should be performed as outlined in the KS Tumor Assessment MOP.

8.2.6 Staging criteria: KS staging will be based on the modified AIDS Clinical Trials Group (ACTG) Oncology Committee Staging Criteria as outlined in Appendix XIII.

8.2.7 HIV plasma quantitative RNA viral load via HIV quantitative PCR within 28 days before initiating study treatment.If the HIV viral load used to determine eligibility is performed within 28 days of the start of protocol therapy, the screening viral load can be used as a baseline test. The results of the baseline HIV viral load do not need to be available prior to the start of protocol therapy.

A CD4 T cell count is required within 28 days prior to study treatment.

8.2.8 Pregnancy prevention counseling for all participants before starting each new cycle of pomalidomide, as required at Appendix VII. Pregnancy testing if FCBP by b-HCG with a sensitivity of at least 25 mIU/mL within 24 hours of starting pomalidomide.

8.2.9 Whole blood collection for serum cytokine studies (one 7 mL red top tube) (Appendix XII) on day 1 prior to the first dose.

8.3 Evaluations During Treatment

Except as noted, evaluations required to ensure safe and timely treatment may be conducted within three days prior to beginning cycles 2-12 of pomalidomide.

8.3.1 KS Tumor Assessment will be performed prior to every cycle.

8.3.2.1 For participants with known pulmonary KS at study entry, a CXR (and CT scan, if available and clinically indicated) will be repeated every third cycle.

8.3.2.2 If during the pre-treatment assessment at cycle 7 day 1 the participant has

stable disease (SD) or progressive disease (PD) the participant must discontinue treatment. If the participant has a partial response (PR) or a complete response (CR), the participant may continue with treatment for up to 12 cycles.

8.3.2 Photographic documentation will be completed at each visit when the KS response category changes (see KS Tumor Assessment MOP for lesion photography guidelines).

8.3.3 Complete physical examination including vital signs, weight, assessment of signs and symptoms and toxicity, neuropathy evaluation (i.e., pain, aching, or burning in hands or feet), and performance status.

8.3.4 Interim medical history, including HIV-related and AIDS-defining events.

8.3.5 Assessment of adherence to ART (by participant report of missed doses).

8.3.6 Assessment of adherence to study therapy.

8.3.7 Review of concurrent medications.

8.3.8 CBC with differential and platelets.

8.3.9 Serum chemistries: sodium, potassium, chloride, bicarbonate, phosphate, glucose, creatinine, albumin, AST, ALT, alkaline phosphatase, and total bilirubin.

8.3.10 HIV plasma quantitative RNA viral load via HIV quantitative PCR, and CD4 T cell count prior to cycles 2, 4, 7, and 10.

8.3.11 Pregnancy prevention counseling for all participants before starting each new cycle of pomalidomide, as required at Appendix VII. Pregnancy testing if FCBP by beta-HCG with a sensitivity of at least 25 mIU/mL within 24 hours of starting each cycle of pomalidomide. Weekly pregnancy testing for FCBP is required during the first cycle. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 10-14 days while on study.

8.3.12 Whole blood collection for serum cytokine studies (one 7 mL red top tube) prior to treatment for cycle 3 day 1 and cycle 7 day 1 (Appendix XII).

8.4 Treatment Discontinuation Evaluations

8.4.1 Participants who complete all treatment per-protocol or who discontinue protocol treatment early for any reason should have the following evaluations and laboratory tests within 1 week and again at 30 days (±7 days) after the last dose of protocol treatment, unless otherwise noted.

8.4.1.1 KS tumor assessment, including re-evaluation of visceral disease if not already done while on study, and photographic documentation.

8.4.1.2 Complete physical examination including vital signs, weight, assessment of signs and symptoms and toxicity, neuropathy evaluation (i.e., pain, aching, or burning in hands or feet), and performance status.

8.4.1.3 Interim medical history, including HIV-related and AIDS-defining events.

8.4.1.4 Assessment of adherence to ART.

8.4.1.5 Assessment of adherence to study therapy.

8.4.1.6 Review of concurrent medications.

8.4.1.7 CBC with differential and platelets.

8.4.1.8 Serum chemistries: sodium, potassium, chloride, bicarbonate, phosphate, glucose, creatinine, albumin, AST, ALT, alkaline phosphatase, and total bilirubin.

8.4.1.9 HIV plasma quantitative RNA viral load via HIV quantitative PCR, and CD4 T cell count within 1 week of last dose of protocol treatment.

8.4.1.10 CXR (and CT if available/indicated) for participants who had either an abnormal CXR/CT at Screening or have clinical evidence for new pulmonary involvement. CXR/CT should only occur once following the last dose of protocol treatment.

8.4.1.11 Pregnancy testing if FCBP by beta-HCG with a sensitivity of at least 25 mIU/mL at study discontinuation, and at Day 28 (±7 days) following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur at study discontinuation, and again at 14 and 28 days (±7 days) after this date.

8.4.1.12 Participants who discontinue treatment will have whole blood collection for serum cytokine studies (one 7 mL red top tube) within 1 week of last dose of protocol treatment (Appendix XII).

8.4.1.13 Participants with stable disease (SD) or progressive disease (PD) at the time of treatment discontinuation will complete all study follow up at the 30 day post-treatment visit and the Off-Study Summary Form will be completed. See Section 6.4.2 for the timeline for routine adverse event reporting.

8.5 Follow-up Evaluations

Only participants who achieve PR or CR will have additional physical examinations repeated every 12 weeks (counting from the last day, Day 28, of the final cycle, ±2 weeks) for up to 48 weeks or until an earlier time of PD requiring additional treatment. AEs must be reported if the AE began any time within 30 days of completing study treatment. Additionally, if a site learns of any occurrence of death, cancer or fetal anomaly that is possibly, probably, or definitely related to the drug at any time after the study is closed, the event should be reported to the AMC through Advantage eClinical within 24 hours of when the investigator learns of the event.

The following procedures should be performed during the follow-up visits:

8.5.1 Complete physical examination including vital signs, signs and symptoms review, toxicity, neuropathy evaluation (i.e., pain, aching, or burning in hands or feet), and performance status.

8.5.2 Review of interim medical history, including AIDS-defining events.

8.5.3 KS tumor assessment.

8.5.4 At a participant's final study visit, the Off-Study Summary Form will be completed.

9.0 MEASUREMENT OF EFFECT

All participants will be evaluated for KS response by physical examination as described in the KS Tumor Assessment MOP within three days prior to the first day of every cycle. See Appendix I for the KS Tumor Assessment schedule.

CTEP-registered advanced practice clinicians who are non-physician investigators (i.e., NP or PA) may perform toxicity and response assessment as allowed per local licensure requirements for this study.

Any non-physician investigator performing assessments on the study must be listed in the site delegation log and be CTEP-registered and IRB approved.

9.1 Definition of Response

Response and progression will be evaluated in this study as follows:

9.1.1 Complete response (CR): CR is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. In some individuals, residual skin color changes may remain visible at one or more site(s) of lesions that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. In the event such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required in order to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered partial (PR). In participants in whom all detectable cutaneous disease has resolved and in whom there are no visible pigmented macules as described above, a confirmatory skin biopsy is not required. In participants known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made.

NOTE: To classify a response as a CR, the participant must have a CR in both the cutaneous and noncutaneous (if applicable) sites of disease and no evidence of progression as defined by the above criteria.

9.1.2 Partial response (PR): PR is defined as no new oral lesions or new or progressive visceral sites of involvement, or the appearance or worsening of tumor-associated edema (as defined in the AMC-100 MOP) or effusions or the development of five or more new cutaneous lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease; AND

- A 50% or greater decrease in the number of all lesions present at entry (either total body or in the representative areas) lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesions become macules, either total body or in the representative areas) present at entry lasting for at least 4 weeks; OR
- A 50% or greater decrease in the area of the cutaneous marker lesions compared with entry lasting for at least 4 weeks; OR

- A 50% or greater decrease in the number or size of all measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions; OR
- Complete disappearance of non-measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions.

NOTE: To classify a response as PR, the participant must have at least a PR in either the cutaneous or noncutaneous sites of disease, and no evidence of progression as defined in the above criteria.

NOTE: Participants with residual tumor-associated edema or effusion who otherwise meet the criteria for CR will be classified as having a PR.

9.1.3 Stable disease (SD) is defined as any response not meeting the criteria for CR, PR, or PD.

9.1.4 Progressive disease (PD) is defined as follows:

For participants with ≤50 cutaneous lesions

PD is defined as any one or more of the following:

- ≥25% increase in the area of the cutaneous marker lesions compared to entry or best response;
- ≥25% increase in the total lesion count**,** or a minimum of five new lesions**,** whichever is greater, compared with entry or best response;
- ≥25% increase in the number of raised lesions, or a minimum of five new raised lesions, whichever is greater, compared with entry or best response.

NOTE: There are body sites where disease is particularly difficult to evaluate, and a few new lesions may be counted in spite of the fact that a participant is not actually progressing. For example, lesions of the foot, particularly those that are flat, are difficult to evaluate because their intensity may vary based on how much edema is present, how much the person walked the day before, how long his/her feet have been in a dependent position prior to the physical exam.

For participants with >50 cutaneous lesions

PD is defined as any one or more of the following:

- ≥25% increase in the area of the cutaneous marker lesions compared to entry or best response;
- ≥25% increase in the total number of lesions in the prospectively defined anatomic sites containing representative lesions;
- a total of five new lesions in anatomic sites that were previously documented as having no evidence of cutaneous disease,
- ≥25% increase in the number of raised lesions in the prospectively defined anatomic sites containing representative lesions (minimum of five raised lesions if there are very few raised lesions, for example <8) whichever is

greater. Photographic documentation of "gross" or significant progression, particularly in areas that were not being followed, will be of particular value.

9.1.5 Noncutaneous progression (PD): Noncutaneous PD includes new oral or visceral sites of involvement or progression of oral or visceral disease or the development of new or increasing tumor-associated edema or effusion that interferes with the participant's normal activities lasting for at least two consecutive evaluations. Progressive oral or visceral disease, for measurable and evaluable disease, should be analogous to cutaneous KS response criteria.

Progressive edema is defined as the following:

- An increase in non-pitting/woody edema in an upper or lower extremity associated with an increase in limb circumference of at least 3 cm from entry or best response, sustained for at least two consecutive evaluations, and measured at a fixed point on the extremity with respect to a bony landmark (e.g., 10 cm below the lower border of the patella); AND/OR
- New appearance of non-pitting/woody edema in an extremity where none was previously present, sustained for at least two consecutive evaluations; AND/OR
- New or worsening edema in a non-extremity site (e.g., periorbital, genital) that interferes with function and is sustained for at least two consecutive evaluations.

9.1.6 Recurrent disease

Recurrent disease is defined as the appearance of tumor following documentation of a complete remission.

9.1.7 Time to response

Time to response is defined as time from the first dose of chemotherapy until documentation of first response.

9.1.8 Time to progression

Time to progression is defined as time from initiation of chemotherapy to documentation of first progression.

9.1.9 Response duration

Response duration is defined as the time from first documentation of response to documentation of first progression.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

Primary endpoints

- Overall response rate
- Complete response rate
- Proportion of participants who experience toxicities of Grade 3 or higher

Secondary endpoints

- Changes in CD4 counts
- Changes in HIV viral loads

10.1.1 Statistical rationale

The sample size is based on determining if pomalidomide administered as monotherapy has sufficient efficacy (overall response rate (ORR) ≥ 30%) to merit consideration of further clinical development in this clinical setting, and is tolerable.

10.1.2 Statistical power calculation

To test the null hypothesis that the ORR = 0.10 against the alternative that it is 0.30 with pomalidomide monotherapy at the one-sided 0.10 significance level with power of 0.90 will require 30 participants. The following stopping rule is based on stopping when the probability of observing more than x dose-limiting toxicities (DLTs) in the first cycle, as defined in Section 4.2, is less than 0.05 with an underlying first cycle DLT rate of 0.10.

Since the enrollment is planned to close at the end of 2023, the target number of enrollment (30 participants) may not be achieved. It is expected that 26 participants will be able to be enrolled before study enrollment closes. As an illustration of statistical power based on the assumption that the null hypothesis that the ORR = 10% against the alternative that it is 30% with pomalidomide monotherapy at the one-sided 10% significance level, statistical power of 87.5% can be achieved with 26 participants. The following stopping rule is based on stopping when the probability of observing more than *x* DLTs in the first cycle, as defined in Section 4.2, is less than 5% with an underlying first cycle DLT rate of 10%.

10.1.3 Stopping Rules

Table 10-1. Stopping Rules for Dose-limiting Toxicity

N	More Than *X* Participants with DLTs
7-8	2
9-14	3

15-20	4
21-26	5

The study team will monitor trial safety and the safety stopping rule using the procedures outlined in the DMSP. The AMC Data and Safety Monitoring Board (DSMB) will perform an annual review of trial safety to evaluate whether DLTs have occurred and that the safety stopping rule has been followed appropriately. Accrual will not be paused for these reviews because they are confirmatory to the study team's process, unless the safety rule is invoked by the study team's review.

Table 10-2. Stopping Rules for Hematologic and Non-Hematologic Toxicity

	Stop if the number of cycle 1 ≥ Grade 3 hematologic toxicities exceeds X OR the number of cycle 1 ≥ Grade 3 non-hematologic toxicities exceeds Y	
N	X (hem)	Y (non-hem)
7	6	2
8	6	2
9	7	3
10	8	3
11	8	3
12	9	3
13	9	3
14	10	3
15	11	4
16	11	4
17	12	4
18	12	4
19	13	4
20	14	4
21	14	5
22	15	5
23	15	5
24	16	5
25	17	5
26	17	5

The stopping rule for hematologic toxicities is based on probability of observing > x ≥ Grade 3 hematologic toxicities < 0.05 if the underlying rate of ≥ Grade 3 hematologic is 0.50.

The stopping rule for non-hematologic toxicities is based on probability of observing > x ≥ Grade 3 non-hematologic toxicities < 0.05 if the underlying rate of ≥ Grade 3 hematologic is 0.10.

10.1.4 Statistical analysis plan

The binomial proportion and its 90% one-sided exact confidence interval will be

used to estimate the overall response rate, the complete response rate, and the proportion of participants who experience a Grade 3 or higher toxicity. If the lower bound of the 90% exact confidence interval for the overall response rate is > 0.10, then the null hypothesis will be rejected.

Changes in CD4 counts and HIV viral load will be evaluated using generalized estimating equations.

To assess the effect of pomalidomide treatment on serum cytokine levels, general estimating equations (GEE) will be used to evaluate changes in cytokine levels from baseline. Logistic regression analyses will be used to determine if changes in cytokine levels from baseline are associated with clinical response.

11.0 ROLE OF DATA MANAGEMENT

11.1 CRF Instructions

Access to the internet data entry system for this study, Advantage eClinical, and instructions for recording of study data on CRFs will be provided by the AMC ODMC at www.AIDSCancer.org. Participating institutions are responsible for submitting data and/or data forms via Advantage eClinical in accordance with the AMC Data Entry Guide and specific form instructions, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

11.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix III, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

11.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. The AMC will ensure that all participating centers, as required by the applicable regulatory requirements in each country in which the trial will be conducted, will submit any required applications to the appropriate authorities for review, acceptance, and/or permission to begin the trial. Any notification/submission should be dated and contain sufficient information to identify the protocol (ICH E6). Documentation of this authorization will be collected by the AMC before each center will be activated to enroll participants.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB or institutional ethics committee (IEC), which specifically approves the protocol and informed consent, before participant enrollment. The IRB/IEC must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB/IEC must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are participant to inspection during or after completion of the study. AEs must be reported to the IRB/IEC according to local procedures. The IRB/IEC should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature, significance and risks associated with the study must be explained to the participant. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of the investigational agent(s) and/or study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the participant to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

12.2 Pomalidomide Counseling Program

Each site must have two counselors trained by Celgene through the Counseling Program. The program is available on the internet for each person who has completed the site counselor identification form and registered with Celgene prior to completing the program. See Appendix XI for the site counselor identification form. Each participant must be counseled prior to dispensing pomalidomide and documentation is kept in the participant's records. Both the training certificates and the completed Pomalidomide Education and Counseling Guidance Documents are auditable documents and must be produced upon

request. Counselors who wish to counsel participants for different protocols at the same site or for the same protocol at different sites should indicate this on the site counselor identification form.

Each site must have two trained counselors available for counseling all participants receiving pomalidomide supplied by Celgene. Trained counselors must complete training using the online program provided free by Celgene, the pomalidomide counseling program. Registration for the program is done by completing the form found in Appendix XI and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to the AMC for documentation. Sites may not order pomalidomide until documentation for two trained counselors is provided to the appropriate office.

12.3 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IRB/IEC of the treating institution. A copy of the written approval of the IRB/IEC and the national regulatory body (if applicable) must be sent to the ODMC.

12.4 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Clinical Trials Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Table 12-1. Accrual Targets

INTERNATIONAL PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	24	0	0	26
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	2	24	0	0	26

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APPENDIX I: SCHEDULE OF EVALUATIONS

The schedule of evaluations below applies to all participants on study. Baseline evaluations are to be conducted within 21 days prior to start of protocol therapy, unless otherwise noted. X-rays (and CT scan, if available and clinically indicated) must be done within 21 days prior to the start of therapy. Evaluations performed during treatment should be repeated within 3 days prior to initiation of the next cycle of therapy, unless otherwise noted.

Evaluation	Screening	Baseline	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	Treatment Discontinu-ation[m]	Post-Treatment Follow-up[n]
Informed consent	X															
Medical history[a]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Medication history[b]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam[c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Diagnostic biopsy[d]	X															
CXR, CT if available and indicated[e]	X					X			X			X			X	
KS tumor assessment with photographic record[f]	X[p]	X		X	X	X	X	X	X[o]	X	X	X	X	X	X	X
KS staging		X														
CBC w/diff, platelets[h]	X			X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistries[h,i]	X			X	X	X	X	X	X	X	X	X	X	X	X	
HIV viral load, CD4 count[j]	X	X		X		X			X			X			X	
1 red top tube (7 mL)[k]			X		X				X						X	
Pregnancy testing and prevention counseling[l]	See table below for requirements.															
Dispense pomalidomide			X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug adherence assessment				X	X	X	X	X	X	X	X	X	X	X	X	

a: To include participant demographic information, and history of AIDS-defining conditions.
b: Medication history to adhere to requirements at Section 8.1.3 at baseline, and will be updated at each subsequent visit, including ART adherence assessment.
c: To include vital signs, weight, assessment of signs and symptoms and toxicity, neuropathy evaluation (i.e., pain, aching, or burning in hands or feet), and performance status. Height documented at screening only.

	d: Biopsy samples must meet requirements for pathology review at Appendix V. e: Chest X-ray performed at baseline for all participants to evaluate for pulmonary KS. CT of the lung will be performed if available and clinically indicated to verify chest X-ray findings. During treatment, chest X-ray (and CT if available/indicated) will be repeated every third cycle for participants with pulmonary involvement. At treatment discontinuation, chest C-ray (and CT if available/indicated) will be performed once. f: Tumor assessment and photographic record may be performed on Day 1 of cycle 1, but no earlier than 7 days before starting treatment. Photographic assessments will be repeated on study only following a change in response status. See MOP for details. g: Serum pregnancy test for females of childbearing potential only. See additional chart below for requirements. h: Perform within 7 days before Day 1 of cycle 1. Perform within 3 days before the start of the next cycle for all other cycles. i: To include sodium, potassium, chloride, bicarbonate, phosphate, glucose, creatinine, albumin, AST, ALT, alkaline phosphatase, and total bilirubin. j: Collect at all visits indicated. At baseline, collect CD4 count within 28 days before study treatment. At baseline collect HIV viral load within 12 weeks of enrollment and within 28 days of the start of protocol therapy. If the HIV viral load test used to determine eligibility is performed within 28 days of start of protocol therapy, the test does not need to be repeated. The results of baseline HIV viral load do not need to be available prior to protocol therapy as long as eligibility measures are available. At treatment discontinuation, collect both within one week after stopping treatment only. k: For serum cytokine studies (see Appendix XII). Collect prior to treatment at all visits indicated. Collect within 1 week of last dose of protocol treatment. l: See additional chart below for requirements m: Evaluations to be performed within 1 week after and at 30 days after the last dose of protocol treatment, unless otherwise noted. n: Follow-up evaluations for participants with CR or PR only to occur every 12 weeks ± 2 weeks until week 48 after treatment discontinuation (defined as Day 28 of the last cycle), unless PD occurs earlier. o: If during the pre-treatment KS assessment on C7D1 the participant has stable disease the participant must discontinue treatment prior to starting cycle 7 of therapy. If the participant has partial or complete response, the participant may continue treatment for up to 12 cycles. p: Tumor assessment to determine that participant does not have visceral disease requiring cytotoxic chemotherapy must be performed within 21 days prior to enrollment.

Celgene Pregnancy Prevention Testing and Counseling Requirements

Procedure	Screening	Cycle 1				Subsequent cycles		Study drug discontinuation
	≤ 14 days from baseline (first day of study drug administration)	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	28 days (±7 days) from the last of day of last cycle
Pregnancy testing [1]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Education and counseling[3]		X[3]				X[3]		X[3]
Dispense pomalidomide		X[4]				X[4]		

[1]Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

[2] Pregnancy tests must occur within 14 days before enrollment and again within 24 hours before initiation of the first cycle of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on study treatment (including breaks in treatment); at discontinuation of pomalidomide and at day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 10-14 days while on study treatment (including breaks in treatment), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix VII: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[3] The Pomalidomide Education and Counseling Guidance Document (Appendix VIII) must be completed and signed by a trained counselor at the participating site prior to each dispensing of pomalidomide treatment. A copy of this document must be maintained in the participant records. The Pomalidomide Information Sheet (Appendix X) will be given to each participant receiving pomalidomide treatment. The participant must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

[4] Only enough pomalidomide for 21 days or one cycle of study treatment (whichever is shorter) may be provided to the participant each cycle.

APPENDIX II: PERFORMANCE STATUS SCALES

Karnofsky Performance Scale		ECOG Performance Status Scale	
Percent	**Description**	**Grade**	**Description**
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX III: AMC DATA AND SAFETY MONITORING PLAN

(Version 9.0 October 6, 2020)

Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct (which may include trials conducted in the U.S., international sites, or both), IND Sponsor (AMC Investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

Monitoring the Progress of Trials and the Safety of Participants

Routine and Expedited AE reporting

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a CI for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S.US, all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include Sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the Sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND Sponsor or its designee will

issue the determination as to whether the AE requires IND safety reporting to FDA as a serious and unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND, in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the Sponsor or Sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC Investigators or industry sponsors.

Expedited Reporting to the Institutional Review Board (IRB)

The requirements for IRB review will be identified in the protocol section on ethical and regulatory obligations. All AMC trials initiated before September 1, 2020 and all international sites for all AMC studies are subject to local IRB review; only U.S.US sites are subject to the NCI requirement to use a single IRB for protocols initiated on or after September 1, 2020. For trials subject to local IRB review, the site principal Investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the single IRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to that IRB, in accordance with its standards of procedure.

To comply with Investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all Investigators upon receipt from the Sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (U.S.US trials subject to single IRB review/CTEP IND agents). The site CI responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

Procedures for Monitoring Trial Progress and Pharmacovigilance

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC Investigators and their staff. It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the protocol chair and

also by the appropriate Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under investigation. Findings from these reviews are communicated to the protocol chairs and all AMC Investigators, and posted to the AMC Operations web site.

Data and Safety Monitoring Board Review (DSMB) Review

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all Phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved by CTEP and, as applicable, required by the IRB of record.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review are prepared by the AMC group statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB charter. This report addresses specific toxicity issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC group chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The group chair or designee is then

responsible for notifying the protocol chair and relevant SWG chair before the recommendations of the DSMB are carried out. In the unlikely event that the protocol chair does not concur with the DSMB, then the OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG chair, group chair, DSMB chair, and NCI division director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC Investigators and staff. It is each site principal Investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by a single IRB, the AMC ODMC will support notification to the IRB as required per its procedures.

Cohort Trial Reviews Not Subject to DSMB Review

For Phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable for Phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage Phase II trial, is based on meeting criteria stated in the protocol, and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met.

Plans for Assuring Compliance with Requirements Regarding AE Reporting

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating Investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal Investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical Investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP Investigator registration, and also for AMC IND studies sponsored by AMC Investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site Investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that

meets expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the Sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC medical monitor review reported AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials monitored by the NCI's Clinical Data Update System (CDUS), AE information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), AE information is transmitted electronically to NCI every two weeks.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For Phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC Investigators, the AMC DSMB will be notified of the suspension and the reason. For Phase I and II trials, the protocol chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into the applicable clinical data entry system for the trial. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative

action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option to implement remedial action(s) for the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site Investigators or staff members.

APPENDIX IV: PARTICIPANT MEDICATION DIARY

YOU MUST KEEP THIS DIARY AND BRING IT TO EVERY APPOINTMENT.

Study Participant ID #: _____

Cycle # ____

Pomalidomide dose: ____ mg (_____ 4 mg capsules and ____ 3 mg capsules) daily x 21 days (no drug on days 22-28)

Please record in the chart below the date and time that your pomalidomide dose was taken. Be sure to record the doses when you take them, and avoid writing entries for several days at once. When you are finished, bring this diary with you when you next see the Doctor or Study Staff. In the "Comments" section write any problems you are having with the medicines or if you missed a dose and why or if you only took part of the medicine.

Your pomalidomide capsules should be taken by mouth once a day around the same time each day, with or without food. Capsules should be swallowed whole and taken with water and not crushed, chewed or opened. DO NOT to bite or chew on the capsule. Drink an extra glass of water immediately if the capsule breaks in your mouth.

Missed pomalidomide doses, regardless of reason, SHOULD be taken within 12 hours of when it would normally be taken. If more than 12 hours have passed, the dose SHOULD NOT be taken. If you skip a dose, the missed dose SHOULD NOT be made up. If you accidentally take more than the prescribed dose of pomalidomide contact the study staff immediately and seek emergency medical care if needed.

Pomalidomide SHOULD NOT be handled by non-patient FCBP or non-patient partners of FCBP unless gloves are worn. If any contact with a broken pomalidomide capsule or the medicine in the capsule occurs, the exposed area should be washed immediately and thoroughly with soap and water.

Day of Cycle	Date DD/MMM/YYYY	Time Pomalidomide Taken (circle AM/PM)	# of 4mg Capsules Taken	# of 3mg Capsules Taken	Comments
1	_____/_____/_____	___:___ AM / PM			
2	_____/_____/_____	___:___ AM / PM			
3	_____/_____/_____	___:___ AM / PM			
4	_____/_____/_____	___:___ AM / PM			
5	_____/_____/_____	___:___ AM / PM			
6	_____/_____/_____	___:___ AM / PM			
7	_____/_____/_____	___:___ AM / PM			

Study Participant ID #: _____

Cycle # ____

Day of Cycle	Date MM/DD/YYYY	Time Pomalidomide Taken (circle AM/PM)	# of 4mg Capsules Taken	# of 3mg Capsules Taken	Comments
8	_____/_____/_____	___:___ AM / PM			
9	_____/_____/_____	___:___ AM / PM			
10	_____/_____/_____	___:___ AM / PM			
11	_____/_____/_____	___:___ AM / PM			
12	_____/_____/_____	___:___ AM / PM			
13	_____/_____/_____	___:___ AM / PM			
14	_____/_____/_____	___:___ AM / PM			
15	_____/_____/_____	___:___ AM / PM			
16	_____/_____/_____	___:___ AM / PM			
17	_____/_____/_____	___:___ AM / PM			
18	_____/_____/_____	___:___ AM / PM			
19	_____/_____/_____	___:___ AM / PM			
20	_____/_____/_____	___:___ AM / PM			
21	_____/_____/_____	___:___ AM / PM			

Please return the unused capsules to your doctor with your diary at your next appointment.

Participant's signature: _____

Date of signature: _____

<u>Study Staff Must Complete This Section</u>:

1. Date of last study visit _____
2. Date of current visit _____
3. Participant's planned total daily dose during that period _____

4. Total number of capsules during that period _____

5. Total number of capsules returned_____

6. Study Staff Signature _____

NOTE: Non-compliance with study agent administration should be noted at the time of diary collection and the participant should be instructed again regarding dosing instructions.

APPENDIX V: CENTRAL PATHOLOGY REVIEW

Handling of Tissues:

Participants must have measurable cutaneous Kaposi sarcoma (KS) that has been pathologically confirmed by an AMC-approved pathologist. Participants must have one of the following for the purposes of external pathology review:

- Diagnostic tissue block or H&E plus five blank FFPE sections for LANA staining at the AMC Sub Saharan Biorepository, or
- High quality images of the LANA staining for electronic submission for pathology review and H&E is available on site

Tissues should be submitted to the AMC sub-Saharan Biorepository for storage, according to the specimen handling requirements and shipping schedules specified in the AMC-100 Manual of Procedures.

Record of Specimens:

This study will track specimens via GlobalTrace^{SM}, a component of the AMC Advantage eClinical system. The GlobalTrace shipment manifest must accompany all specimen shipments.

Pathology Review:

Pathology review will be conducted under the supervision of Dr. Ethel Cesarman of Weill-Cornell Medical College, at the AMC Pathology Core Laboratory.

APPENDIX VI: LIST OF PROHIBITED AND CAUTIONARY MEDICATIONS

The following medications may not be taken while participating on this study through 30 days after the last dose of protocol treatment:

Use of agents containing zidovudine (including Combivir® and Trizivir®) are prohibited. In order to be eligible, participants taking zidovudine must change to a different regimen at least 7 days prior to therapy initiation. Changes to ART therapy during the study may be made if medically necessary (toxicity, failure of regimen, etc.).

Use of medications or substances that are strong inhibitors of CYP1A2, which include amiodarone, cimetidine, fluoroquinolones (e.g., ciprofloxacin, enoxacin), fluvoxamine; and ticlopidine are excluded.

Co-administration of efavirenz, an inhibitor of CYP1A2, with strong inhibitors of CYP3A4 and P-glycoprotein (P-gp) is prohibited.

Use of erythropoietin is prohibited.

Because there is a potential for interaction of pomalidomide with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Due to known cytochrome P450 inhibitory effects of protease inhibitors, particularly for ritonavir, the case report form will particularly note the use of ritonavir for HIV management.

Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

APPENDIX VII: POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks associated with pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

Definition of females of childbearing potential (FCBP)

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Definition of females not of childbearing potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

Counseling

For a FCBP, pomalidomide is contraindicated unless all of the following are met (i.e., all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed.
- She must be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy.
- She understands the need to commence pomalidomide as soon as it is dispensed following a negative pregnancy test.
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan and in the Informed Consent.
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding.
- Acknowledges the aforementioned requirements.

Females NOT of childbearing potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (i.e., all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of childbearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male participants taking pomalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP.
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP.
- Understand the potential teratogenic risk if the participant donates semen or sperm.

Contraception

Female participants of childbearing potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence [e.g. calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception) from heterosexual contact during the following time periods related to this study:

1. For at least 28 days before starting pomalidomide;
2. While taking pomalidomide;
3. Dose interruptions; and
4. For at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraceptive method appropriate to the participant. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgetrel-releasing intrauterine system [IUS], medroxyprogeterone acetate depot injections, ovulation inhibitor progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy

**** For purposes of this study, birth control pills and partner's vasectomy will not be considered highly effective methods of contraception.***

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in participants with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a participant is currently using combined oral contraception the participant should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in participants with neutropenia.

Male participants

Male participants must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of Childbearing Potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The participant may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

Regular menses are defined as a 28-day (+/- 7 days) cycle.

A participant's menses are considered irregular if the cycle length is less than 21 days or greater than 35 days. If a participant is unable to recall the date of her last menstrual period, the irregular menses pregnancy testing schedule must be followed.

Pregnancy Precautions for Pomalidomide Use

Before Starting Pomalidomide

Female participants of childbearing potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The participant may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

Male participants

Male participants must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

During and After Study Participation

Female participants

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a participant, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a participant misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

Male participants

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male participant while taking pomalidomide, the Investigator must be notified immediately.

Additional precautions

- Participants should be instructed to never give pomalidomide to another person.
- Participants should be instructed to return any unused capsules to the study doctor.
- Participants should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 21-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

APPENDIX VIII: POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE PARTICIPANTS

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Study Participant ID: _____

(Check the appropriate box to indicate risk category)

Female

If female, check one:

☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

☐ NOT FCBP

Female of childbearing potential

1. I have verified and counseled the participant regarding the following:

- Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
- That the required pregnancy tests performed are negative.
- The participant confirmed that she is using TWO reliable methods of birth control at the same time or complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).
- One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Examples of highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
    - Tubal ligation
    - Partner's vasectomy

      **** For purposes of this study, birth control pills and partner's vasectomy will not***

be considered highly effective methods of contraception.

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

- The participant confirmed that even if she has amenorrhea she must comply with advice on contraception.
- Pregnancy tests before, during administration of pomalidomide and at last dose of pomalidomide, even if the participant agrees not to have reproductive heterosexual contact.
- Frequency of pregnancy tests to be done:
  - Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days and a second within 24 hours of the start of pomalidomide.
  - Every week during the first 28 days of this study and a pregnancy test every 28 days while the participant is taking pomalidomide if menstrual cycles are regular
  - Every week during the first 28 days of this study and a pregnancy test every 14 days while the participant is taking pomalidomide if menstrual cycles are irregular.
  - If the participant missed a period or has unusual menstrual bleeding.
  - When the participant is discontinued from the study and at day 28 after the last dose of pomalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after the last dose of pomalidomide.
- The participant confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.
- The participant confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.
- The participant confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.
- The participant confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.
- The participant has not and will never share pomalidomide with anyone else.
- The participant has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- The participant has not and will not break, chew, or open pomalidomide capsules at any point.
- The participant confirmed that she will return unused pomalidomide capsules to the study doctor.

I have provided the Pomalidomide Information Sheet to the participant.

Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy)

I have verified and counseled the participant regarding the following:

- Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- The participant has not and will never share pomalidomide with anyone else.
- The participant has not and will not donate blood while taking pomalidomide, during dose

interruptions and for at least 28 days after the last dose of pomalidomide.
- The participant has not and will not break, chew, or open pomalidomide capsules at any point.
- The participant confirmed that she will return unused pomalidomide capsules to the study doctor.

I have provided the Pomalidomide Information Sheet to the participant.

<u>Do Not Dispense Pomalidomide if</u>:

- **The participant is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The participant states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The participant stated that she has or does not want to adhere to pregnancy precautions outlined within this Pregnancy Prevention Plan (PPP).**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

****Maintain a copy of the Education and Counseling Guidance Document in the patient records****

APPENDIX IX: POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE PARTICIPANTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Participant Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The participant confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g. calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The participant confirmed that he has not impregnated his female partner while in the study.
   - ☐ The participant confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The participant has not and will never share pomalidomide with anyone else.
   - ☐ The participant confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The participant has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The participant has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The participant confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the participant.

Do Not Dispense Pomalidomide if:

- **The participant stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

APPENDIX X: POMALIDOMIDE INFORMATION SHEET FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits. **If you are a female who is able to become pregnant:**

   - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting pomalidomide
     - while taking pomalidomide
     - during breaks (dose interruptions) of pomalidomide
     - for at least 28 days after stopping pomalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of pomalidomide
     - 24 hours prior to the first dose of pomalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking pomalidomide if you become pregnant while taking pomalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute who will report the case to the pharmaceutical collaborator Celgene Corporation.
   - **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**
     - The study doctor will be able to advise you where to get additional advice on contraception.

   If you are a female not able to become pregnant

   In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

1. Male participants (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking pomalidomide
    - During breaks (dose interruptions) of pomalidomide
    - For at least 28 days after the last dose of pomalidomide
2. **Male participants should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute who will report the cases to the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

All participants

1. **Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
2. **Do not donate blood** while you take pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
3. **Do not break, chew, or open pomalidomide capsules at any point.**
4. You will get no more than a 28-day supply of pomalidomide at one time.
5. Return unused pomalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX XI: POMALIDOMIDE COUNSELING PROGRAM SITE COUNSELOR

Celgene Corporation

Celgene Pregnancy Prevention & Counseling Program Site Counselor Identification Form
NCI Protocol #: AMC-100

IDENTIFICATION FORM

- **Please identify at least two (2) counselors and fax back to 888-314-2392**
- **Use one form per counselor.**
- **Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.**
- **If you have any questions, please email (**coop_ma@celgene.com**)**

General Information

Principal Investigator: _____ Institution Name: _____

Counselor Information

CTEP person ID: _____ CTEP site ID: _____

First Name: _____ Middle Initial: _____ Last Name: _____

License Type: (circle one) MD PhD PA CNP RN LPN RPh Other: _____

Email Address: _____

Phone: _____ Fax: _____

Institution Street Address: _____

City: _____ State/Region: _____

Zip/Post Code: _____ Country: _____

Which training will you require? ☐ **Adult** ☐ **Pediatric**

Were you previously approved as a Counselor? ☐ **No** ☐ **Yes (Previous training)** ☐ **Adult** ☐ **Pediatric**

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution

APPENDIX XII: COLLECTION AND SHIPPING INSTRUCTIONS FOR PERIPHERAL BLOOD FOR IMMUNE RESPONSE (CYTOKINES AND SOLUBLE RECEPTORS)

1.0 OBJECTIVES

The aims of this correlative study are to evaluate the effect of therapy with pomalidomide on serum levels of biomarkers of immune activation to identify the clinical correlates with regard to tumor response.

2.0 BACKGROUND

Pomalidomide was designed to further increase the anti-angiogenic and immunomodulatory effects compared to the prior IMiD compounds. Pomalidomide promotes T helper cell (Th)-1 differentiation in vitro (Xu 2008) and increased Th-1 cytokine production in animal models (Dredge 2002).

It is unknown to what extent pomalidomide will alter the cytokine environment in participants with HIV-associated Kaposi sarcoma. Additionally, it is unclear if changes to the cytokine environment can be correlated with tumor response.

Serum samples will be collected at baseline, after cycle 2, and at treatment discontinuation for testing for CRP, VEGF (angiogenesis), IP10/CXCL10 (an IFN-inducible inflammation-associated chemokine), IL8, TNF-alpha, IL17A, IL17E, IL6, IFN-gamma, and IL10 (inflammation-associated cytokines), and soluble (s)TNF-receptor type 2 (sTNFR2), sCD27 (a TNFR family molecule), sIL2R alpha, sCD14 and sCD163 as macrophage activation/inflammation-associated molecules. Assays will be performed using the Luminex platform (Luminex, Austin, Texas, USA), using multiplexed fluorescent bead-based assays (R&D Systems, Minneapolis, MN) at the AMC Protein Biomarker Profiling Core Laboratory.

Luminex assay data will be analyzed using a BioPlex 200 apparatus and BioPlex Manager software (Bio-Rad, Hercules, California, USA). All samples from an individual will be tested on one plate to minimize variability. Results will be correlated with clinical responses to provide preliminary information on the cytokines that may play a role in pomalidomide's activity against KS.

3.0 RATIONALE

The recent availability of multiplexed immunometric assays has made possible the simultaneous assessment of several of these immune activation and inflammation-associated factors, using small volumes (<500 µl) of serum or plasma.

The results of this study will provide information on immune activation/inflammation-associated biomarker serum levels in HIV+ cancer participants treated with pomalidomide.

4.0 EVALUATIONS

Serum levels of cytokines and inflammation-associated molecules will be determined at the following study visits: pre-study (entry), and after cycle 2 of therapy, and then after cycle 6 or at the early discontinuation visit.

5.0 ANALYSES

The working hypothesis that will be tested is that participants who are treated with pomalidomide will display elevated levels of T cell-produced cytokines following treatment initiation, and that the level of T cell cytokine responses will diminish with time, following the conclusion of therapy.

Levels of cytokines and inflammation-associated biomarkers will be determined using two multiplexed (Luminex platform) panels. Testing for CRP, VEGF (angiogenesis), IP10/CXCL10 (an IFN-inducible inflammation-associated chemokine), IL8, TNF-alpha, IL17A, IL17E, IL6, IFN-gamma, and IL10 (inflammation-associated cytokines), and soluble (s)TNF-receptor type 2 (sTNFR2), sCD27 (a TNFR family molecule), sIL2R alpha, sCD14 and sCD163 as macrophage activation/inflammation-associated molecules will be performed, using multiplexed assays from R&D Systems. Analysis will be performed using the Luminex platform, a fluorescent bead-based assay.

Samples will be processed on site and shipped to the AMC SSA Biorepository for storage. At the end of the study, serum will be sent in batch to the AMC Biomarkers Laboratory (Epeldegui laboratory at UCLA) for analysis.

6.0 SHIPPING INSTRUCTIONS AND SAMPLE PROCESSING

Refer to the AMC-100 Manual of Procedures for instructions.

APPENDIX XIII: KS STAGING CRITERIA

	GOOD RISK (0) (All of the following)	POOR RISK (1) (Any of the following)
Tumor (T)	- Confined to skin and/or lymph nodes and/or minimal oral disease[1]	- Tumor-associated edema or ulceration - Extensive oral KS - Gastrointestinal KS - KS in other nonnodal viscera
Immune system (I)	- CD4 cells > 200/µL	- CD4 cells < 200/µL
Systemic illness (S)	- No history of OI or thrush - No "B" symptoms[2] - Performance status > 70 (Karnofsky)	- History of OI and/or thrush - "B" symptoms present - Performance status < 70 - Other HIV-related illness (e.g., neurological disease, lymphoma)

T_0 = tumor confined to skin, lymph nodes and/or minimal oral disease.
T_1 = any tumor falling under the "Poor Risk" criteria.
S_0 = no history of OI or thrush, no "B" symptoms, and Karnofsky Performance status $\geq$ 70.
S_1 = any "Poor Risk" systemic illness signs and symptoms.

NOTE: Staging criteria taken from: Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immunodeficiency syndrome: A proposal for uniform evaluation, response, and staging criteria. J Clin Oncol 1989; 7: 1201-1207. These criteria were adopted by the ACTG Oncology Committee.

[1] Minimal oral disease is nonnodular KS confined to the palate.
[2] "B" symptoms are unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhea persisting more than 2 weeks.

APPENDIX XIV: AIDS MALIGNANCY CONSORTIUM (AMC) DATA SHARING PLAN

The National Institutes of Health (NIH) requires the sharing of final research data generated from NIH funded studies with the research community for research purposes. The NIH Data Sharing Policy (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) lists many reasons for sharing data from NIH-supported studies. Data to be shared may include aggregate data (e.g., summary statistics and tables), as well as individual-level data. The primary sources of AIDS Malignancy Consortium (AMC) data are the Clinical Data Commons and the Lab Data Commons. In all cases the Operations and Data Management Center (ODMC) will code data shared beyond the ODMC and Statistical and Data Analysis Center (SDAC) in such a way as to protect privacy concerns with respect to sensitive data. Prior to making data from a specific AMC study available for sharing, the ODMC will construct a data dictionary describing data elements available from that study so that interested parties may be informed of what data are available for request. For studies where the AMC sites participate and enroll study participants, but the data management activities are supported by another entity such as a data coordinating center for another clinical trial network, or studies that include another entity and the ODMC and SDAC support the study, data sharing policies and procedures will be determined through negotiations between the AMC and the other entity(ies).

I. Data Access

a. Within the AMC

AMC investigators may request de-identified data from completed AMC studies for the pursuit of research questions ancillary to the protocol-specified study aims. AMC investigators must submit a written Ancillary Study Form to the AMC Executive Committee detailing the research question, the analytic approach, publication plans, and the data required for the proposed study for review and approval. Upon approval of the request by the AMC Executive Committee, the requester will be required to sign a Data Use Agreement with the ODMC which covers data analysis, data confidentiality, authorship, and intellectual property sharing prior to release of the data. Requests to have a statistical analyst outside of the AMC SDAC perform the data analysis requires Executive Committee approval.

b. Outside the AMC

There are currently no plans to release the individual participant-level data to investigators outside of the AMC until release of the data to a public data repository. If the AMC leadership determines that individual participant-level data will be shared with investigators outside of the AMC, an SOP will be developed to describe the process.

II. Public Use Dataset

It is anticipated that following the acceptance of a manuscript that addresses the primary and secondary objectives of an AMC clinical trial, the ODMC will establish a CDISC-mapped, de-identified version of the data with appropriate documentation to be submitted to a public data repository such as the National Clinical Trials Network (NCTN) Data Archives.

III. Model Organisms

At present, no new, genetically modified variants of model organisms (including non-human mammalian and non-mammalian eukaryotic models) will be generated. In the event that model organisms are generated from future studies, we will adhere to the NIH Grant Policy Sharing Model Organisms (effective October 2018).

IV. Genomic Data Sharing

To date, no genome-wide association studies (GWAS) have been proposed. In the event that future studies proposed by the AMC include GWAS studies, we will follow the NIH Grants Policy Genomic Data Sharing (GDS) Policy/Policy for Genome-Wide Association Studies (GWAS) (effective October 2018). AMC will work to ensure that, with IRB approval, the GWAS data generated by AMC projects are deposited into NIH's Database of Genotype and Phenotype (dbGaP) housed at the National Center for Biotechnology Information in the National Library of Medicine where they may be available to the broader research community. Data will be released no later than after acceptance for publication of the main findings of these studies