**Abbreviated Title:** Pomalidomide in Kaposi sarcoma
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**Title:** A Phase I/II Study of the Safety, Pharmacokinetics and Efficacy of Pomalidomide (CC-4047) in the Treatment of Kaposi Sarcoma in Individuals with or without HIV.

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**Investigational Agents:**

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|---|---|
| Drug Name: | Pomalidomide (CC-4047) |
| IND Number: | 113751 |
| Sponsor: | Center for Cancer Research |
| Manufacturer: | Celgene Corporation |
| Supplier | Celgene Corporation |

**Commercial agents:** None

## PRÉCIS

### Background

Kaposi Sarcoma (KS) is an incurable, multicentric angioproliferative tumor that most frequently involves the skin. It is seen most frequently in people with HIV or other forms of immune compromise. Current therapies are limited by toxicities, including cumulative cardiotoxicity, while effective oral agents, agents deliverable in resource-limited settings, and agents deliverable long-term for relapsing disease are all lacking.

### Objective

The primary objective of this study is to:

- Assess the safety, tolerability and pharmacokinetics of pomalidomide in subjects with Kaposi sarcoma, whether HIV associated or not.

### Eligibility

- Age ≥18 years
- Measurable, pathologically confirmed KS
- Any HIV status; HIV-associated KS subjects must be receiving and able to comply with HAART and have achieved an HIV viral load <10,000 copies/mL
- Hematologic and biochemical parameters within prespecified limits at baseline
- Willing to use effective birth control, as defined in the full protocol
- For subjects enrolled in the anti-tumor activity assessment phase, if KS is HIV-associated it must be increasing despite HAART and HIV suppression for ≥2months, or stable despite HAART for ≥3months
- No symptomatic pulmonary or visceral KS
- No specific KS therapy within 4 weeks (6 weeks if that therapy was bevacizumab)
- Neither pregnant nor breast feeding

### Design

This is an open label single agent phase I/II study of pomalidomide in patients with KS. In the phase I portion, up to six subjects will initially be treated with pomalidomide 5mg daily for 21 days of a 28 day cycle. Subject to toxicity evaluation, this dosage may be deescalated to 3mg daily for 21 days of a 28 day cycle in a second cohort of up to six subjects. If either dose proves tolerable, the study will proceed to the phase II portion, and additional subjects to a goal of 15 HIV positive and 10 HIV negative subjects evaluable for response will be added at the highest tolerable dose to gain preliminary information on activity.

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 INTRODUCTION

## 1.1 STUDY OBJECTIVES

### *1.1.1 Primary Objective:*

- Assess the safety, tolerability and pharmacokinetics of pomalidomide at an oral dose regimen of 5mg once daily for 21 days of a 28 day cycle in subjects with Kaposi sarcoma, whether HIV associated or not, or in the case that the initial dosing schedule of pomalidomide is not tolerated, assess the safety, tolerability and pharmacokinetics of pomalidomide at 3mg daily for 21 days of a 28 day cycle.

### *1.1.2 Secondary Objectives:*

- Explore in a preliminary manner the antitumor effect of pomalidomide at whichever of the dosing schedules described above is determined to be tolerable
- Assess the variation in pomalidomide pharmacokinetics in relation to common antiretroviral agents, especially potentially nephrotoxic agents such as tenofovir
- Assess changes in quality of life in subjects receiving pomalidomide
- Explore in a preliminary manner the safety, tolerability and antitumor effect of a second course of pomalidomide in patients who manifest KS requiring therapy after deriving clinical benefit from initial treatment with pomalidomide.

## 1.2 BACKGROUND AND RATIONALE

### *1.2.1 Kaposi Sarcoma and Kaposi sarcoma-associated herpesvirus*

#### 1.2.1.1 Epidemiology

Kaposi Sarcoma (KS) is a multicentric angioproliferative tumor that most frequently involves the skin but may also involve lymphatic channels and nodes, and viscera including the lungs and gastrointestinal tract(1). It is now known to be caused by Kaposi sarcoma herpesvirus (KSHV,

also called human herpesvirus 8 [HHV-8])(2). It is remarkable for its tendency to progress or regress based on host immune factors(3). KS was originally described by Moritz Kaposi in 1872 as an indolent tumor usually seen in elderly men in the Mediterranean (now called classical KS)(4), but the tumor also exists in endemic form in Africa (often in women and in younger patients, and perhaps more clinically aggressive) and in immunosuppressed populations, including transplant recipients and persons with HIV (epidemic KS)(5).

In addition to KS, KSHV is established as the causative agent of primary effusion lymphoma (PEL), a distinct form of multicentric Castleman disease (KSHV-MCD)(2, 6, 7), and a newly-described inflammatory syndrome, the KSHV inflammatory cytokine syndrome (KICS)(8). While most common in HIV-infected individuals, each of these tumors has also been reported in other immunosuppressed and older individuals(9). KSHV is a necessary, but not sufficient, cause of KS. Indeed, in the absence of cofactors such as HIV infection or iatrogenic immunosuppression, the risk of developing KSHV-associated diseases among KSHV-infected individuals is relatively low: only about 1 in 400 to 1 in 1500 KSHV-infected individuals develop KS, with the incidence increasing with age (likely in response to waning cellular immunity)(10-12). In contrast, in the absence of effective antiretroviral treatment, as many as 1 in 2 patients co-infected with HIV and KSHV will develop KS(13, 14). In the US, up to 80% of cases of KS occur in people with HIV/AIDS(15).

Supporting the role of host immune factors in KS pathogenesis, the risk of KS development is strongly associated with defects in cellular immunity(3). Decreasing CD4 cell count is associated with increasing risk of KS in both AIDS-associated KS and classic KS(13, 16). Furthermore, KSHV infected patients with KS have been shown to have decreased KSHV-specific CD4 responses when compared to HIV/KSHV co-infected individuals without KS (17). Response to therapy has been associated with increases in both absolute CD4 count and KSHV-specific T-cell responses in treatment naive patients with HIV-associated KS(18), as well as in organ transplant recipients whose KS regressed with reduction in immunosuppression(19).

The incidence of KS in developed countries declined markedly with effective antiretroviral therapies, falling gradually through the 1990s following the development of nucleoside inhibitors for HIV and then dramatically after the introduction of highly active combination antiretroviral regimens (HAART)(13, 20-25). In sub-Saharan Africa, where the prevalence of both HIV and KSHV is very high and widespread access to HAART is still limited, KS remains one of the most common tumors(26-29).

#### 1.2.1.2 Pathogenesis

KSHV is a large (165kB) double-stranded DNA virus which, like Epstein-Barr virus (EBV), is a member of the gammaherpesvirus family(2, 30). Like all herpesviruses, KSHV infection exhibits both latent and lytic phases, distinguished by their viral gene expression patterns(31-33). Latency, with extremely limited gene expression, is established in endothelial cells and B-lymphocytes(34). Following lytic activation via the lytic switch gene RTA, the full complement of viral encoded genes is expressed, and host cellular machinery is redirected to the manufacture and assembly of progeny virions(35-37).

KSHV is notable for its molecular piracy of genes homologous to cellular regulatory genes(38, 39) and its modulation of cellular survival, angiogenic and immune regulatory pathways(40, 41). Many of the genes expressed in latency are directed to these ends, including ORF K9/vIRF-1 and ORF K11.5/vIRF-2, which inhibit interferon signaling and ORF16/vBcl-2, an inhibitor of

apoptosis(31, 42). Similarly, genes expressed in lytic stage include a viral homolog of human interleukin-6, called viral IL-6 (encoded by ORF K2) and a constitutively active G-protein coupled receptor (vGPCR) encoded by ORF74(43-46). Viral IL-6 functions both as a B-cell survival factor and a promotor of angiogenesis(47, 48) while vGPCR is constitutively active and modulates a range of cellular processes with immunomodulatory and additional pro-angiogenic functions(45, 49). Its pro-angiogenic functions are mediated via stabilization of hypoxia inducible factor-1α (HIF-1α) and induction of vascular endothelial growth factor-A (VEGF-A) and basic fibroblast growth factor (bFGF) (45, 49-52). Additional virally encoded pro-angiogenic factors include three macrophage inflammatory proteins (viral MIP-1, -2, and -3)(44). KSHV also modulates the host cell response through induction of host cytokines including human IL-6 and IL-10 (the latter via viral non-coding microRNAs(53)) and TNF-α, among others(54-56).

While there are no suitable *in vitro* or animal models of KS, studies of KS tissue and KSHV-infected cell lines suggest that, in the absence of effective host immunological control of the virus, these factors contribute the pathogenesis of KS(41). KS tumors are notable for the proliferation of pathognomonic abnormal spindle cells, mixed inflammatory infiltrates, and the formation of aberrant, leaky vascular channels(57, 58). Most of the spindle cells in KS lesions contain KSHV, and express vascular epithelial growth factor receptor type 2 (VEGFR-2) and VEGF-R3 (Flt-4)(59-63). Moreover, spindle cells derived from KS patients have been shown to proliferate in response to VEGF, VEGF-C (a ligand for VEGF-R3) and bFGF(59, 62). The inflammatory infiltrate is composed largely of KSHV-uninfected cells including B-lymphocytes(64, 65). Lesions consequently are characterized by high local expression of TNF-α and hIL-6 (from both KSHV-infected and uninfected inflammatory cells), while in severe cases pro-inflammatory cytokine abnormalities are detectable even systemically(8, 66, 67).

Most of the spindle cells in KS lesions contain KSHV in a latent form, while a smaller number of cells express KSHV lytic gene products(68). The role of the interplay of lytic and latently infected cells in KS tumor tissue is the subject of ongoing investigation(32, 69). However, it is hypothesized that production and induction of pro-angiogenic and inflammatory factors by the few cells undergoing lytic KSHV replication together with pro-survival and pro-angiogenic signaling in latently infected cells are critical(67). Activation of KSHV via vGPCR/ORF74 is considered to play a central role in this process(54). Intermittent lytic cycles may also contribute to viral and tumor persistence and to internal dissemination of KS lesions, by allowing the infection of additional host cells.

#### 1.2.1.3 Therapies

In patients with HIV-associated KS, HAART is a cornerstone of management. It appears that HIV infection can promote the development of KS in a variety of ways, including immunosuppression, cytokine dysregulation, and direct effects of HIV in enhancing spindle cell proliferation and KSHV cellular infection(13, 16, 18, 70, 71). Institution of HAART alone can alone lead to KS regression, and may be sufficient therapy in some cases, presumably through its effect on these factors(18, 72, 73). Remissions are most likely to occur in patients who have not previously received antiretroviral therapy, those with effective HIV suppression and associated immune reconstitution, and those who have limited disease(18, 72). Patients with KS who are already receiving effective HAART are much less likely to respond to continued antiretroviral therapy alone(71). Regardless of the extent of KS, HAART improves durability of response and overall survival in patients with HIV-associated KS. Hence, for those patients who do not

respond to HAART alone or who are felt to need additional specific KS therapy, HAART should accompany specific KS therapy.

In patients with symptomatic visceral disease, advanced cutaneous or lymphatic involvement, or disease whose response to HAART is unsatisfactory, additional systemic therapy with cytotoxic agents is indicated. First line cytotoxic therapy in the United States generally comprises liposomal doxorubicin (as the liposomal preparation likely improves delivery to the lesions), based on phase III studies with liposomal preparations of doxorubicin and daunorubicin conducted prior to widespread availability of HAART. These demonstrated overall response rates of approximately 46-75%, superior to those seen with combination chemotherapy, and good tolerability(74-81). Paclitaxel is also FDA-labeled for use in KS, based on phase II studies conducted by HAMB investigators and others(82-84). In a recently-published multicenter study comparing liposomal doxorubicin with paclitaxel conducted by the AIDS Malignancy Consortium, overall response rates were similar for each agent (46% versus 56%, respectively)(85). However, the paclitaxel arm was characterized by somewhat hematologic and gastrointestinal toxicity and a higher proportion of patients failing to complete therapy.

Standard approaches to therapy for patients with non-HIV-associated KS are not well defined. For patients whose KS is associated with iatrogenic immunosuppression, for example following solid organ transplantation, reduction in immunosuppression or substitution with mTOR pathway inhibitors such as rapamycin/sirolimus (which inhibit vGPCR downstream signaling through PI3K/AKT(86, 87)) should be considered in the first instance, with cytotoxic therapy reserved for advanced or refractory disease(88). In classical KS that requires treatment, liposomal doxorubicin is again commonly used as first line therapy in the United States.

In addition to HAART, several other immune modulatory approaches have shown evidence of benefit in KS. In both the pre-HAART and HAART eras(89-91), studies with interferon-α showed moderate clinical activity, with response rates of 38-42% in highly immunosuppressed cohorts, albeit associated with significant toxicity including constitutional symptoms and cytopenias(92). More recently, HAMB investigators have reported studies with interleukin-12 both alone and in combination with cytotoxic chemotherapy). Overall response rates were 71% with IL-12 alone at doses from 300-620ng/kg, and 83% when used initially in combination with liposomal doxorubicin followed by a consolidation phase with IL-12 monotherapy(93-95). We have also observed a partial response to IL-2 in a single patient with non-HIV-associated KS (Uldrick and Yarchoan, personal communication), an observation that may in part be explained by indirect inhibition of vGPCR via IP-10/CXCL10 modulation(54, 96).

HAMB investigators and others have also previously explored the activity of the oral immunomodulatory agent thalidomide in patients with KS, with or without HIV. These studies were largely conducted prior to the introduction of HAART. In the HAMB study of HIV-associated KS, 47% (8) patients achieved a partial response, and an additional 12% (2) had stable disease(97). Notably however, in the HAMB cohort the median dose utilized was high: up to 1000mg, median 500mg, compared with the standard dose in multiple myeloma of 200mg daily. Clinical toxicities were correspondingly relatively severe, including sedation and depression. Another group demonstrated somewhat lower response rates (35% partial responses) at a dose of 100mg daily, in a similar patient cohort(98). Toxicities were similar to those seen in the HAMB cohort. A retrospective case series of 11 patients with non-HIV-related Kaposi's sarcoma, including one renal transplant recipient, three patients (27%) achieved a partial response and 4 (36%) had a stable disease; several discontinued therapy early due to peripheral neuropathy(99).

Other case reports and small series have also reported activity(100, 101). More recently, the thalidomide derivative lenalidomide has been reported to have clinical activity in a case series of three patients with HIV-associated KS(102).

Direct targeting of dysregulated angiogenesis has also shown therapeutic efficacy in KS. HAMB is also investigating the vascular endothelial growth factor (VEGF) pathway inhibitors bevacizumab and sorafenib. For bevacizumab as a single agent, the overall response rate was 31%, with minimal toxicity(103) (also, Uldrick and Yarchoan, personal communication). These agents remain the subject of investigation, including the ongoing HAMB study of bevacizumab in combination with liposomal doxorubicin followed by bevacizumab maintenance in patients with severe KS (study 09-C-0130) and the HAMB phase 1 study of sorafenib in patients with limited KS (study 06-C-0083).

Notwithstanding the availability of these agents, there is a substantial unmet clinical need for novel, effective and readily deliverable agents for KS(104). Each of the established therapies, while effective, has important limitations. In particular, there is a lack of effective oral agents; the tolerability of available immune modulatory agents is poor(89, 97); and the most effective cytotoxic agents (liposomal doxorubicin and daunorubicin) exhibit cumulative cardiotoxicity(105). The latter is particularly significant given that KS commonly recurs: one year progression free survival following initial therapy is approximately 70% and patients often have to be treated, at least intermittently, for years. This significantly limits the utility of anthracyclines in the many patients with recurrent or refractory disease(106). Importantly too, with the exception of HAART, no effective agent for KS is both tolerable and readily deliverable within the existing health infrastructure to affected populations in resource-limited areas such as sub-Saharan Africa. The development of effective anti-KS agents that are safely deliverable orally even in resource limited settings could assist in addressing this significant global health problem.

### *1.2.2 Immunomodulatory derivatives of thalidomide*

Immunomodulatory derivatives of thalidomide (IMiDs), including pomalidomide (CC-4047) and lenalidomide (CC-5013) are structural derivatives of thalidomide, itself a glutamic acid derivative(107). Pomalidomide is derived by the addition of an amino group to the fourth carbon of the phthaloyl ring of thalidomide (see also Section **14.1**)(108). This class of compounds share activities including modifying immune system function and angiogenesis, while differing in potency and other pharmacologic properties. The derivatives were selected with the aim of optimizing the parent compound's anti-angiogenic and (primarily) TNF-α inhibitory actions while minimizing its toxicities, particularly neurotoxicities(109).

The mechanisms of action of IMiDs are diverse, and likely vary in differing tissue and tumor types(107, 110). For pomalidomide, these include effects on T and NK cell function and profiles, cytokine regulation, inflammation, and angiogenesis. Its immunomodulatory effects, particularly T cell and NK activation and anti-TNF-α activities, are several-fold more potent than thalidomide or lenalidomide: for example it is up to 50,000 times more potent than thalidomide in its inhibition of TNF-α(107, 109). Conversely, the anti-angiogenic properties of all three agents appear approximately equivalent *in vitro* models(107, 108). Compared with thalidomide, pomalidomide and lenalidomide also exhibit enhances direct tumor anti-proliferative activity and ability to disrupt tumor-microenvironment interactions(107). Importantly too, pomalidomide may have activity in patients previously treated with other members of the class(111, 112).

### *1.2.3 Pomalidomide*

#### 1.2.3.1 Mechanisms of Action

Pomalidomide augments T cells responsiveness and proliferation by several mechanisms, leading to increased production of IL-2 and interferon-γ (IFN-γ) (113-116). It enhances CD4- and CD8-positive T cell co-stimulation, associated with increased tyrosine phosphorylation of CD28 on T cells and activation of the PI3-K signaling pathway, and enhances transcriptional activity of activated protein-1 (AP-1), a key driver of IL-2(109), (113-116). This T cell reprogramming is mediated at least in part by induction of the transcription factor T-bet(117). In addition, T regulatory (Treg) cell expansion and FOXP3 expression on Tregs are inhibited without affecting survival or apoptosis, or Treg expression of IL-10 or TGF-β(118). Th1 cytokine production is also enhanced. These effects were confirmed *in vivo* in patients with multiple myeloma treated with pomalidomide, who showed increased CD45RO expression on CD4- and CD8-positive T cells, with a concomitant decrease in CD45RA, together with increased IL-2 and IL-12 levels: all consistent with activation of T cells and monocytes(119).

The immunomodulatory activity of pomalidomide also includes inhibition of pro-inflammatory cytokine and chemokine production by peripheral blood mononuclear cells (PBMCs) (114-116). Key effects include inhibition of TNF-α, IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP-1α) (108, 116, 120). IL-2 production is enhanced from both CD4- and CD8-positive T cells, independent of T cell proliferation(115). RANTES (regulated upon activation, normal T cell expressed, and secreted) production is inhibited(108). IL-10 and IL-12 production may be augmented or inhibited, depending on the cell type and other factors; production from PBMCs appears to be inhibited, while T-cell production is augmented(108, 115) (116, 120). Pomalidomide exhibited additional anti-inflammatory effects through inhibition of cyclooxygenase-2 (COX-2) and reduction in TNF-α production from LPS stimulated monocytes(116).

Pomalidomide effects on angiogenesis have been demonstrated in *in vitro* models of endothelial sprout formation and vessel migration and other systems(121, 122). In both rat aorta and human umbilical artery explants, pomalidomide caused inhibition of microvessel formation and in a human umbilical vein endothelial cell (HUVEC) tube formation, in a dose dependent manner(108, 123). Pomalidomide also inhibited HIF-1α expression in HUVECs(123). It also significantly inhibited endothelial cell invasion through fibronectin coated membranes towards VEGF, bFGF, transforming growth factor-α (TGF-α) and TNF-α in cell migration assays(108).

In myeloma, NHL, ALL, breast, non-small cell lung cancer and Namalwa tumor cell lines (the latter being hematopoetic cells with one copy of chromosome 5 deleted), pomalidomide demonstrated inhibition of cellular proliferation(121, 124-126). The mechanisms of this effect likely include induction of cyclin dependent kinase (CDK) inhibitors p21, p27 and p15, resulting in G0/G1 cell cycle arrest(108, 127), together with down-regulation of nuclear factor (NF) kB and early growth response genes-1 and 2 (Erg-1 and -2), PU.1 and SPARC (secreted protein activated and rich in cysteine) (108, 128, 129). In addition, direct tumor cell killing was exhibited by mechanisms thought to involve NK cell activation(122, 130, 131). Pomalidomide enhanced killing of chronic myeloid leukemia and multiple myeloma cell lines in PBMC co-culture systems, while this effect was blocked by NK cell depletion, cyclosporine A administration, and IL-2 blockade(125). Similar effects have been observed in different systems with prostate cancer, NHL and ovarian tumor cell lines(108).

### 1.2.3.2 Animal Studies

Animal studies with pomalidomide have been conducted in mice, rats, rabbits and monkeys. In all cases, pomalidomide was rapidly observed following oral administration, while renal excretion of metabolites was the predominant route of clearance(108). In both rodent models, whether by oral or intravenous (IV) administration there were no deaths and no significant clinical effects in doses up to 2000mg/kg orally and up to 50mg/kg IV. For rats undergoing continuous oral dosing for 90 days at up to 1500mg/kg daily the no-observable adverse event level (NOAEL) was 1500mg/kg daily. In cynomolgus monkeys, an ongoing study at up to 1mg/kg daily orally showed adverse effects at the highest dose level including cutaneous and deep tissue abscesses, with increased white cell counts (but not neutropenia) and hypoalbuminemia. Since monkeys were the most sensitive species in the toxicology program, the NOAEL of 0.2mg/kg daily was used to calculate the human equivalent dose of 0.06mg/kg daily for continuous oral doing (4mg for a 60 kilogram person). No significant or cardiac or respiratory safety concerns were apparent in rodents, dogs or monkeys, and pomalidomide was not mutagenic in bacterial or mammalian mutagenesis assays.

Pomalidomide, like other IMiDs, may cause fetal malformations. In preclinical studies, in pregnant rabbits (the species most sensitive to the teratogenic effects of thalidomide) who were administered pomalidomide at doses from 10 to 250mg/kg daily, external and cardiac malformations were observed. A relationship was noted between increasing pomalidomide dose and both the frequency of occurrence of each type of malformation and the number of fetuses affected(108).

### 1.2.3.3 Pharmacology

The pharmacokinetics of pomalidomide were characterized in healthy male subjects at doses from 1 to 50mg (single administration)(108). Following oral dosing, there was moderately rapid absorption with a $C_{max}$ that was less than dose proportional occurring at a median $t_{max}$ of 2.5 to 6 hours post dose. After reaching $C_{max}$, plasma concentrations of pomalidomide declined in an apparent biphasic manner. The systemic exposure of pomalidomide, as determined from the area under the plasma concentration time curve ($AUC_{0\text{-}tz}$ and $AUC_{0\text{-}\infty}$) increased in an approximately dose proportional manner. The $T_{1/2}$ ranged from 8.2 to 10.8 hours, with no apparent dose-related trend. Excretion was urinary, predominantly as metabolites. These characteristics were very similar to those seen in a separate phase 1b study in subjects with multiple myeloma[119].

Pomalidomide did not inhibit CYP 1A2, 2B6, 2C8, 2C19, 2D6, 2E1 or 3A4/5 activity in human liver microsomes *in vitro* ($IC_{50}$>30 μM; <10% inhibition at 30 μM)(108). Treatment of cultured hepatocytes with up to 3 μM pomalidomide twice daily for three consecutive days caused no changes in any of the CYP enzyme activities examined (1A2, 2B6, 2C9, 2C19 and 3A4/5). Hence pomalidomide is not likely to cause drug/drug interactions due to enzyme inhibition or induction when co-administered with CYP substrates.

### 1.2.3.4 Clinical Studies

Four completed studies in humans have been conducted with pomalidomide as a single agent in various malignancies(108, 119, 132); in addition there is one completed study in combination with dexamethasone in multiple myeloma (111) and one additional study in combination with gemcitabine in patients with pancreatic cancer (133). Two studies in myelofibrosis have also been completed(134, 135). In addition, studies are ongoing in small cell lung cancer, miscellaneous solid tumors (combined) and non-malignant conditions including myelofibrosis,

chronic graft-versus host disease and sickle cell disease, with over 250 patients enrolled to date. In consideration of adverse events, it should be emphasized that dose and schedule vary substantially between studies: in particular, there is variation in whether pomalidomide is administered using continuous dosing (with arbitrarily-distinguished 28 day 'cycles') or cyclic dosing (21 days followed by a 7 day 'rest' period to complete a 28 day cycle, as is used with lenalidomide).

In the first-in-human phase 1 study, 30 healthy male subjects received single doses of pomalidomide, escalated from 1 to 50mg(108). Adverse events were mild or moderate in all cases, with no grade 3/4 events. There were no clinically significant laboratory abnormalities in any subject. A mild, dose related decline in CD4-positive T cells was observed, greatest at the 50mg dose level.

In the phase 1b study in 24 patients with relapsed or refractory multiple myeloma(119), 24 patients received a dose-escalating regimen of oral pomalidomide, administered continuously with arbitrarily defined 28 day cycles and commencing at a dose of 1mg daily (escalated to 2, 5, and 10mg). Dose limiting toxicities were assessed during the first four weeks of therapy. The most common drug-related toxicity was neutropenia, with grade 3/4 neutropenia occurring in 14 patients overall and increasing in a dose dependent manner. One deep venous thrombosis was observed in the DLT assessment timeframe, though this was probably due to unrelated melanoma developing in a groin lymph node, and three additional subjects developed thromboses after 4, 9 and 11 months of therapy respectively. No other severe (grade 3/4) non-hematologic toxicity was observed. Hematologic toxicity was less severe after the initial cycle, with the median time to grade 3/4 neutropenia in those experiencing this event being 3 weeks on therapy. The maximum tolerated dose in this population was 2mg daily continuous dosing.

A second arm of the phase 1b study (reported separately(132)) utilized the same dose levels (1mg escalated to 2, 5, and 10mg) but in an alternate-daily dosing schedule, again continuously for a 28 day 'cycle'. A further 24 patients were enrolled. The most common drug-related toxicity was again neutropenia, which was grade 3 in 6 of 17 patients (35%) treated at or below the 5mg dose level (with no grade 4 toxicity at these levels), and grade 4 in three patients, all at the 10mg alternate daily dose level. No other serious possibly drug-related adverse events were reported. The maximum tolerated dose in this population was therefore 5mg alternate daily.

Similarly in the separate phase 2 study in combination with dexamethasone, the major toxicities were hematologic(111). This enrolled 34 patients with relapsed or refractory patients all of whom were refractory to the related compound lenalidomide. Grade 3 or 4 hematologic toxicity occurred in 13 patients (38%), consisting of neutropenia in 10 patients (29%), anemia in 4 patients (12%) and thrombocytopenia in 3 (9%). The most common grade 3/4 non-hematologic toxicity was fatigue in 3 patients (9%). No thrombotic complications were seen. Interestingly, this combination was active even in lenalidomide-refractory patients: the overall response rate was 47%, including 3 very good partial responses, with a median response duration of nine months.

Two further small phase 2 studies of pomalidomide as a single agent in solid tumors have been completed. In 44 patients with advanced prostate cancer, receiving 1 or 2mg of pomalidomide daily using a continuous dosing regimen, only one serious (grade 3/4) possibly drug-related adverse event was reported, acute renal impairment(108). Other adverse events were grade 1/2 only. Significant neutropenia was not observed, though there was a trend to lower neutrophil

counts at the higher dose, suggesting a significant difference in toxicities and tolerability in non-hematologic malignancies. In the next study of 7 patients with advanced soft tissue sarcomas, subjects received 7mg of pomalidomide daily continuous dosing, for a relatively short duration (median treatment duration 49 days, median 2 cycles of therapy)(108). Leukopenia (including one grade 4 event), neutropenia including febrile neutropenia (none worse than grade 3) and anemia (none worse than grade 3) were the only serious adverse events reported, though the majority of subjects experienced some decline in hematologic indices.

One completed study examined pomalidomide in combination with an established cytotoxic agent in pancreatic cancer using a dose escalating design(133). In this study, 23 patients received 2 to 10mg of pomalidomide daily for 21 days of a 28 day cycle, in combination with gemcitabine 1000mg/m$^2$ days 1, 8 and 15. Patients were not heavily pretreated, and the median ECOG performance status (PS) was zero (in 87% of those enrolled). Adverse events included neutropenia (grade 3/4 in 38% of cycles), deep venous thrombosis (22%) and anemia (9%); the investigators note that gemcitabine as a single agent is also associated with substantial hematotoxicity, and that the thrombotic risk in pancreatic cancer is significantly elevated. No other severe (grade 3/4) non-hematologic drug-related toxicity was observed. The maximum tolerated dose of pomalidomide in combination with gemcitabine was 10 mg daily for 21 of 28 days.

Interim analysis of a further dose-escalating study of pomalidomide alone in advanced solid tumors has been presented in abstract form(136). In its initial form, patients of any PS with "adequate organ function" and any number of prior regimens were eligible. Dosing was continuous, with arbitrarily defined 28 day cycles. Using these inclusion criteria, adverse events were relatively severe: at the 3mg daily dose level, they included grade 4 neutropenia, pulmonary embolus, gastrointestinal bleeding, and an infection resulting in death. Following amendment to limit ECOG PS to ≤1 and prior regimens to fewer than three, no dose limiting toxicities were reported at either the 3 or 4mg daily dosing levels. At the 5mg level, dose limiting neutropenia was observed, and the cohort is presently being expanded at the 4mg daily continuous dose level.

Based on these studies, the major serious adverse events appear to be reversible dose and schedule dependent hematotoxicity (most notably neutropenia with anemia and thrombocytopenia less frequent) and deep venous thrombosis (assessment of the frequency of which is complicated by high underlying rates of thrombosis in the malignancies studied), with other adverse events less common and generally mild. Patients with solid tumors were able to tolerate substantially higher total doses than those with hematologic malignancies. Prior cytotoxic exposure and patient PS also appear to influence the frequency and severity of adverse events. Cyclic or alternate daily dosing may reduce the severity of hematopoietic side effects while maintaining similar total dose delivery (for example, use of 5mg 21/28 days rather than 4mg continuously)(132-134). Significant neurotoxicity (whether sedation, peripheral neuropathy, or otherwise) has not been observed. Serious adverse events reported to the sponsor from the ongoing studies mentioned above have been consistent with those published(108). In light of the teratogenic effects observed in preclinical studies, all human studies have used stringent contraceptive guidelines.

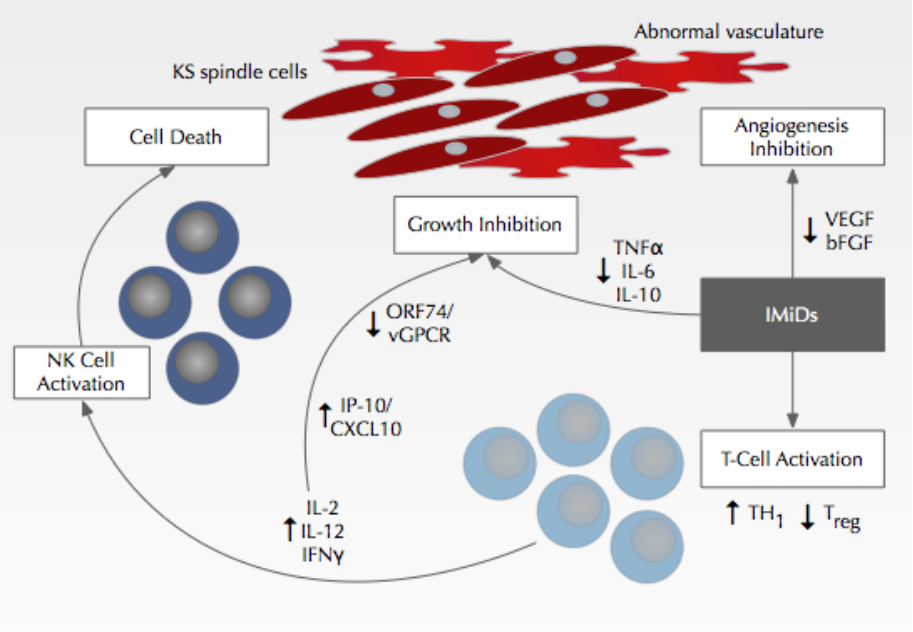
### *1.2.4 Pomalidomide in Kaposi Sarcoma*

#### 1.2.4.1 Rationale

The development of novel IMiDs presents an opportunity to extend prior investigations of thalidomide in KS and potentially address the ongoing clinical needs outlined above(104), potentially with reduced toxicity. The AIDS Malignancy Consortium is currently undertaking a complementary phase 1/2 study with the related compound lenalidomide (NCT01057121) in the United States, while the French National Agency for Research on AIDS and Viral Hepatitis is planning a phase 2 study of lenalidomide in France (NCT01282047). Unlike the present study, these are each restricted to patients with HIV-associated KS. Given the emerging evidence from other tumor types that patients refractory to thalidomide or lenalidomide may respond to pomalidomide, establishing the tolerability and activity, if any, of both lenalidomide and pomalidomide could significantly expand therapeutic options for patients with KS, whether HIV-associated or not.

Taken together, the current understanding of the pathogenesis of KS and the activities of pomalidomide in pre-clinical models and other tumor types suggest several possible mechanisms of activity for pomalidomide in KS (**Figure 1**). In particular, inhibition of TNF-α, IL-6 and IL-10; induction of IL-2 and IL-12; T cell co-stimulation and inhibition of T regulatory activity; and inhibition of pro-angiogenic factors including bFGF and VEGF are each rational targets in KS, and each are modulated by pomalidomide. The mechanism of the observed responses to thalidomide in HIV-associated KS remains to be fully elucidated; notably though, in the HAMB study of thalidomide, TNF-α levels decreased significantly from baseline in this cohort, while we did not observe statistically significant changes in serum bFGF, VEGF, or IL-6 (T cell activation and KSHV-specific T cell responses were not assessed in this study)(97).

**Figure 1: Possible Modes of Action of Pomalidomide in KS**




#### 1.2.4.2 Special Considerations and Dosing

The dose for exploration in KS has been determined with consideration of the special characteristics particularly of patients with HIV-associated KS. Patients with uncomplicated KS (whether HIV-associated or not) rarely if ever exhibit significant marrow involvement(1). Hence the initial dosing here is derived from solid tumor studies. The present study will also be restricted to patients with limited disease and good performance status, factors which also appear to reduce the incidence of severe hematotoxicity with pomalidomide. However, patients with HIV not infrequently exhibit mild cytopenias (predominantly anemia), and benign ethnic neutropenia is also common in this population(137). We therefore selected a cyclic regimen to allow a period of hematopoietic regeneration prior to repeat dosing, and a starting dose (5mg for 21 of 28 days) which is well within the current tolerated range in solid tumor patients. This is slightly lower in total dose delivered per cycle than a 4mg continuous regimen. Should this prove more toxic than expected, the dose will be de-escalated to 3mg for 21 of 28 days, which is within the current tolerated range in patients with hematologic malignancies (intermediate in total dose delivered per cycle between a 2mg continuous regimen and a 5mg alternate daily regimen, both of which were tolerated in patients with multiple myeloma). It should be noted that advances in HIV therapy and supportive care have allowed the safe delivery in this population of even markedly hematotoxic regimens, including paclitaxel and EPOCH(82),(138).

The baseline thrombotic risk associated with KS is not well-established, while HIV infection is established as a thrombotic risk factor (particularly when poorly controlled or associated with comorbidities)(139-141). These factors play an important part in estimating the potential risk of thrombosis with pomalidomide therapy. One case series in the pre-HAART era, of patients with relatively severe KS, reported an increased incidence of thrombosis in limbs affected by KS(141). This has not been confirmed, and in more recent studies of thrombotic risk in patients with HIV, KS has not emerged as an independent risk factor(139, 142) (also, Musselwhite and Sereti, personal communication). One case-control study in post-transplant KS showed an increased occurrence of DVT in KS cases, but the small number of cases and long time elapsed between KS and DVT (over 2 years) raise the possibility that this finding was coincidental(143). No thromboses were seen in either of the phase 2 studies of thalidomide in KS(97, 98, 143). Nonetheless, it would not be unexpected that the peripheral venous stasis and endothelial damage that may be seen in patients with extensive KS, combined with effects of HIV in those with HIV-associated disease, could elevate thrombotic risk. Thromboprophylaxis will therefore be employed for all subjects.

Two recent randomized studies of the related compound lenalidomide used as maintenance therapy in multiple myeloma have reported an increased number of malignancies in the lenalidomide arm(144, 145). In both studies, the most commonly reported malignancies were myelodysplastic syndromes and myeloid leukemias. Notably, there is an elevated baseline risk of these malignancies in multiple myeloma as well as with the use of alkylating agents that are used in this patient population. The impact of this and other possible confounding factors including increased survival in the treatment arms and ascertainment of malignancies in the control arms are currently being evaluated(146). Individuals with HIV are generally not at high risk of developing myeloid malignancies, but do incur a 10-1000 fold elevated risk of lymphoproliferative disorders and lymphoma, where IMiDs may have a therapeutic benefit(20, 25). Given the uncertainty surrounding these observations and these characteristic of the proposed study population, the impact (if any) of pomalidomide on the risk of subsequent malignancies is unknown, and it is possible that the net effect will be protective. Subjects will be

followed for five years following completion of therapy, with surveillance for second malignancies comprising part of this follow up.

Importantly for patients with HIV-associated KS, pomalidomide is not anticipated to cause or be affected by drug-drug interactions due to inhibition or induction when co-administered with cytochrome P450 substrates[108]. As many antiretrovirals do affect the P450 system this is a potential advantage to the use of pomalidomide, particularly in resource-limited settings where the choice of antiretroviral regimens may be limited. It is also therefore not expected that the use of differing HAART regimens will have a clinically significant impact on subjects, and for practical reasons and to improve generalizability they will not be standardized. As a practical matter, the variation in HAART regimens is not great: approximately 85% of HAMB patients are in any case on regimens incorporating the same nucleoside reverse transcriptase inhibitor backbone (tenofovir/emtricitabine), and in approximately 65% of patients this is used in combination with the non-nucleoside reverse transcriptase inhibitor efavirenz. The remainder of patients receive a variety of protease inhibitor regimens with a minority (approximately 5%) on other, deep salvage regimens (Polizzotto and Yarchoan, personal communication). It is possible however, given the dependence on renal excretion, that pomalidomide levels may be affected by potentially nephrotoxic antiretrovirals (such as tenofovir), and this will be explored.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

### *2.1.1 Inclusion Criteria*

2.1.1.1 Age ≥18 Years.
2.1.1.2 Any HIV status.
2.1.1.3 Kaposi sarcoma pathologically confirmed by Department of Pathology, Clinical Center, National Institutes of Health.
2.1.1.4 At least five measurable KS lesions with no previous local radiation, surgical or intralesional cytotoxic therapy that would prevent response assessment for that lesion.
2.1.1.5 ECOG Performance Status ≤2
2.1.1.6 Life expectancy ≥6 months
2.1.1.7 For patients with HIV-associated KS:
- 2.1.1.7.1 Must be receiving, and adherent to, a HAART regimen consistent with current clinical guidelines.
- 2.1.1.7.2 Must have been receiving HAART for at least one month.
- 2.1.1.7.3 Must have achieved an HIV VL <10,000 copies/mL.

2.1.1.8 The following hematological parameters:
- 2.1.1.8.1 Hemoglobin ≥10 g/dL
- 2.1.1.8.2 Platelets ≥75,000 cells/$mm^3$
- 2.1.1.8.3 Absolute neutrophil count (ANC) ≥1000 cells/$mm^3$

2.1.1.9 The following biochemical parameters:
- 2.1.1.9.1 Estimated or measured creatinine clearance ≥45mL/minute (see **Appendix 9** for estimation of creatinine clearance)
- 2.1.1.9.2 Serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal

2.1.1.9.3 Serum aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal

2.1.1.9.4 Bilirubin ≤ 1.5x upper limit of normal unless the patient is receiving protease inhibitor therapy (e.g. indinavir, ritonavir, nelfinavir, or atazanavir) known to be associated with increased bilirubin, in which case total bilirubin ≤7.5 mg/dL with direct fraction ≤ 0.7 mg/dL.

2.1.1.10 Females of childbearing potential (FCBP) as defined in **Appendix 1** must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 14 days prior to and again within 24 hours before starting pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method 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. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Section **16.1 Appendix 1**, Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, and also Section **16.2**, **Appendix 2: Pomalidomide Education and Counseling Guidance Document**.

2.1.1.11 All study participants must agree to be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.

2.1.1.12 Females of reproductive potential must be willing to adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.

2.1.1.13 Able to take aspirin 81mg daily or if intolerant of aspirin, able to take a substitute thromboprophylaxis such as low molecular weight heparin at a thromboprophylactic dose (such as enoxaparin 0.5mg/kg once daily).

2.1.1.14 Willing and able to give informed consent.

2.1.1.15 For subjects with HIV-associated entered after a tolerable dose has been determined, KS lesions must be either:

2.1.1.15.1 Increasing despite HAART and HIV suppression below the limit of detection (48 copies/mL) in the two months prior to screening *or*

2.1.1.15.2 Stable despite HAART for at least three months. Stable disease must be symptomatic (examples of symptomatic disease include disease associated with pain, edema, psychological distress and/or social withdrawal).

This is to gain preliminary information about pomalidomide activity without confounding due to HAART initiation.

### *2.1.2 Exclusion Criteria*

2.1.2.1 Symptomatic pulmonary KS.

2.1.2.2 Symptomatic visceral KS (except for non-ulcerating disease restricted to the oral cavity).

2.1.2.3 Specific KS therapy, including cytotoxic chemotherapy but not including HAART, within the past 4 weeks (6 weeks if the therapy was bevacizumab).

2.1.2.4 Use of other anticancer treatments or agents within the past 4 weeks (6 weeks if the therapy was a monoclonal antibody).

2.1.2.5 History of malignant tumors other than KS, unless:

2.1.2.5.1 In complete remission for ≥1 year from the time response was first documented *or*

2.1.2.5.2 Completely resected basal cell carcinoma *or*

2.1.2.5.3 *In situ* squamous cell carcinoma of the cervix or anus.

2.1.2.6 History of infection meeting any of the following criteria:

2.1.2.6.1 Any infection that would be scored as grade 4 by CTCAE that occurred *within six weeks* of study screening.

2.1.2.6.2 Any infection that would be scored as grade 3 by CTCAE that occurred *within two weeks* of study screening.

2.1.2.6.3 History of fungal and mycobacterial infections, unless *at least six weeks* has passed since the completion of induction antimicrobial therapy. Patients may be receiving consolidation therapy for infections of these types.

2.1.2.7 Any abnormality that would be scored as a ≥grade 3 toxicity by CTCAE, *except*:

2.1.2.7.1 Obesity is not considered an abnormality for the purposes of eligibility assessment unless in the opinion of the Principal Investigator or Lead Associate Investigator its clinical consequences in a particular subject places the subject at unacceptable risk if they were to participate in the study or confounds the ability to interpret data from the study.

2.1.2.7.2 Lymphopenia

2.1.2.7.3 Asymptomatic hyperuricemia, hypophosphatemia, or creatine kinase (CK) elevations

2.1.2.7.4 Direct manifestations of KS

2.1.2.7.5 Direct manifestations of HIV infection, except for neurologic or cardiac manifestations

2.1.2.7.6 Direct manifestations of HIV therapy, except for neurologic or cardiac manifestations.

2.1.2.8 History of venous or arterial thromboembolism, *unless*:

2.1.2.8.1 Line-related thrombosis without embolus occurring ≥1 year prior to screening.

2.1.2.8.2 Complications resulting from atherosclerotic coronary artery disease, peripheral vascular disease, or cerebrovascular disease (including infarction) are not considered exclusion criteria unless in the opinion of the Principal Investigator or Lead Associate Investigator their clinical consequences in a particular subject places the subject at unacceptable risk if they were to participate in the study or confounds the ability to interpret data from the study.

2.1.2.9 Known drug-related, inherited, or acquired 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.

2.1.2.10 Pregnancy

2.1.2.11 Breast feeding (if lactating, must agree not to breast feed while taking pomalidomide).

2.1.2.12 Prior therapy with pomalidomide.

2.1.2.13 Known hypersensitivity to thalidomide, lenalidomide or pomalidomide. including prior development of erythema nodosum if characterized by a desquamating rash while taking thalidomide, lenalidomide or pomalidomide.

2.1.2.14 Any condition, including the presence of laboratory abnormalities, which in the opinion of the Principal Investigator or Lead Associate Investigator places the subject at unacceptable risk if they were to participate in the study or confounds the ability to interpret data from the study.

## 2.2 RESEARCH ELIGIBILITY EVALUATION

Potential subjects will be evaluated by a HAMB physician investigator for protocol eligibility. Baseline evaluation will include a complete medical history, review of systems, and physical examination including documentation of the presence and extent of any KS lesions.

### *2.2.1 Clinical Examination*

2.2.1.1 Complete medical history

2.2.1.2 Comprehensive physical examination.

### *2.2.2 Clinical Laboratory Data*

(studies performed in Clinical Center Department of Laboratory Medicine except HIV, HBV and HCV viral load monitoring performed in Clinical Center Blood Bank)

2.2.2.1 CBC with differential and reticulocyte count

2.2.2.2 Acute care panel (Sodium, Potassium, Chloride, CO2, Creatinine, Glucose, and Urea Nitrogen)

2.2.2.3 Mineral panel (Phosphorus, Magnesium, Albumin, and Calcium)

2.2.2.4 Hepatic panel (Alkaline Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)

2.2.2.5 C-reactive protein

2.2.2.6 Creatine kinase, uric acid, LDH, amylase and lipase

2.2.2.7 APTT, PT, thrombin time (TT), fibrinogen, D-dimer

2.2.2.8 Lymphocyte phenotype TBNK (requires simultaneous CBC and automated differential)

2.2.2.9 HIV Western blot (unless prior lab evaluation by Department of Laboratory Medicine, Clinical Center, NIH shows that the patient is HIV infected)

2.2.2.10 HIV viral load if HIV seropositive by Western Blot

2.2.2.11 RPR

2.2.2.12 Tuberculosis testing by PPD or interferon gamma release assay (Quantiferon Gold)

2.2.2.13 Urinalysis.

### *2.2.3 Pregnancy Testing*

2.2.3.1 Urine and serum β-hCG (female subjects only). Must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.

### *2.2.4 Radiographic studies*

2.2.4.1 Chest X-ray.

2.2.4.2 If clinically indicated, a Chest CT may be performed where necessary to assess abnormal chest x-ray findings or unexplained respiratory symptoms.

2.2.4.3 Endoscopic studies may be performed when clinically indicated to evaluate and measure visceral KS. Such studies are indicated where there are symptoms suggestive of KS involvement at the site (including but not limited to hemoptysis, melena, unexplained dyspnea) and/or findings on Chest CXR or computer tomography which could represent visceral KS. Studies may include bronchoscopy, upper and/or lower gastrointestinal endoscopy. Evaluation is not required in the absence of symptoms or imaging abnormalities.

### *2.2.5 KS Tumor Biopsy*

2.2.5.1 Where pathological tissue for confirmation of the diagnosis has not already been obtained, biopsy of skin or other involved tissue will be performed.

2.2.5.2 Where diagnostic biopsies are obtained, the specimens will be handled as follows:

2.2.5.2.1 Place sufficient tissue for diagnostic purposes directly into formalin and submit to Laboratory of Pathology for histopathology and immunohistochemistry including KSHV-LANA and KSHV-vIL-6.

2.2.5.2.2 Additional research tests may be performed on the screening tissue biopsy *only* where the patient has enrolled on study 01-C-0038 (Collection of Blood, Bone Marrow, Tumor, or Tissue Samples from Patients with HIV Infection, KSHV Infection, Viral-related Pre-Malignant Lesions, and/or Cancer). See Section **5.1.2.3.1** for handling and prioritization instructions.

## 2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

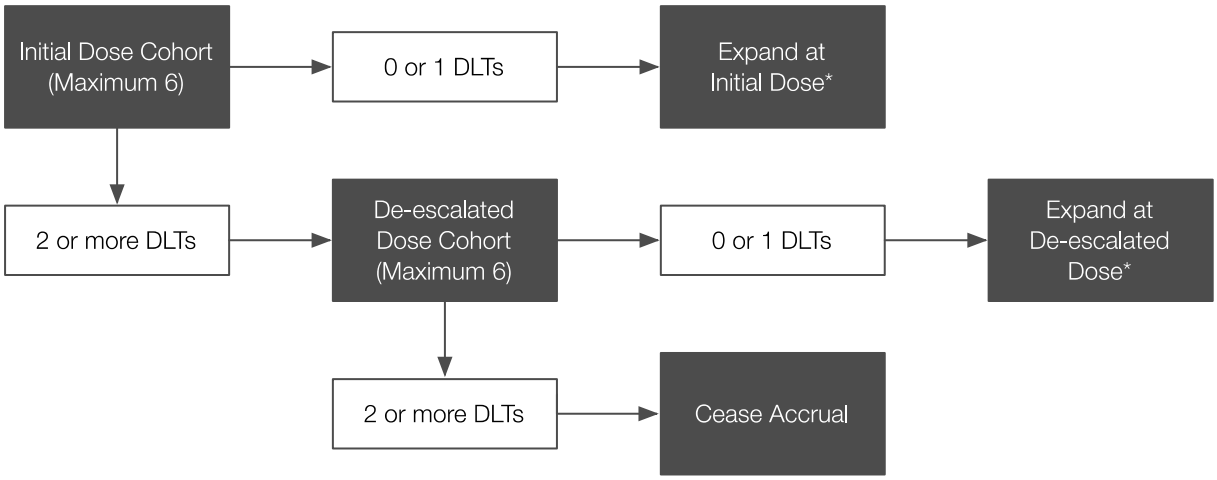
# 3 STUDY IMPLEMENTATION

## 3.1 STUDY DESIGN

This is an open label single agent study of pomalidomide in patients with KS, whether HIV associated or not.

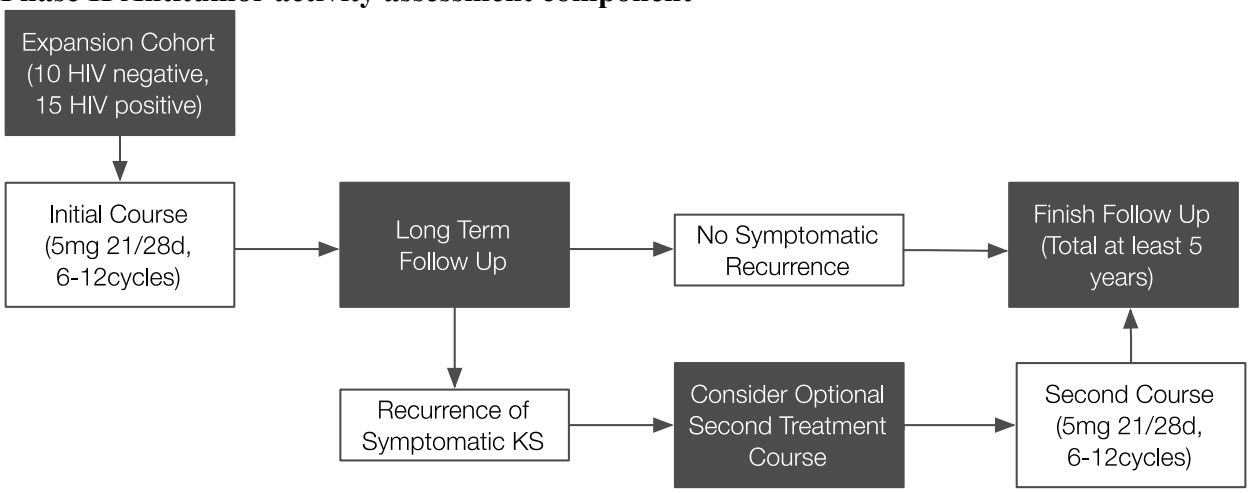
### *3.1.1 Study Schema*

**Phase I Dose-establishment component:**




*Expansion cohort accrual goals will be 15 evaluable HIV positive and 10 evaluable HIV negative patients
For patients with HIV-associated KS, dose expansion cohort requires additional eligibility criteria
(stable disease despite 3 months of cART or progression despite 2 months of cART)

**Phase II Antitumor activity assessment component**




*Guidelines for duration of therapy in the antitumor assessment phase are give in S3.1.4
Eligibility criteria for optional second treatment course are given in S3.1.6.
Schedule of visits and duration of long term follow up are given in S3.4.3.6

### *3.1.2 Dose Limiting Toxicity*

For purposes of defining the toxic dose and as a basis of discussion for off-study criteria, the following is the definition of dose-limiting toxicity (DLT). It should be noted that neither pre-existing manifestations of HIV infection, nor of therapy for HIV infection, nor of KS (including bleeding from KS) will be considered dose-limiting. Dose limiting toxicities will be assessed over the first 8 weeks (2 cycles) of drug administration.

If a patient meets the criteria defined below, they will be considered as having dose-limiting toxicity.

3.1.2.1 **Any grade 4 toxicity** not including lymphopenia, CD4 lymphopenia, neutropenia, anemia and bilirubin or CK elevation that is at least possibly due to pomalidomide and is not attributable to HIV, its therapy or KS.

3.1.2.2 For lymphopenia, CD4 lymphopenia, neutropenia, or anemia and bilirubin or CK elevation additional restrictions apply to better separate drug effects from manifestations of HIV and/or its therapy. For these parameters, the definition of dose-limiting toxicity is as follows:

3.1.2.2.1 For lymphopenia and CD4 counts, a decrease that (1) represents a grade 4 toxicity; (2) represents a 80% decrease from the entry value; (3) occurs in a patient with controlled HIV (<1,000 copies/mL); **and** (4) represents a 50 cell/mm$^3$ decrease from entry will be considered dose-limiting if found to be present on two successive determinations. If a CD4 count meets the numerical criteria on one determination, it should be repeated at the next possible visit to see if it is confirmed.

3.1.2.2.2 Neutropenia will only be considered dose-limiting if grade 4 for 14 days or more (including with G-CSF administration) or if grade 4 febrile neutropenia occurs.

3.1.2.2.3 Anemia will only be considered dose limiting if grade 4 and other causes are not identified (for example, antiretroviral therapy with agents such as zidovudine).

3.1.2.2.4 For patients on HIV protease inhibitors who manifest hyperbilirubinemia, an increase total bilirubin of ≥5.0 mg/mL over baseline with an increase in indirect bilirubin of ≥4.5 mg/ml over baseline is considered dose-limiting. This is because bilirubin is frequently elevated in patients receiving these medications. This does not apply to patients whose HAART regimen does not include a protease inhibitor.

3.1.2.2.5 Grade 4 creatine kinase (CK) elevations will not be considered dose-limiting if it is determined that this is at least possibly due to recent exercise or trauma. This is because it is our experience that some KS patients and HIV-infected patients on clinical trials develop substantially increased CK levels from exercise or trauma.

3.1.2.3 **Any grade 3 toxicity** that is at least possibly due to pomalidomide and is not attributable to HIV, its therapy, or KS with the following restrictions:

3.1.2.3.1 Those toxicities excluded above in section **3.1.2.2**

3.1.2.3.2 Grade 3 thrombocytopenia will only be considered dose limiting if grade 3 for 14 days or more (all grade 4 thrombocytopenia will be considered dose limiting).

3.1.2.3.3 Grade 3 asymptomatic hyperuricemia or hypophosphatemia will not be considered dose limiting, as these are often caused by HIV infection or antiretroviral therapy.

3.1.2.3.4 Grade 3 amylase elevations will not be considered dose-limiting if it is determined that it is not of pancreatic origin.

3.1.2.3.5 For rash, grade 3 toxicity is considered dose-limiting only if it does not decrease to grade 1 within 4 weeks off therapy; if it recurs on re-challenge with pomalidomide; or if it is erythema nodosum characterized by a desquamating rash.

3.1.2.3.6 For hypertension, grade 3 toxicity is considered dose limiting where systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥100 mm Hg is not controlled with antihypertensive medications (all grade 4 hypertension will be considered dose limiting).

3.1.2.4 Any arterial or deep venous thrombembolic event or a second superficial thromboembolic event that is at least possibly due to pomalidomide.

3.1.2.5 Inability to deliver pomalidomide on at least 50% of scheduled days during the first two cycles of therapy as a result of toxicity that is probably or definitely attributable to pomalidomide will be considered dose limiting. Delivery interruptions not related to pomalidomide (for example, due to unrelated intercurrent illness, patient personal emergencies, or other exigencies) will not be considered for this criterion.

### *3.1.3 Dose De-escalation*

Up to six subjects will initially be treated with pomalidomide at dose level 1, 5mg PO daily for 21 days followed by 7 days 'rest' to complete the 28 day cycle. Subject to toxicity evaluation (Section **3.1.2**), this dosage may be deescalated to dose level minus 1, 3mg PO daily for 21 days followed by 7 days 'rest' to complete the 28 day cycle in a second cohort of up to six subjects.

A dose will be considered as toxic if two or more of the subjects entered at that dose level develop a DLT within the first 8 weeks (2 cycles) of drug administration. This time period has been selected, in line with prior HAMB studies, as in the great majority of cases KS will require

at least 8 weeks of treatment. The tolerated dose will be defined as the highest dose level administered as part of the protocol where 0 or 1 of 6 subjects experience a dose limiting toxicity within the first 8 weeks of drug administration.

If it is determined that a dose is toxic then subjects in that group who have not experienced a DLT or off-therapy criterion will be dropped to the next lower level. In the case that the lowest predetermined dose is determined to be toxic, all subjects will cease therapy unless in the interim the protocol has been amended by seeking IRB approval to include an additional lower dose level.

### *3.1.4 Antitumor Activity Assessment*

If either dose proves tolerable, additional subjects will be added at the highest tolerable dose to gain preliminary information on activity, to a goal of 15 HIV positive and 10 HIV negative subjects evaluable for response. Only subjects who complete at least two cycles of therapy will be considered evaluable for response. For subjects in the anti-tumor activity assessment phase whose KS is HIV-associated, more stringent entry criteria will apply to be considered evaluable for response (Section **2.1.1.15**); all subjects with non-HIV-associated KS who complete at least two cycles of therapy will be considered evaluable for response.

In the absence of off-therapy criteria, therapy will continue for 24 weeks (6 cycles of 4 weeks each). Subjects who, in the opinion of the investigators, are continuing to derive benefit may continue on therapy for up to an additional 24 weeks (6 additional cycles). Examples of derived benefit to be used in consideration of possible additional therapy include, but are not limited to, the following:

3.1.4.1 Achievement of partial response from baseline (Section **6.2**) with evidence of continuing disease improvement on therapy

3.1.4.2 Achievement of stable disease (Section **6.2**) in subjects whose disease was progressing at baseline

3.1.4.3 Improvement in tumor-associated edema or pain (objective as measured by limb circumference, or subjective as measured by analgesia or diuretic requirements)

3.1.4.4 Improvement in quality of life measures, such as KS-associated impairment of activity or mobility or social withdrawal.

Up to two subjects at each dose level who are removed from study prior to the completion of 8 weeks of therapy for reasons other than drug toxicity, whether in the dose establishment phase or antitumor activity assessment phase, may be replaced at the discretion of the Principal Investigator or Lead Associate Investigator.

### *3.1.5 Phase 2 (Expansion Cohort)*

As of 06/28/2012, the first six patients completed the first 8 weeks of therapy without DLTs. Hence, the planned Phase I dose assessment phase has been completed, establishing that 5mg pomalidomide for 21 of 28 days is tolerable in this population. This is therefore the dose to be used for Phase II response assessment.

### *3.1.6 Option of Second Course of Pomalidomide (effective with Amendment D version date: 01/22/2013)*

Following completion of the initial course of pomalidomide therapy (up to 48 weeks), subjects (from the Phase 1 or 2 portion of the study) who again manifest KS requiring therapy while not

taking pomalidomide within the study follow up period (5 years) may be considered for an additional course of therapy at the Phase 2 dose of 5mg 21 of 28 days, so long as each of the following criteria apply:

3.1.6.1 The subject achieved a tumor response (complete or partial) or derived other clinical benefit from their initial course of therapy (examples of clinical benefit being given in Section **3.1.4.2-3.1.4.4**)

3.1.6.2 The KS present is progressing while not taking pomalidomide and either symptomatic (for example with pain, edema) or causing psychological distress)

3.1.6.3 The eligibility criteria described in Section **2.1** are again met at the time of consideration of an additional course of therapy, and no exclusion criteria are present except that item **2.1.2.12** (prior therapy with pomalidomide) will not apply. Screening evaluations described in Section **2.2**. will be repeated at the time of consideration of an additional course of therapy.

3.1.6.4 Interval administration of other therapies for KS (local or systemic) will not preclude consideration of a second course of pomalidomide within the protocol, so long as the above criteria are met.

3.1.6.5 Drug administration, evaluations, and off-therapy criteria and correlative studies for the optional second course of therapy parallel those described for the initial course, except that pharmacokinetic studies and optional on-therapy research biopsies will not be performed for the second course. These evaluations are detailed in Section **3.4.2**, "Optional Second Treatment Course Study Calendar".

In the absence of off-therapy criteria, the second course of therapy will continue for 24 weeks (6 cycles of 4 weeks each). Subjects who, in the opinion of the investigators, are continuing to derive benefit may continue on the second course therapy for up to an additional 24 weeks (6 additional cycles). Thus the maximal duration of pomalidomide therapy that may be administered within the protocol is 96 weeks (two courses of 48 weeks each); though in most cases the amount administered will be considerably less.

## 3.2 DRUG ADMINISTRATION

### *3.2.1 Pomalidomide*

3.2.1.1 Pomalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with pomalidomide. This step will be documented with a completed Education and Counseling Guidance Document (**Appendix 2**) and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Pomalidomide Information Sheet (**Appendix 3**) will be supplied with each medication dispensed.

Subjects will be counseled regarding pomalidomide risks of fetal exposure, pregnancy testing guidelines and acceptable birth control methods (**Appendix 1**) prior to commencement of therapy and at least every 28 days while on therapy. In addition, the

'Pomalidomide Education and Counseling Guidance Document' (**Appendix 2**) will be completed prior to each dispensing of study drug by a clinical investigator with the subject, and the subject will be provided with a copy of the 'Pomalidomide Information Sheet for Patients Enrolled in Clinical Research Studies' (**Appendix 3**).

3.2.1.2 Pomalidomide will be self-administered on an outpatient basis at the assigned dose once daily. Subjects will be instructed to take pomalidomide at approximately the same time every morning. Subjects should fast (water to drink only) for at least 2 hours prior to taking a dose to at least 30 minutes post-dose of pomalidomide. A light breakfast (such as tea without sugar and dry toast) may be taken in the morning but must be completed at least 2 hours prior to taking a morning dose. Sugary and fatty foods should be avoided prior to taking the medication doses.

3.2.1.3 Subjects will keep a daily diary recording pomalidomide administration including the time of administration, and any clinical toxicity or other observations made during the cycle (**Appendix 8**). This will be used as only an *aide memoire* for subjects. The clinical research team will maintain the primary source record of events including toxicities.

3.2.1.4 Thromboprophylaxis with aspirin 81mg or an acceptable alternative agent will continue throughout therapy (days 1-28 of each cycle), as described in Section **4.1.2**.

3.2.1.5 Treatments and corresponding evaluations may be rescheduled to the closest day possible without constituting a protocol violation (e.g. for Federal holidays or unforeseen circumstances such as travel difficulties, snow closures and the like).

**3.2.1.6 Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle.**

3.2.1.7 Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

3.2.1.8 If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

3.2.1.9 Subjects who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

### *3.2.2 Special Handling Instructions*

Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

### *3.2.3 Record of administration*

Accurate records will be kept of all study drug administration (including dispensing and dosing) will be made in the source documents.

## 3.3 DOSE MODIFICATIONS

All treatment modifications should be discussed with the senior clinical investigators on the study. Dose modification guidelines apply to the Phase 1 and Phase 2 portions of the study as well as the Second Optional Course of Therapy.

For Phase 1: Subjects who are enrolled on the initial (5mg) dose level who experience a DLT *not including a thromboembolic event* that resolves to grade 1 (or the grade they had at entry) *within*

*28 days* and continue to have KS may be considered for further therapy at the 3mg dose level if they continue to have KS requiring therapy. Response assessment for any such patients is described in Section **10.4**.

**Table 1: Dose Modification of Pomalidomide**

| Event | Action | Resumption of Therapy |
|---|---|---|
| Neutropenia. ANC 500 to <1000 cells/mm³ (CTCAE Grade 3) | *If observed **during cycle** (day 2 of cycle onward) therapy may continue with additional weekly CBCs. If observed **day 1 of new cycle**, therapy should be held. Consider G-CSF. (filgrastim) 5mcg/kg/daily SC rounded by ±10% to use the most economical combination of available products (commercial vials contain 300 mcg or 480 mcg). Pegylated filgrastim should not be used. Pomalidomide should not be administered during G-CSF treatment or within 24 hours after a G-CSF dose. | CBCs should be evaluated weekly and a new cycle of treatment may commence at the same dose level on or after day 29 once ANC ≥1000 cells/mm³. |
| Neutropenia. ANC <500 cells/mm³. (CTCAE Grade 4) | *Suspend or hold pomalidomide. Administer G-CSF (filgrastim) 5mcg/kg/daily SC rounded by ±10% to use the most economical combination of available products (commercial vials contain 300 mcg or 480 mcg). Pegylated filgrastim should not be used. Pomalidomide should not be administered during G-CSF treatment or within 24 hours after a G-CSF dose. | CBCs should be evaluated weekly and a new cycle of treatment may commence at the same dose level on or after day 29 once ANC ≥1000 cells/mm³ so long as criteria for a DLT are not met. |

| Event | Action | Resumption of Therapy |
|---|---|---|
| Febrile Neutropenia. ANC <1000 cells/mm³ with a single temperature >38.3°C *or* T≥38°C for more than one hour. | Suspend or hold pomalidomide. Supportive care including intravenous antibiotics as outlined in Section **4.2.2**. Administer G-CSF (filgrastim) 5mcg/kg/daily SC rounded by ±10% to use the most economical combination of available products (commercial vials contain 300 mcg or 480 mcg). Pegylated filgrastim should not be used. Pomalidomide should not be administered during G-CSF treatment or within 24 hours after a G-CSF dose. | CBCs should be evaluated weekly and a new cycle of treatment may commence at the same dose level on or after day 29 once ANC ≥1000 cells/mm³ so long as criteria for a DLT are not met. |
| Thrombocytopenia.: platelet count 25,000 to <50,000 cells/mm³. (CTCAE Grade 3) | If observed **during cycle** (day 2 of cycle onward), pomalidomide may continue with additional weekly CBCs. If observed **day 1 of new cycle**, pomalidomide should be held. Hold thromboprophylaxis until platelet count ≥ 50000 cells/mm³. | CBCs should be evaluated weekly and a new cycle of treatment may commence at the same dose level on or after day 29, once platelet count ≥ 50000 cells/mm³ so long as criteria for a DLT are not met. |
| Thrombocytopenia: platelet count < 25,000 cells/mm³ (CTCAE Grade 4) | Discontinue therapy. Consider platelet transfusion if Plt ≤10000 cells/mm³, bleeding or risk factors for bleeding present as outlined in Section **4.2.4**. Hold thromboprophylaxis until platelet count ≥ 50,000 cells/mm³. | Not to resume |
| Anemia. Hb <8.0 g/dL (CTCAE Grade 3) | Consider red cell transfusion if symptomatic, or as required to maintain Hb ≥10.0g/L during therapy. | Pomalidomide may continue at the same dose level once Hb ≥10.0g/L so long as criteria for a DLT are not met. |

| Event | Action | Resumption of Therapy |
|---|---|---|
| Thromboembolic events (first episode of superficial venous thrombosis) | Suspend or hold pomalidomide. | On or after day 29 and following documentation of complete resolution (e.g. by ultrasonography) at the same dose level. |
| Thromboembolic events (Arterial, deep venous, or second episode of superficial venous thrombosis) | Discontinue therapy. | Not to resume. |
| Infection at any site (≥CTCAE Grade 3) at least possibly attributable to pomalidomide | Suspend or hold Pomalidomide. | On or after day 29 and following documentation of resolution to ≤CTCAE Grade 1 at the same dose level. Therapy may resume during oral antibiotic consolidation therapy if there is no clinical or laboratory evidence of active infection. |
| CK elevation at least possibly attributable to pomalidomide (≥ CTCAE Grade 3) | Hold pomalidomide for a maximum of 2 weeks. Encourage increased oral fluid intake and avoidance of strenuous physical activities. Administer intravenous fluid if CK >10,000 U/L. | Resume therapy at the same dose level once resolution to ≤CTCAE Grade 2. Permanently discontinue if not at ≤CTCAE Grade 2 after a total of 3 weeks off drug (including the time off drug during the last week of the cycle) or if CK rises again to grade 4 and it is not possibly attributable to excess exercise or to trauma. |
| Any other DLT of CTCAE Grade 3 at least possibly attributable to pomalidomide | Suspend or hold pomalidomide. | On or after day 29 and following resolution to ≤CTCAE Grade 1 at the same dose level (see Section 3.5). |

| Event | Action | Resumption of Therapy |
|---|---|---|
| Any other DLT of CTCAE Grade 4 at least possibly attributable to pomalidomide | Discontinue therapy. | Not to resume (see section **3.3**). |

*At the discretion of the investigators, subjects who experience grade 3 or 4 neutropenia requiring G-CSF during a cycle as described below may receive G-CSF 5mcg/kg/daily SC rounded by ±10% to use the most economical combination of available products during the 'rest' days of subsequent cycles to minimize recurrent neutropenia.

## 3.4 STUDY CALENDAR

### *3.4.1 Initial Treatment Course Calendar*

| Evaluation | Screen | Pre Therapy[1] | First Cycle | | Second and Third Cycles | | Fourth and Later Cycles | Post Therapy | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Day 1 | Day 15 | Day 1 | Day 15 | Day 1 | Day 29 Final Cycle | 28 ± 7 days later |
| History and physical[2] | X | | X | X | X | | X | X | X |
| Clinical Labs[3] | X | | X | X | X | X | X | X | X |
| Pregnancy Test[4] | X | | X | X | X | | X | X | X |
| Pomalidomide Education and Counseling[5] | | X | X | | X | | X | | |
| HIV Western blot | X | | | | | | | | |
| Chest X-ray | X | | | | | | | | |
| Electrocardiogram | X | | | | | | | | |
| KS Response Evaluation | | | | | | | | | |
| KS Tumor Measurements | | X | | | X | | X | X | |
| KS Tumor Photography[6] | | X | | | X | | X | X | |
| KS Non-invasive Tumor Imaging [6] | | X | | | X | | X | X | |
| Tumor Biopsies[7] | X | | | | X | | | X | |
| Quality of Life Assessment[8] | | X | | | | | X | | X |
| Pharmacokinetics[9] | | | X | X | | | | | |
| Adverse Event Monitoring | | | X | | | | | | X |
| KSHV VL (PBMCs and saliva), viral IL-6, human cytokines[10] | | | X | | X | | X | X | |
| KSHV Immune Response Assays[11] | | X | | | | | | | X |
| Monocyte and T cell activation and subsets[11] | | X | | | | | X | | X |
| HIV VL (Single Copy Research Assay)[12] | | X | X | | X | | X | X | X |

[1] *Pre-therapy studies will be performed after screening and enrollment, and at least 48 hours before commencement of therapy.*
[2] *Includes current medications and ECOG performance status*
[3] *See Section **2.2.2** for screening labs, **3.4.3** for baseline labs, **3.4.4** for on treatment labs and **3.4.5** for post treatment labs. Note as described in Section **3.4.4**, day 8, 15 and 22 of cycle 1 and Day 15 of cycles 2 and 3 are limited laboratory toxicity checks only. Laboratory toxicity checks may be performed by the patient's primary care physician through a certified outside laboratory with results to be provided to NCI investigators, for patients living at a distance from the Clinical Center.*
[4] *In females of child-bearing potential (FCBP), as defined in **Appendix 1**. Urine and serum β-HCG will be performed within 14 days prior to starting pomalidomide, again within 24 hours of starting pomalidomide, and then performed weekly for the first 28 days of study participation and then every 28 days while on study, at study drug discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.*
[5] *All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. See **Appendix 1**: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods and: **Appendix 2** Pomalidomide Education and Counseling Guidance Document.*
[6] *Pre-therapy, day one of subsequent cycles until the sixth cycle and then (for patients receiving more than six cycles) day one of odd-numbered cycles (beginning with Cycle 7) and again at the end of first course of therapy.*
[7] *Pathological confirmation of diagnosis in Department of Pathology, Clinical Center, National Institutes of Health is required for eligibility screening, and may be undertaken using a recent biopsy from an outside institution if available. In this case, an additional research biopsy at baseline is optional. Research biopsy day one of cycle three (only) is optional. Diagnostic and research biopsy at end of first course of therapy is optional. Optional on-therapy research biopsies will not be performed for subjects receiving a second course of therapy.*
[8] *Pre-therapy, day one of cycle four, and end of first course of therapy.*
[9] *See Section **5.1.1.2** for full pharmacokinetic studies schedule. Not to be performed for subjects receiving a second course of therapy.*
[10] *At each collection: 1 yellow top tube for PBMCs; 1 blue top tube for saliva; 2 red top tubes for viral IL-6; 3 green top tubes for cytokines; 2 yellow top tubes for storage*
[11] *Repeated day one of cycle four and 28±7 days following the end of the first course of therapy*
[12] *Only in HIV infected subjects whose HIV VL is undetectable by conventional assays.*
*As noted in Section **3.2.1.5**, with the exception of pharmacokinetics, treatments and corresponding evaluations may be rescheduled to the closest day possible without constituting a protocol violation (e.g. for Federal holidays or unforeseen circumstances such as travel difficulties, snow closures and the like).*

### *3.4.2 Optional Second Treatment Course Calendar*

| Evaluation | Pre Therapy[1] | First Cycle | | Second and Third Cycles | | Fourth and Later Cycles | Post Therapy | |
|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 15 | Day 1 | Day 15 | Day 1 | Day 29 Final Cycle | 28 ± 7 days later |
| History and physical[2] | X | X | X | X | | X | X | X |
| Clinical Labs[1] | X | X | X | X | X | X | X | X |
| Pregnancy Test[3] | X | X | X | X | | X | X | X |
| Pomalidomide Education and Counseling[4] | X | X | | X | | X | | |
| HIV Western blot | X | | | | | | | |
| Chest X-ray | X | | | | | | | |
| Electrocardiogram | X | | | | | | | |
| KS Response Evaluation: | | | | | | | | |
| KS Tumor Measurements | X | | | X | | X | X | |
| KS Tumor Photography[5] | X | | | X | | X | X | |
| KS Non-invasive Tumor Imaging[5] | X | | | X | | X | X | |
| Tumor Biopsies[6] | Not performed for second course | | | | | | | |
| Quality of Life Assessment[7] | X | | | | | X | | X |
| Pharmacokinetics[8] | Not performed for second course | | | | | | | |
| Adverse Event Monitoring | | X | | | | | | X |
| KSHV VL (PBMCs and saliva), viral IL-6, human cytokines[9] | | X | | X | | X | X | |
| KSHV Immune Response Assays[10] | X | | | | | | | X |
| Monocyte and T cell activation and subsets[10] | X | | | | | X | | X |
| HIV VL (Single Copy Research Assay)[11] | X | X | | X | | X | X | X |

[1] *Pre-therapy studies will be performed at least 2 days before commencement of second course of therapy.*
[2] *Includes current medications and ECOG performance status*
[3] *In females of child-bearing potential (FCBP), as defined in* ***Appendix 1****. Urine and serum β-HCG will be performed within 14 days prior to starting pomalidomide, again within 24 hours of starting pomalidomide, and then performed weekly for the first 28 days of study participation and then every 28 days while on study, at study drug discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.*
[4] *All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. See* ***Appendix 1****: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods and:* ***Appendix 2****Pomalidomide Education and Counseling Guidance Document.*
[5] *Pre-therapy, day one of subsequent cycles until the sixth cycle and then (for patients receiving more than six cycles) day one of odd-numbered cycles (beginning with Cycle 7) and again at the end of second course of therapy.*
[6] *Research biopsies will not be performed for subjects receiving a second course of therapy.*
[7] *Pre-therapy, day one of cycle four, and end of second course of therapy.*
[8] *Pharmacokinetics will not be performed for subjects receiving a second course of therapy.*
[9] *At each collection: 1 yellow top tube for PBMCs; 1 blue top tube for saliva; 2 red top tubes for viral IL-6; 3 green top tubes for cytokines; 2 yellow top tubes for storage*
[10] *Repeated day one of cycle four and 28±7 days following the end of second course of therapy.*
[11] *Only in HIV infected subjects whose HIV VL is undetectable by conventional assays.*
*As noted in Section* ***3.2.1.5,*** *treatments and corresponding evaluations may be rescheduled to the closest day possible without constituting a protocol violation (e.g. for Federal holidays or unforeseen circumstances such as travel difficulties, snow closures and the like).*

### *3.4.3 Baseline Studies*

Screening clinical laboratory and radiographic studies may be used for baseline evaluation provided they were obtained within 14 days of study enrollment or within 28 days of first dose of therapy, *except* baseline CBC and acute care, mineral and hepatic panel and (for females) a pregnancy test is required within 24 hours prior to first dose of therapy. CBC, acute care, mineral and hepatic panels, and pregnancy test repeated within 24 hours of first dose must continue to meet eligibility criteria (Sections **2.1.1.8** to **2.1.1.10**) for the subject to commence therapy. Pharmacokinetics studies must be performed day one of cycle one. Correlative studies must be performed pre-therapy (for Immune Activation and KSHV Immune Response Assays) or day 1 of cycle one (for Cytokine, Angiogenesis and Virologic Studies) as specified in Section **5.1.2**.

3.4.3.1 Clinical Examination

3.4.3.1.1 Complete medical history

3.4.3.1.2 Comprehensive physical examination

3.4.3.2 Clinical Laboratory Data

3.4.3.2.1 CBC with differential and reticulocyte count

3.4.3.2.2 Acute care panel (Sodium, Potassium, Chloride, CO2, Creatinine, Glucose, and Urea Nitrogen)

3.4.3.2.3 Mineral panel (Phosphorus, Magnesium, Albumin, and Calcium)

3.4.3.2.4 Hepatic panel (Alkaline Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)

3.4.3.2.5 C-reactive protein

3.4.3.2.6 Creatine kinase, uric acid, LDH, amylase and lipase

3.4.3.2.7 Thyroid stimulating hormone (TSH)

3.4.3.2.8 APTT, PT, thrombin time (TT), fibrinogen, D-dimer

3.4.3.2.9 Lymphocyte phenotype TBNK (requires simultaneous CBC and automated differential)

3.4.3.2.10 HIV viral load if HIV seropositive by Western Blot

3.4.3.2.11 EBV viral load if seropositive

3.4.3.2.12 CMV viral load if seropositive

3.4.3.2.13 Hepatitis A antibody screen

3.4.3.2.14 Hepatitis B antibody screen (HBV S Ag, HBV S Ab, HBV core Ab) and viral load if there is evidence of past or current infection

3.4.3.2.15 Hepatitis C antibody screen and HCV viral load

3.4.3.2.16 RPR

3.4.3.2.17 Tuberculosis testing by PPD or interferon gamma release assay (Quantiferon Gold)

3.4.3.3 Pregnancy Testing

3.4.3.4 Urine and serum β-hCG (female subjects only)

3.4.3.5 Electrocardiogram (EKG)

3.4.3.6 Pharmacokinetic Studies (see Section **5.1.1**)

3.4.3.7 Correlative Studies (see Section **5.1.2**)

3.4.3.8 Baseline assessment for response evaluation (see Sections **6.2.1** and **6.2.2**)

### *3.4.4 Treatment Phase Studies*

Clinical examination and clinical laboratory evaluation will be repeated each cycle, except for additional clinical assessment on day 15 of cycle one and additional laboratory toxicity checks on day 15 of cycle one, two and three (see Section **3.4**). Laboratory toxicity checks may be performed by the patient's primary care physician through a certified outside laboratory with results to be provided to NCI investigators, for patients living at a distance from the Clinical Center.

3.4.4.1 Clinical Examination

Evaluation will be repeated on or immediately before day 1 of each cycle, and on day 15 of cycle 1. Objective signs, relevant positive and negative findings on history and examination, and clinical toxicities will be evaluated and recorded each visit.

3.4.4.2 Clinical Laboratory Data

3.4.4.2.1 Evaluations will be repeated on or immediately before day 1 of each cycle.

3.4.4.2.2 CBC with differential and reticulocyte count

3.4.4.2.3 Acute care panel (Sodium, Potassium, Chloride, CO2, Creatinine, Glucose, and Urea Nitrogen)

3.4.4.2.4 Mineral panel (Phosphorus, Magnesium, Albumin, and Calcium)

3.4.4.2.5 Hepatic panel (Alkaline Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)

3.4.4.2.6 C-reactive protein

3.4.4.2.7 Creatine kinase, uric acid, LDH, amylase and lipase

3.4.4.2.8 Thyroid stimulating hormone (TSH)

3.4.4.2.9 APTT, PT, thrombin time (TT), fibrinogen, D Dimer

3.4.4.2.10 HIV viral load if HIV seropositive

3.4.4.2.11 Lymphocyte phenotype TBNK (requires simultaneous CBC and automated differential)

3.4.4.2.12 EBV viral load if seropositive

3.4.4.2.13 CMV viral load if seropositive

3.4.4.2.14 HBV viral load if evidence of past or current infection

3.4.4.2.15 HCV viral load if evidence of past or current infection.

3.4.4.3 Additional Clinical Laboratory Toxicity Check

3.4.4.3.1 Evaluations will be repeated on day 15 of cycles one, two and three only. Results from these evaluations will be used to determine if dose adjustments are required for *subsequent* days of the cycle (as outlined in **Table 1**).

3.4.4.3.2 CBC with differential and reticulocyte count

3.4.4.3.3 Acute care panel (Sodium, Potassium, Chloride, CO2, Creatinine, Glucose, and Urea Nitrogen)

3.4.4.3.4 Mineral panel (Phosphorus, Magnesium, Albumin, and Calcium)

3.4.4.3.5 Hepatic panel (Alkaline Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)

3.4.4.4 Pregnancy Testing

In females of child-bearing potential (FCBP) urine and serum β-HCG will be performed weekly for the first 28 days of study participation and then every 28 days while on study, at study drug discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.

3.4.4.5 Correlative Studies (see section **5.1.2**)

3.4.4.6 Response evaluation (see sections **6.2.1** and **6.2.2**)

### *3.4.5 Post-treatment Evaluation*

Subjects will be reviewed at day 29 of their final cycle, and further evaluated for short term toxicity a further 28 days (±7 days) after completion of the final cycle. Objective signs, relevant positive and negative findings on history and examination, and clinical toxicities will be

evaluated and recorded each visit. If any drug toxicity remains at the follow-up evaluation, subjects will be followed as medically indicated until the toxicity stabilizes or resolves.

3.4.5.1 Clinical Examination

3.4.5.2 Clinical Laboratory Data

3.4.5.2.1 CBC with differential and reticulocyte count

3.4.5.2.2 Acute care panel (Sodium, Potassium, Chloride, CO2, Creatinine, Glucose, and Urea Nitrogen)

3.4.5.2.3 Mineral panel (Phosphorus, Magnesium, Albumin, and Calcium)

3.4.5.2.4 Hepatic panel (Alkaline Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)

3.4.5.2.5 C-reactive protein

3.4.5.2.6 Creatine kinase, uric acid, LDH, amylase and lipase

3.4.5.2.7 Thyroid stimulating hormone (TSH)

3.4.5.2.8 APTT, PT, thrombin time (TT), fibrinogen, D Dimer

3.4.5.2.9 HIV viral load if HIV infected

3.4.5.2.10 Lymphocyte phenotype TBNK (requires simultaneous CBC and automated differential)

3.4.5.2.11 EBV viral load if seropositive

3.4.5.2.12 CMV viral load if seropositive

3.4.5.2.13 HBV viral load if evidence of past or current infection

3.4.5.2.14 HCV viral load if evidence of past or current infection.

3.4.5.3 Pregnancy Testing

In females of child-bearing potential (FCBP) urine and serum β-HCG will be performed at study drug discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur at study drug discontinuation, and at days 14 and 28 following study drug discontinuation.

3.4.5.4 Correlative Studies (see section **5.1.2**)

3.4.5.5 Response Evaluation (see sections **6.2.1** and **6.2.2**)

3.4.5.6 Long-term follow up

Subjects will be clinically evaluated every 3 months for the first 6 months after completion of therapy, then every six months to a total of two years after therapy, and then annually to a total of five years after completion of therapy to evaluate for disease progression and the development of secondary malignancies. CBC, Acute care, mineral and hepatic panels, HIV VL if HIV infected, and Lymphocyte phenotype TBNK will be rechecked or, if performed by primary care in the community, outside results will be reviewed.

For subjects who receive an additional course of pomalidomide, clinical evaluation will be for five years following the completion of the *first* course of therapy including a minimum of two years following the completion of the *second* course of therapy in any case where follow up would otherwise be completed in less than two years after the second course. The visit schedule will be increased as follows to be: every 3 months for the first 6 months after completion of the

second course of therapy, then every six months to a total of two years after the second course of therapy, and then annually to a total of five years after completion of the first course of therapy.

During follow-up visits, KS lesions will be assessed, and if patients have not received additional systemic therapy for KS (except for antiretroviral therapy), disease progression will be assessed. For patients who have received other therapies or have previously progressed, this information as well as the status of their KS lesions will be recorded at the time of the visit (without necessarily assessing disease progression).

The time of the visits may be accelerated or delayed somewhat if need be because of difficulty scheduling, etc. This follow up will be in parallel with primary care provision in the community.

If patients cannot or refuse to come in for follow-up visits, an attempt will be made to obtain data on the patient's general status, their KS treatment, the status of their KS, and secondary malignancies from their primary care providers in the community, and this will not constitute a protocol deviation. For this protocol, "secondary malignancies" will be defined as all new malignancies, whether or not they have been previously reported as associated with pomalidomide. It will include malignancies known to be associated with KSHV or HIV infection.

## 3.5 COST AND COMPENSATION

### *3.5.1 Costs*

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not generally be provided or paid for by the NIH Clinical Center.

### *3.5.2 Compensation*

Participants will not be compensated on this study.

### *3.5.3 Reimbursement*

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

## 3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 28 days (±7 days) following the last dose of therapy.

### *3.6.1 Off-Therapy*

3.6.1.1 Any toxicity which is grade 4 and a dose limiting toxicity as defined in Section **3.1.2** at least possibly related to pomalidomide.

3.6.1.2 Any toxicity which is grade 3 and a dose limiting toxicity as defined in Section **3.1.2** at least possibly related to pomalidomide that does not resolve within 28 days to either grade 1 or the grade the patient had at entry.

3.6.1.3 Development of deep venous or arterial thrombosis, whether symptomatic or not, or development of a second on-study superficial venous thrombosis.

3.6.1.4 Pregnancy.

3.6.1.5 Achievement of pathologically confirmed complete remission.

3.6.1.6 Completion of six cycles of therapy (unless continuing to derive clinical benefit, as described in Section **3.1.4**, in which case up to 12 cycles may be administered).

3.6.1.7 Clinically significant progressive disease compared with the tumor baseline for the current course of therapy by NCI-HAMB modified ACTG KS response criteria, sustained for eight weeks and not attributed to immune reconstitution syndrome. As KS may wax and wane, and improvements may be seen despite an initial period of progression, physician investigators may continue therapy through the first 6 cycles, despite meeting formal criteria for progressive disease, as long as disease progression is not clinically significant. Such cases must be discussed with the Principal Investigator and study subject. Clinically significant progression includes all symptomatic visceral disease and disease which is organ- or life-threatening.

3.6.1.8 ECOG performance status ≥3.

3.6.1.9 Significant non-adherence to protocol therapy or HAART (the latter only in subjects with HIV-associated KS).

3.6.1.10 Inability to achieve HIV viral control, defined as failure to maintain an HIV VL <10,000 copies/mL persisting on at least two successive determinations at least four weeks apart and persisting despite optimization of HAART regimen. If a change in HAART regimen is required, a further period of up to eight weeks to assess the effect of this change on HIV VL is allowable.

3.6.1.11 Subject requests to be withdrawn from active therapy

3.6.1.12 Subjects may be taken off therapy at the discretion of the Principal Investigator

### *3.6.2 Off Study Criteria*

3.6.2.1 Subjects may be taken off study at the discretion of the Principal Investigator.

3.6.2.2 Subjects may withdraw from the study as a matter of personal preference.

3.6.2.3 Subject has completed the study follow-up period

3.6.2.4 Death

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# 4 CONCOMITANT MEDICATIONS/MEASURES

## 4.1 CONCURRENT THERAPIES

### *4.1.1 Antiretroviral therapy*

4.1.1.1 HIV infected subjects must be receiving, and adherent to, HAART.

4.1.1.2 Referring physicians may manage this component of care while liaising with study physician investigators, at the discretion of the Principal Investigator or Lead Associate Investigator.

4.1.1.3 Recommended combination therapy will be based on Department of Health and Human Services Guidelines for treatment of HIV infection. However, patients may have extenuating circumstances requiring deviation from these guidelines.

### *4.1.2 Thromboprophylaxis*

4.1.2.1 Subjects will receive thromboprophylaxis for the duration of pomalidomide therapy (including 'rest' days), ceasing 28 days following the last cycle of pomalidomide.

4.1.2.2 Recommended thromboprophylaxis is aspirin 81mg PO once daily.

4.1.2.3 In subjects intolerant of the above, an appropriate alternate regimen may be used. Alternatives include but are not limited to enoxaparin 0.5mg/kg to a maximum of 40mg SC once daily Enoxaparin dose may be rounded to accommodate available commercial prefilled syringes with. Enoxaparin may also be considered in subjects with additional thrombotic risk factors, such as immobility or significant KS-associated edema. Patients receiving therapeutic anticoagulation for another indication (for example atrial fibrillation), whether with warfarin, enoxaparin, or another agent, may continue that agent in lieu of thromboprophylaxis.

4.1.2.4 Neither aspirin nor low molecular weight heparin will be administered when platelet count <50,000 cells/$mm^3$.

### *4.1.3 Pneumocystis jiroveci (PCP) prophylaxis*

4.1.3.1 *Pneumocystis jiroveci* prophylaxis is indicated if the CD4 count is ≤ 200cells/μL and for patients with a history of PCP infection.

4.1.3.2 Recommended therapy is trimethoprim/sulfamethoxazole DS PO three times weekly.

4.1.3.3 In patients intolerant of the above, an appropriate alternate regimen may be used. Alternatives include but are not limited to dapsone 50–100 mg PO daily or 100 mg PO twice weekly; atovaquone 1500 mg PO daily; aerosolized pentamidine monthly.

### *4.1.4 Mycobacterium avium complex (MAC) prophylaxis*

4.1.4.1 Consider for patients whose CD4 cells are below 50-75/$mm^3$, and for those with historic CD4 nadir ≤75/$mm^3$.

4.1.4.2 Recommend azithromycin 1200 mg once weekly, but other agents are acceptable.

### *4.1.5 Contraindicated Therapies*

4.1.5.1 Corticosteroids may be given only if the Principal Investigator or a physician Associate Investigator approves them. In general, except for physiologic replacement, corticosteroids (including topical preparations) should be avoided wherever possible, as they can have adverse effects on KS.

4.1.5.2 Radiation therapy is contraindicated for patients receiving therapy on protocol, as the effects of radiation therapy in combination with pomalidomide in patients with KS are unknown.

## 4.2 SUPPORTIVE CARE

### *4.2.1 General Principles of Supportive Care*

Medications may be administered as clinically indicated, or at the discretion of the Principal Investigator, with the exception of other specific therapies for KS

### *4.2.2 Febrile Neutropenia*

Subjects who develop febrile neutropenia will be hospitalized and treated with appropriate broad-spectrum intravenous antibiotics. See Section **3.3** for treatment modifications and guidelines for filgrastim use pertaining to neutropenia.

### *4.2.3 Anemia*

If subject develops symptomatic anemia, or if the hemoglobin falls below 8.0 mg/dL transfusion may be considered. Appropriate evaluation for etiology of the anemia, including but not limited to pomalidomide, HIV and its therapy, should be initiated.

### *4.2.4 Thrombocytopenia*

Thrombocytopenia should be treated conservatively. In the absence of bleeding or a planned invasive procedure, platelet transfusions should be given for a platelet count below 10,000/$mm^3$. For subjects with risk factors for bleeding, including fever, platelet transfusion may be considered for platelet counts below 20,000/$mm^3$. If invasive procedures are planned or the patient develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count > 50,000/$mm^3$.

### *4.2.5 Opportunistic Infections*

Subjects who develop opportunistic infections, including but not limited to *pneumocystis jiroveci* pneumonia, mycobacterial diseases, cytomegalovirus (CMV), and fungal infections will be treated using standard regimens. All opportunistic infections will be discussed with the Principal Investigator. Consultation with the Infectious Disease Service is mandatory for subjects diagnosed with mycobacterium tuberculosis.

### *4.2.6 Nutritional Assessment and Psychological Support*

4.2.6.1 HIV and KS may compromise nutritional status. Careful attention will be paid to nutritional status, and consultation with nutrition healthcare workers to optimize caloric intake will be undertaken as necessary.

4.2.6.2 The chronic, incurable and potentially life-threatening nature of this disease and the stigmatizing nature of visible lesions is a profound psychological stressor. All such subjects on the study will be informed of and encouraged to see a NIH Social Worker for evaluation and support.

# 5 BIOSPECIMEN COLLECTION

## 5.1 CORRELATIVE AND PHARMACOKINETIC STUDIES FOR RESEARCH.

Correlative studies to be performed during treatment with pomalidomide include assessment of changes in tumor blood flow by non-invasive imaging techniques(147, 148); assessment of changes in systemic cytokines and angiogenic factors including IL-1β, IL-2, IL-5, human IL-6, viral IL-6, IL-8, IL-10, IL-12, IFN-γ, TNF-α, VEGF-A, IP-10/CXCL-10 and RANTES; assessment of changes in HIV and KSHV viral loads (VL), including changes in HIV VL occurring below the conventional limit of detection; assessment of biochemical changes in KS tumor tissues (including the Notch ligands Dll1, Dll3, Dll4, Jag1 and Jag2; the Notch receptors Notch1,2, 3 and 4; Notch intracellular domain (ICD); the Notch target genes Hey1 and Hey2; the transcription factors ZEB1, ZEB2, Slug and snail; EphrinB2 and EphB receptors; and markers of

NFkB activation [p65, p50IkBalpha and IKK1]); and preliminary assessment of changes in immunologic parameters, including monocyte activation, T-cell activation and subsets, and anti-KSHV specific T-cell immune responses. Correlative assays may be performed in batches.

### *5.1.1 Pharmacokinetic studies*

Pharmacokinetic studies will be performed during the first course of therapy at the time of first dose (day one to two of cycle one), and be repeated at steady state (day 15 to 16 of cycle one).

5.1.1.1 Pharmacokinetic sample collection and analysis will be carried out in all enrolled subjects. For determination of pomalidomide pharmacokinetics, serial venous blood samples (6mL sodium heparin tube) will be obtained before and after drug administration on day 1 of cycle 1 (first administration) and day 15 of cycle 1 (steady state). The following time points for collection will be used: pre-dose, 1, 2, 3, 4, 6, 8, 24, according to the following table, in order to capture a fair estimate of the $C_{max}$ and terminal elimination phase.

**5.1.1.2** Pharmacokinetic Sample Schedule for Pomalidomide (times as close as feasible to those specified)**:**

| Cycle | Day | PK Sampling | Scheduled Time | Tube |
|---|---|---|---|---|
| 1 | 1 | Pomalidomide | Pre-dose | 1 |
| 1 | 1 | Pomalidomide | 1 hour after dose | 2 |
| 1 | 1 | Pomalidomide | 2 hours after dose | 3 |
| 1 | 1 | Pomalidomide | 3 hours after dose | 4 |
| 1 | 1 | Pomalidomide | 4 hours after dose | 5 |
| 1 | 1 | Pomalidomide | 6 hours after dose | 6 |
| 1 | 1 | Pomalidomide | 8 hours after dose | 7 |
| 1 | 2 | Pomalidomide | 24 hours after dose | 8 |
| 1 | 15 | Pomalidomide | Pre-dose | 9 |
| 1 | 15 | Pomalidomide | 1 hour after dose | 10 |
| 1 | 15 | Pomalidomide | 2 hours after dose | 11 |
| 1 | 15 | Pomalidomide | 3 hours after dose | 12 |
| 1 | 15 | Pomalidomide | 4 hours after dose | 13 |
| 1 | 15 | Pomalidomide | 6 hours after dose | 14 |

| Cycle | Day | PK Sampling | Scheduled Time | Tube |
|---|---|---|---|---|
| 1 | 15 | Pomalidomide | 8 hours after dose | 15 |
| 1 | 16 | Pomalidomide | 24 hours after dose | 16 |

5.1.1.3 Handling of Pharmacokinetic Samples

5.1.1.3.1 The Blood Processing Core (BPC) (Figg Laboratory. 5A-09, 301-594-6131 or 301-402-3622) will coordinate sample collection, processing and pharmacokinetic analysis. Research nurses will give the lab 24 hours advance notice on PK blood draws.

5.1.1.3.2 The date, planned time and exact draw time and cycle day of collection for each specimen will be recorded on a pharmacokinetic form containing the study number and unique patient identifier. The exact time of draw and cycle timepoint will be recorded by research or floor nurses on the blood tube label.

5.1.1.3.3 Research nurses will page 102-11964 (Figg laboratory) immediately prior to blood draw. Blood will be drawn into green-top tubes to which 0.1% hydrochloric acid has been added. These will be supplied in capped tubes by the Figg laboratory to the clinical team prior to the patient starting treatment. After drawing, blood samples must be thoroughly mixed for drug stability and placed immediately on wet ice for transport to the Figg laboratory.

5.1.1.3.4 Samples will then be centrifuged within 30 minutes of collection, for 10 minutes at 2000g (4°C), and plasma supernatants will be transferred to individually labeled tubes, barcoded, anonymized, and stored at -80 °C until analysis. Patient data will be entered into a secure and encrypted LabSamples database maintained by the Clinical Pharmacology Program, Office of the Clinical Director.

5.1.1.3.5 An ultra high pressure liquid chromatography-tandem mass spectrometry analytical method will be used to quantify pomalidomide plasma concentrations.

5.1.1.3.6 Pharmacokinetic parameters calculated by noncompartmental analysis will be the maximum plasma concentration ($C_{max}$), the time at $C_{max}$ ($T_{max}$), the $C_{max}$ at steady-state ($C_{max}$ ss), $T_{max}$ ss, apparent clearance (CL/F), and the apparent volume of distribution (Vss/F), the area under the plasma concentration time curve on day 1 extrapolated to infinity ($AUC_{0-\infty}$) and at steady state ($AUC_{0-24}$), terminal elimination half-life ($T_{1/2}$). The study will include exploratory population pharmacokinetic correlative analysis of drug-interaction effects on pomalidomide plasma exposure for subjects on antiretroviral medications.

### *5.1.2 Correlative Studies*

5.1.2.1 Sample Collection

5.1.2.1.1 Correlative Cytokine, Angiogenesis and Virologic Studies

Evaluations will occur on day 1 of each cycle as well as on day 29 of the final cycle. There will also be an additional pre-therapy collection for single copy HIV VL.

5.1.2.1.1.1 KSHV viral load in peripheral blood mononuclear cells

- One yellow top tube (send to Whitby laboratory)

5.1.2.1.1.2 KSHV viral load in saliva

- One blue top conical polypropylene tube (no additive) of saliva obtained with Scope® mouthwash (BD Falcon® Ref 353070) (send to Whitby laboratory).

5.1.2.1.1.3 viral IL-6, human IL-6, human IL-10, IL-1β, IL-5 IL-8, IL-12, IFN-γ, TNF-α, RANTES and IP-10/CXCL-10

- Two red top tubes (send to Leidos Biomedical Research Inc., Frederick)

5.1.2.1.1.4 Measurement of VEGF, FGF-2, Dll4/Notch and Ephrinb2/Ephb2

- Three sodium heparin green top tubes (send for storage to Leidos Biomedical Research Inc. Frederick)

5.1.2.1.1.5 Single copy HIV VL (only in patients with HIV infection)

- One 6mL lavender top (EDTA) tubes for measurement of single copy HIV VL. Send to Leidos Biomedical Research Inc., Frederick to be frozen at -40°C. These samples will be transferred to the Maldarelli laboratory when ready for batched testing. Samples will be run only in patients whose HIV VL by conventional techniques is approaching or below the limit of detection.

5.1.2.1.1.6 Two yellow top tubes (send for storage to Leidos Biomedical Research Inc., Frederick).

5.1.2.1.2 Immune Activation and KSHV Immune Response Assays

Studies will be performed on one occasion pre-therapy (to be after screening and enrollment and at least 2 days before commencement of therapy and repeated 28 days (±7 days) after completion of the final cycle. Monocyte and T-cell Activation and Subset assays *only* will also be repeated day 1 of cycle 4. If a fresh monocyte sample is planned and the Sereti laboratory is unable to receive the fresh monocyte sample on the day of a planned draw (for example due to staff illness, equipment failures, or other exigencies) the fresh monocyte sample may be drawn on the next available cycle or run from frozen specimens without constituting a protocol deviation; for the pre-therapy draw samples may be drawn any day prior to drug administration up to and including cycle 1 day 1.

If immune activation studies and KSHV immune response assays have been performed on a subject as part of the HAMB Tissue Procurement study (01-C-0038) within 14 days of enrolment on 12-C-0047, then at the discretion of the Principal Investigator or Lead Associate Investigator the samples drawn under 01-C-0038 may be used for the pomalidomide pre-therapy baseline and this draw does not need to be repeated pre-therapy. In these cases, the investigator will confirm that the patient gave consent for future use of specimens when the consent for 01-C-0138 was signed.

5.1.2.1.2.1 KSHV Serology, KSHV miRNA Typing and KSHV-specific T-cell Responses

- Performed in the laboratory of Dr. Denise Whitby, NCI-Frederick.
- Serology and miRNA Typing will be performed at the pre-therapy draw only.
- Samples for KSHV-specific T-cell Responses will be stored and performed in batches with paired samples from individual subjects assayed together for consistency.

- Send 34mL blood in four yellow top (ACD) tubes to Leidos Biomedical Research Inc., Frederick for storage prior to transfer to Whitby laboratory.

5.1.2.1.2.2 Monocyte and T-cell Activation and Subset Assays

- Performed in the laboratory of Dr. Irini Sereti, NIAID.
- As of amendment E, fresh monocyte studies from EDTA samples will not be performed. Monocyte studies will be performed from frozen sodium heparin samples.
- T-cell studies will be stored and performed in batches with paired samples from individual subjects assayed together for consistency: send 40mL blood in green top (sodium heparin) tubes to Leidos Biomedical Research Inc., Frederick for storage.

5.1.2.2 Description of Studies

5.1.2.2.1 Human Cytokine Assays

Human multiplex inflammatory cytokine ELISA (Meso-Scale Discovery, Gaithersburg, MD: Cat.# K15008), human IL-5 ELISA (Cat.# K111AJA), VEGF ELISA (Cat.# K111BMA), RANTES (Cat.# K111BFA) and IP-10/CXCL-10 (Cat.# K111AVA) will be performed in the AIDS Monitoring Laboratory, Leidos Biomedical Research Inc., Frederick.

5.1.2.2.2 Viral IL-6 Assay

Performed in the laboratory of Dr. Robert Yarchoan, using a modification of the method previously described by our group(69).

5.1.2.2.3 KSHV Serology, KSHV Viral Load, and KSHV Specific T-cell Responses

Performed in the laboratory of Dr. Denise Whitby, Leidos Biomedical Research Inc., Frederick, using methods previously described by her group(19),(149-151).

5.1.2.2.4 HIV Viral Load Single Copy Assay

Performed in the laboratory of Dr Frank Maldarelli, NCI, using real-time reverse transcriptase-initiated PCR assays previously described by his group(152).

5.1.2.2.5 Monocytes and T-cell Activation, Stimulation and Subset Assays

Performed in the laboratory of Dr Irini Sereti, NIAID. Assays of monocyte activation and T cell polyclonal stimulation and activation, including HLA DR/38/Ki67/PD-1/CD57/Ro/CD27/FoxP3/CD25 will be performed by flow cytometry.

5.1.2.2.6 Systemic Angiogenesis Assays

Performed in the laboratory of Dr. Giovanna Tosato, NCI. Assays of FGF-2, Dll4/Notch and Ephrinb2/Ephb2 will be performed by ELISA and/or Western blot on blood samples.

5.1.2.2.7 KS Tissue Angiogenesis and Signaling Assays

Performed in the laboratory of Dr. Giovanna Tosato, NCI.
Assays of the Notch ligands Dll1, Dll3, Dll4, Jag1 and Jag2; the Notch receptors Notch1,2, 3 and 4; Notch intracellular domain (ICD); the Notch target genes Hey1 and Hey2; the transcription factors ZEB1, ZEB2, Slug and snail; EphrinB2 and EphB receptors; and markers of NFkB activation p65, p50IkBalpha and IKK1 will be performed using mRNAs for quantitative PCR, Westerns blots, and immunohistochemistry for confocal microscopy.

5.1.2.2.8 KSHV RNA and Protein Expression Analysis

Performed in the laboratory of Dr Joseph Ziegelbauer, HAMB, CCR, NCI. After cell separation, cells will be lysed to extract RNA and protein. These samples will be analyzed using quantitative PCR, gene expression arrays and Western blots with a focus on KSHV miRNA target genes.

5.1.2.3 KS Tumor Biopsies

5.1.2.3.1 From screening material

If additional research tests are to be performed on the screening biopsy (see Section **2.2.5.2.2**), please divide the specimen remaining after sufficient tissue for diagnostic purposes has been submitted to Laboratory of Pathology in formalin for histopathology and immunohistochemistry and distribute in the priority indicated in Section **5.1.2.3.3**.

5.1.2.3.2 Additional optional biopsies:

5.1.2.3.2.1 On therapy biopsy

Where there is cutaneous disease, an optional biopsy for research purposes may be performed during the treatment phase on day one of cycle three (or day 28 of cycle two if this is more convenient). A 2-3mm cutaneous punch biopsy only will be obtained. Where an on-treatment research biopsy is obtained, the specimens will be handled as follows, in this priority:

- Place sufficient tissue for diagnostic purposes directly into formalin and submit to Laboratory of Pathology for histopathology and immunohistochemistry including KSHV-LANA and KSHV-vIL-6.
- Divide the remainder and provide to the 1. Tosato laboratory (fresh, on gauze damp but not wet with saline, at 4°C) for tissue expression of Dll4/Notch, Jag1/Notch, Jag2/Notch, Notch ICD (intracellular domain), Hey1/Hey2 and EphrinB/EphB, and markers of NFkB activation (including p65, p50IkBalpha, IKK1)

5.1.2.3.2.2 Post-therapy biopsy

Additional optional 6 mm cutaneous punch biopsies may be performed in one or both of the following two circumstances if clinically indicated: after therapy has been completed, if clinically indicated and subject to patient agreement, to confirm clinical complete response; or during therapy to document progressive disease if there is clinical uncertainty about new lesions. Where such biopsies are obtained, the specimens will be handled as follows, in this priority:

- Place sufficient tissue for diagnostic purposes directly into formalin and submit to Laboratory of Pathology for histopathology and immunohistochemistry including KSHV-LANA and KSHV-vIL-6.
- Divide the remainder and distribute in the priority indicated in Section **5.1.2.3.3**

5.1.2.3.3 Distribution of Biopsy Material

1. Tosato laboratory (fresh, on gauze damp but not wet with saline, at 4°C) for tissue expression of Dll4/Notch, Jag1/Notch, Jag2/Notch, Notch ICD (intracellular domain), Hey1/Hey2 and EphrinB/EphB, and markers of NFkB activation (including p65, p50IkBalpha, IKK1)
2. Whitby laboratory (frozen, on dry ice or trizol) for KSHV gene expression

3. Ziegelbauer laboratory (fresh, on saline-soaked gauze, at 4°C) for KSHV RNA and protein expression analysis with a focus on KSHV miRNAs and miRNA target gene evaluation
4. For any residual tissue, freeze as soon as possible for storage at -40°C and send via messenger to the AIDS Monitoring Laboratory (AML), Leidos Biomedical Research Inc., at NCI-Frederick (see Section **5.2**).

5.1.2.4 Biospecimens for storage

Assays will be performed in batches with the exception of monocyte functional assays and pharmacokinetic testing. Samples for the batched correlative studies above will be sent via messenger to the AIDS Monitoring Laboratory (AML), Leidos Biomedical Research Inc. in the NCI-Frederick (See Section **5.2**) for storage until assays are performed. Collection schedule and sample requirements are given in Section **3.4**, and Section **5.1.2.1**.

## 5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

It is understood that per the NCI policy regarding the Requirements for the Research Use of Stored Human Specimens and Data, prospective NIH IRB approval and continuing IRB oversight must be obtained for research involving identified or coded samples or data where investigators can identify the source. This policy applies to research protocols where the remaining research activities are limited to data analysis and to the subsequent research use of specimens or data previously collected under a now terminated protocol. The following guidelines describe how these principles apply to this specific protocol.

- AIDS Monitoring Laboratory, Science Applications International Corporation
  - Many samples on this study will be processed and stored in the AIDS Monitoring Laboratory (AML) run by Leidos Biomedical Research Inc. in the NCI-Frederick facility located with Fort Detrick. The samples are stored under code, and the information linking these unique codes to the subjects is kept on the AML database. The laboratory informatics system conforms to NIH Information Technology Security Requirements and NIH Protection of Human Research Subjects Guidelines. All laboratory staff is trained to adhere to NIH Information Technology Security Requirements and NIH Protection of Human Research Subjects Guidelines. Computers used to access inventory systems require username and password for login. The laboratory database is housed in a secure, protected environment and backups are performed routinely. Access to specimen information, clinical data, and stored specimens is limited to approved laboratory staff and the investigator in charge of the study (or individuals authorized by the investigator).
- Specimen Withdrawal for Research Purposes
  - The protocol team will inform the AML staff when tests are to be run with the specimens, and the samples used for testing will be tracked by the AML. This information will in turn be shared with the protocol team. The research nurse on the study will be in charge of tracking this information for the protocol team.
- Specimens Sent to the Whitby Laboratory
  - Some of the specimens are sent to the laboratory of Dr. Denise Whitby, also in Leidos Biomedical Research Inc., in the NCI-Frederick facility located with Fort Detrick. This is a locked laboratory, and a log is kept of the specimens and when they are

utilized. The samples sent are coded by the protocol research team and have no patient identifiers. They are logged in by Dr. Whitby's laboratory and are run in batch when enough specimens are collected. Records are kept when the specimens are used for analysis.

Denise Whitby PhD
Leidos Biomedical Research Inc., Frederick
50 Boyles St, Building 535, Room 428A
Frederick, MD
301-846-5828

- Specimens Sent to the Yarchoan Laboratory
  - A limited number of samples are sent to Dr. Yarchoan's laboratory. This is a locked laboratory, and a log is kept of the specimens and when they are utilized.

    Robert Yarchoan, MD
    Building 10, Room 5A25
    Bethesda, MD
    301-402-3630
- Specimens Sent to the Tosato Laboratory
  - A limited number of samples are sent to Dr. Tosato's laboratory. This is a locked laboratory, and a log is kept of the specimens and when they are utilized. The samples sent are coded by the protocol research team and have no patient identifiers. They are logged in by Dr. Tosato's laboratory and are run in batch when enough specimens are collected. Records are kept when the specimens are used for analysis.

    Giovanna Tosato, MD
    Building 37, Room 4124
    Convent Drive
    Bethesda, MD
    301-594-9596
- Specimens Sent to the Ziegelbauer Laboratory
  - A limited number of samples are sent to Dr. Ziegelbauer's laboratory. This is a locked laboratory, and a log is kept of the specimens and when they are utilized. The samples sent are coded by the protocol research team and have no patient identifiers. They are logged in by Dr. Ziegelbauer's laboratory and are run in batch when enough specimens are collected. Records are kept when the specimens are used for analysis.

    Joseph Ziegelbauer, PhD
    Building 10, Room 5A21
    10 Center Dr
    Bethesda, MD
    301-594-6634
- Specimens Sent to the Maldarelli Laboratory
  - A limited number of samples are sent to Dr. Maldarelli's laboratory. This is a locked laboratory, and a log is kept of the specimens and when they are utilized. The samples sent are coded by the protocol research team and have no patient identifiers. They are logged in by Dr. Maldarelli's laboratory and are run in batch when enough specimens are collected. Records are kept when the specimens are used for analysis.

Frank Maldarelli, MD
Building 10, 5A06
10 Center Dr
Bethesda, MD
301-435-8019

- Specimens Sent to the Sereti Laboratory
  - A limited number of samples are sent to Dr. Sereti's laboratory. This is a locked laboratory, and a log is kept of the specimens and when they are utilized. The samples sent are coded by the protocol research team and have no patient identifiers. They are logged in by Dr. Sereti's laboratory and are run in batch when enough specimens are collected. Records are kept when the specimens are used for analysis.

    Irini Sereti, MD
    Building 10, 11B07
    10 Center Dr
    Bethesda, MD
    301-496-5533
- Clinical Testing of Stored Specimens
  - Clinical testing of all samples will be one in accordance to the protocol. The protocol team will inform the AML staff when tests are to be run with the specimens, and the samples used for testing will be tracked by the AML. This information will in turn be shared with the protocol team. The research nurse on the study will be in charge of tracking this information for the protocol team.
- Clinical Center Processing and Storage of Clinical Specimens
  - Many routine samples and a sample of the biopsy specimens are sent to the Laboratory of Pathology (CCR), Department of Laboratory Medicine, and Department of Transfusion Medicine at the NIH Clinical Center. These samples will be handled according to the procedures of these departments. Results for clinical testing are generally available via the CRIS electronic medical record.
- Co-enrollment on 01-C-0038
  - If subjects have co-enrolled on study 01-C-0038 (Collection of Blood, Bone Marrow, Tumor, or Tissue Samples from Subjects with HIV Infection, KSHV Infection, Viral-related Pre-Malignant Lesions, and/or Cancer), then the samples may also be tested under the specifications of that study. Similarly, if subjects have co-enrolled on other studies approved by the NIH Intramural IRB that call for maintaining and testing the samples, then they may be transferred to those studies.
- Handling of Specimens at Study Termination
  - At the termination of the protocol, if subjects have co-enrolled on study 01-C-0038 (Collection of Blood, Bone Marrow, Tumor, or Tissue Samples from Patients with HIV Infection, KSHV Infection, Viral-related Pre-Malignant Lesions, and/or Cancer), then the samples will be transferred to that study unless the patient requests that this not occur. Also, if subjects have co-enrolled on other studies approved by the NIH Intramural IRB that call for maintaining the samples, then they will be maintained on those protocols. Otherwise, the unused samples will be destroyed.
- Loss or Destruction of Samples

- The Principal Investigator will record any loss or unanticipated destruction of the samples as a deviation. Reporting will be per the requirements of Section **7.2**.

# 6 DATA COLLECTION AND EVALUATION

## 6.1 DATA COLLECTION

- Members of the HIV/AIDS Malignancy Branch clinical research team will collect data on study subjects according to the Schedule of Evaluations outlined in Section **3.4**. Complete records will be maintained on each patient including supplementary information obtained from outside laboratories, radiology reports, or physician's records. These will serve as the primary source material that forms the basis for the research record. The primary source documentation will assure the following:
  - The patient satisfied each eligibility criterion.
  - Signed informed consent was obtained prior to registration and treatment.
  - Treatment was given according to protocol or any protocol violations documented and justified.
  - Toxicity and response were assessed according to protocol.
  - Drug accountability records were kept on each patient.
- Clinical data will be coded for database entry. Data will be stored in the CCR C3D clinical trials database. Dr. Robert Yarchoan, the Principal Investigator, will be responsible for the protocol.
- The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 28 days (±7 days) after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

**End of study procedures:** Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

## 6.2 RESPONSE CRITERIA

While the evaluation of the response of KS to an agent or regimen is difficult to grade by means of commonly used oncologic definitions, in an effort to standardize the evaluation of therapy against KS, the AIDS Clinical Trial Group Oncology Committee has devised a set of staging and response definitions for KS. We will use a modification of these criteria to assess responses, which is consistent with the criteria used in our previous KS studies. It should be noted that there is some observer variability in the evaluation of the number, size, nodularity, and color of lesions, and this must be taken into account when measurements are interpreted.

- For the purposes of this study, patients should be evaluated at baseline and re-evaluated for response on day 1 of every cycle or every other cycle depending on study (see sections **6.2.1** and **6.2.2** below) and at the end of treatment.
- For assessment of response, only patients who complete at least two cycles of therapy are evaluable.
- For evaluation of less than complete responses in subjects with more than 50 lesions at entry, only the previously selected 1 - 3 representative areas that contain at least 20 lesions will be considered. However, complete responses still require the absence of any detectable disease over the entire body (i.e. not confined to the representative areas).

### *6.2.1 Methods of Evaluation for Measurable Disease*

#### 6.2.1.1 KS Tumor Photography

Baseline whole body photographs will be obtained upon entry into the study. At this time, 5 lesions (hereafter called marker lesions), representative of the patient's disease and, if possible, located on separate areas of the body will be selected. These marker lesions should be lesions that have never been treated with local therapies such as radiation therapy or intralesional injections. An attempt will be made to distribute the "marker" lesions between the representative areas (described below in section **6.2.1.3.1**) and the rest of the body. Detailed photographs of these lesions will be obtained with a metric rule beside them.

After baseline, photography will be repeated day one of the first six cycles; for any patients receiving more than six cycles, photography will be repeated on alternate cycles (on odd-numbered cycles, starting with cycle 7) thereafter. Photography will also be performed on day 29 of the final cycle.

For subjects receiving a second course of pomalidomide (Section **3.1.6**), a new tumor baseline will be determined immediately prior to commencement of the second course as described above. Documentation of extent of disease and response to therapy will follow the same schema described for the initial course of therapy, with all comparisons made against this new baseline.

#### 6.2.1.2 Documentation of Marker Lesions

The size, color and nodularity of the marker lesions will be recorded on Day 1 of each cycle and on day 29 of the final cycle. Documentation will depend on the number of lesions.

#### 6.2.1.3 Documentation of Extent of Disease

6.2.1.3.1 *Subjects with 50 or more KS lesions:* for subjects with 50 or more lesions at entry, between 1 and 3 representative areas will be selected at baseline and these will be used for each subsequent evaluation. Representative areas are sections of the body (e.g. the back, a leg, an arm, etc.), which contain at least 20 KS lesions. The total number of lesions in these representative areas will be counted and a record made of whether they are flat or raised. If, in the course of treatment, a single lesion breaks up into 2 or more smaller lesions whose area does not extend beyond the boundary of the initial lesion, these lesions will still be counted as single lesions for the purpose of assessing total numbers in defining a response to therapy.

After baseline, the number of lesions within the representative areas will be counted at the completion of each cycle.

6.2.1.3.2 *Subjects with fewer than 50 KS lesions:* for subjects with less than 50 lesions at entry, the total number of lesions will be counted and a record made of whether they are flat or raised.

After baseline, the number of lesions within the representative areas will be counted at the completion of each cycle.

6.2.1.3.3 Additional studies for visceral KS involvement: additional studies, including but not limited to, gastrointestinal endoscopy and bronchoscopy will be performed at entry where clinically indicated, based on clinical evaluation of the patient.

6.2.1.4 KS Tumor Non-invasive Imaging

Evaluation of the vascularity in KS will be performed using 3 non-invasive modalities: laser Doppler imaging, multi-spectral imaging, and infrared thermal imaging. Imaging will use the modalities previously explored in study 01-C-0158(144, 145). A target lesion of KS as well as normal skin will be identified and recorded for follow-up studies. The target lesion will also be measured and photographed. These are correlative studies performed in parallel with tumor response assessment, and are not considered in the evaluation of KS response by modified ACTG criteria.

After baseline, imaging will be repeated on day one of the first six cycles; and for any patients receiving more than six cycles, imaging will be repeated on alternate cycles (on odd-numbered cycles, starting with cycle 7) thereafter. Imaging will also be performed on day 29 of the final cycle.
For subjects receiving a second course of pomalidomide (Section **3.1.6**), a new tumor baseline will be determined immediately prior to commencement of the second course as described above. Documentation of extent of disease and response to therapy will follow the same schema described for the initial course of therapy, with all comparisons made against this new baseline.

6.2.1.5 KS tumor biopsies

See section **5.1.2.3**

### *6.2.2 Quality of Life Evaluation*

Quality of life assessment will be performed using the Functional Assessment of HIV Questionnaire(153) (see also www.facit.org), adapted with the inclusion of three additional questions directed at specific assessment of KS impact on quality of life developed for a prior AIDS Malignancy Consortium study in KS(85) (

**Appendix** 6 [English] and **Appendix 7** [Spanish]). The questionnaire will be self-administered by subjects in an environment providing visual and auditory privacy and free from distractions. Questionnaires will be administered at baseline, on day 1 of cycle 4 and 28 days after the completion of the final cycle.

For subjects who are not fluent in English or Spanish, where an approved translated version of the FAHI questionnaire for the patient's first language is available from the Functional Assessment of Chronic Illness Therapy group (www.facit.org/questionnaires) these may be used in place of the questionnaire in

**Appendix** 6 and **Appendix 7**. Where a suitable questionnaire is not available, the English version may be used *only* with the assistance of an approved translator.

For subjects whose written literacy in the language of FAHI questionnaire administration is questionable, the questionnaire may be administered orally with the verbal and recording assistance of an approved translator or member of the study clinical team.

For subjects receiving a second course of pomalidomide (Section **3.1.6**), a new quality of life baseline will be determined immediately prior to commencement of the second course as described above. Questionnaires will be administered immediately prior to commencement of the second course, on day 1 of cycle 4 of the second course, and 28 days after the completion of the final cycle of the second course. Comparisons will be made to the new baseline.

### *6.2.3 Response Criteria*

Complete Response:

- The absence of any detectable residual disease, including tumor associated edema, persisting for at least 4 weeks.
- For subjects with pigmented macular skin lesions persisting after apparent complete response, a biopsy of at least one representative lesion is required to document the absence of malignant cells. If a lesion has not been biopsied, the patient may be classified as having a clinical CR.
- For subjects with visceral disease, the diagnostic radiologic or endoscopic study should be repeated if not medically contraindicated and found to be negative for evidence of disease. If such procedures are medically contraindicated but the patient has no clinical evidence of visceral disease, the patient may be classified as having a clinical CR.

Clinical Complete Response:

- The absence of any detectable residual disease, including tumor associated edema, persisting for at least 4 weeks.
- For subjects with pigmented macular skin lesions persisting after apparent complete response, if a representative lesion has not been biopsied.

For subjects with visceral disease, the diagnostic radiologic or endoscopic study should be repeated if not medically contraindicated and found to be negative for evidence of disease. If such procedures are medically contraindicated but the patient has no clinical evidence of visceral disease, the patient may be classified as having a clinical CR.

Partial Response

- No progressive disease (see below and noting, that single lesions which split up into 2 or more smaller lesions during the course of treatment will still be counted as one); no new lesions occurring in previously uninvolved areas of the body; no new visceral sites of involvement or the appearance or worsening of tumor-associated edema or effusions and:
- A 50% or greater decrease in the number and/or size of previously existing lesions lasting for at least 4 weeks *or*
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all previously nodular or plaque-like lesions become macular) lasting for at least 4 weeks *or*
- A 50% decrease in radiologically measurable visceral lesions sustained without evidence of re-growth for at least 4 weeks *or*
- A 50% decrease in radiologically measurable visceral lesions sustained without evidence of re-growth for at least 4 weeks *or*
- Subjects who otherwise meet the criteria for a CR but still have residual tumor-associated edema or effusions will be classified as having a PR.

Progressive Disease

- For those criteria that involve measurement of lesions in the clinic, the designation of progression should be made, when feasible, only when the criteria below have been met in two measurements spaced at least 1 week apart. For the assignment of progressive disease for the primary outcome analysis, progression will be defined in comparison to baseline measurements.
- An increase of 25% or more over baseline in the number of lesions and/or the size (sum of the products of the largest perpendicular diameters) of the marker lesions *or*
- A change in character from macular to plaque-like or nodular of at least 25% of the lesions *or*
- New visceral sites of involvement or progression of visceral disease *or*
- The development of new or increasing tumor-associated edema or effusion that lasts at least 1 week and interferes with the patient's normal activities.
- Clarification: There is a certain variability in the measurement of KS lesions, and this becomes particularly problematic if patients have very few lesions. To mitigate against this effect, if the cutaneous burden of KS is at any time 8 or less lesions, progressive disease will require the development of at least 2 new lesions. Similarly, if the cutaneous burden of KS is at any time 8 or less nodular lesions, progressive disease will require the development of at least 2 new nodular lesions.

Stable Disease

- Any tumor measurement not meeting the criteria for Complete Response, Partial Response, or Progressive Disease.

Overall Response

- Overall response rate is the sum of complete responses, clinical complete responses, and partial responses.

### 6.3 TOXICITY CRITERIA

- The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. Adverse events occurring during the study will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm
- Toxicity Attribution
  - The Principal Investigator or physician Associate Investigator will meet at least weekly to discuss adverse events, and document the relationship of the protocol intervention to each adverse event by assigning attribution per adverse event at time of clinical evaluation. Attribution will be rated as follows:
    - Unrelated: the adverse event is *clearly not* related to the investigational agents.
    - Unlikely related: the adverse event is *doubtfully* related to the investigational agents.
    - Possibly related: the adverse event *may be* related to the investigational agents.
    - Probably related: the adverse event is *likely* related to the investigational agents.
    - Definitely related: the adverse event is *clearly* related to the investigational agents

## 7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

### 7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

### 7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

#### *7.2.1 Expedited Reporting*

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

#### *7.2.2 IRB Requirements for PI Reporting at Continuing Review*

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

### 7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

## 7.4 NIH Required Data and Safety Monitoring Plan

### *7.4.1 Principal Investigator/Research Team*

The clinical research team will meet on a regular basis (weekly) when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

# 8 SPONSOR PROTOCOL/SAFETY REPORTING

## 8.1 Definitions

### *8.1.1 Adverse Event*

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

### *8.1.2 Serious Adverse Event (SAE)*

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see Section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### *8.1.3 Life-threatening*

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

### *8.1.4 Severity*

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.

### *8.1.5 Relationship to Study Product*

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

## 8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **6.1 Error! Reference source not found.**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

### 8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

### 8.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

All events listed below must be reported in the defined timelines to OSROSafety@mail.nih.gov.

CCR OSRO will send all reports to the manufacturer as described below.

- Serious adverse events (SAE) are defined above. If any SAE is required to be reported to the sponsor according to Section **8.1.2** (i.e. within 28 days of receiving drug or assessed as being possibly related to drug administration), the sponsor should inform Celgene of the SAE within 1 business day of being aware of the event. This must be documented on a Celgene SAE form or FDA 3500A or MEDWATCH form. This form must be completed and supplied to Celgene within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH. A final report to document resolution of the SAE is required. The Celgene tracking number (PO-KS-NCI-0050) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

  All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC on file for records retention information). The investigator is responsible for reporting adverse events to Celgene as described below.

In addition, if secondary malignancies that do not fall under the criteria for expedited reporting in section **7.2.1** are reported to the sponsor, the sponsor should inform Celgene of the malignancy within 7 working days of receiving the report using the same forms.

### *8.4.1 IND Annual Reports to Celgene*

As the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Operations
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Tel: (908) 673-9000

## 8.5 REPORTING PREGNANCIES

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on investigational product (IP), or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor within 24 hours, and the Sponsor will report this to Celgene Drug Safety within one business day by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The Investigator will follow the female subject until completion of the pregnancy and up to 1 year to monitor the baby, and must notify CCR and the CCR in turn will notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

### *8.5.1 Maternal exposure*

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.
Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **8.1.2**) should be reported as SAEs.
The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

### *8.5.2 Paternal exposure*

Male participants should refrain from fathering a child or donating sperm during the study and for 28 days after the last dose of Pomalidomide.
Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 28 days after the last dose should, if possible, be followed up and documented.

## 8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

# 9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

This trial will be monitored by personnel employed by an CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 DEMOGRAPHIC DIVERSITY

- Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Outreach efforts will be made to extend accrual to a representative population.
- It should be noted that in the US, KSHV seroprevalence is relatively low in females with or without HIV infection. However, recent HAMB studies have increasingly accrued female immigrants from Africa and transgendered persons.

## 10.2 AGE EXCLUSION

Patients under the age of 18 will be excluded. KSHV infection and its complications including KS and HIV infection are each very rare in North American children, making it unlikely that pediatric cases of KS will be seen.

## 10.3 ACCRUAL TIMELINE

As the subjects being evaluated for toxicity may or may not be evaluable for response as part of the stringent eligibility response cohort, after an amendment to evaluate HIV positive and HIV negative patients in separate cohorts, the study may require enrolling from 25 to 40 subjects, depending on the final dose level and the number of those evaluated for toxicity that may also be evaluable for response.

It is anticipated that ten to twelve patients per year may enroll onto this trial. In order to allow for the possibility of a very small number of inevaluable subjects, the accrual ceiling will be set at 40 subjects. Accrual is expected to be completed within two to three years.

HAMB has an established cohort of KSHV-seropositive subjects, most with KS or a history of KS through protocol 01-C-0193 and other ongoing studies of KS, KSHV-MCD and KSHV-associated lymphoma as well as a referral base in the HIV and infectious disease community which together provide a population to support projected accrual. Accrual will be regularly reviewed against projections, and consideration given to additional promotional activities should it fall short of projections.

## 10.4 STATISTICAL ANALYSES

An initial toxicity assessment phase of the trial will be conducted in which up to six subjects will be treated with pomalidomide at 5mg daily for 21 days of a 28 day cycle. If two or more subjects experience a DLT within the first two cycles (eight weeks), then up to six subsequent subjects will be treated at 3 mg daily for 21 days of a 28 day cycle. The highest dose at which zero or one of six subjects experience a DLT during the first two cycles (eight weeks) will be used to determine potential clinical activity.

Once the dose for assessment of clinical activity is determined, two expansion cohorts will be established to investigate response rate. These will be established with the goal of enrolling ten evaluable HIV negative patients, and fifteen evaluable HIV positive patients. Where KS is HIV-associated, these latter subjects will have somewhat more stringent entry criteria with respect to KS not responding to HAART to enable a better assessment of any anti-tumor activity uncomplicated by tumor responses associated with HAART initiation (inclusion criterion **2.1.1.15** above). Subjects treated at the dose chosen for assessment during the toxicity

assessment phase who met these additional eligibility criteria at study entry will be considered evaluable for response for this part of the study, in the appropriate cohort.

There are two circumstances under which an individual subject's dose could be de-escalated: first if two other subjects on the same dose level experience a DLT (Section **3.1.3**), and second if the subject experiences a non-thromboembolic DLT on the higher dose level which resolves within 28 days (Section **3.3**). In either instance, if the subject is evaluable they will be considered part of the initial (higher) dose cohort for the purposes of evaluating response.

At the dose for assessment of clinical activity, two cohorts of patients will be evaluated according to their HIV status as follows:

Of the ten evaluable subjects enrolled in the HIV negative expansion cohort, the probability of three or more responding (complete responders plus partial responders) is 83.3% if the true probability of a response is 40%, and 7.0% if the true probability of a response is 10%. Thus, obtaining at least three subjects with a response in the ten HIV negative evaluable subjects is more likely to be consistent with a ≥40% true response rate than with a ≤10% true response rate. This outcome (three or more responders) will be considered sufficiently positive for further investigation of the agent in this group.

Of the fifteen evaluable subjects enrolled in the HIV positive expansion cohort, the probability of four or more responding (complete responders plus partial responders) is 90.9% if the true probability of a response is 40%, and 5.6% if the true probability of a response is 10%. Thus, obtaining at least four subjects with a response in the 15 evaluable HIV positive subjects is more likely to be consistent with a ≥40% true response rate than with a ≤10% true response rate. This outcome (four or more responders) will be considered sufficiently positive for further investigation of the agent in this group. As of the submission of amendment G, fifteen evaluable subjects in the HIV positive expansion cohort have been accrued to address the primary question of assessing the anti-tumor effect of pomalidomide in those patients. The responses for these 15 subjects will be reported together with the 7 subjects enrolled to date in the HIV negative expansion cohort. The protocol allows for accrual up to 18 HIV (+) patients and 10 HIV (-) patients. As the endpoint for activity has been reached for the HIV (+) patients at this time, the initial analysis describing the activity of pomalidomide in KS will include only patients entered up until this time. Any additional subjects accrued after this point in either cohort (up to 3 in each cohort) will be primarily evaluated for correlative endpoints; they will also be included in any description of long term clinical outcomes at a later point.

At the conclusion of the trial, the response rates from the two cohorts will be compared and if they are sufficiently similar ($p>0.30$ by a two-tailed Fisher's exact test), in addition to being reported separately, they can be pooled together and also reported in that manner. Also, after the all patients have been evaluated for response, 95% confidence intervals will be formed about the response rate in both cohorts, as well as together, if sufficiently similar. The maximum confidence interval widths would be +/-32% with 10 patients, +/-26% with 15 patients, and +/-20% with 25 patients.

To allow for the possibility of different accrual rates between these two cohorts in this rare disease, up to an additional three subjects may be accrued to the evaluable HIV positive cohort (for a maximum of eighteen) in the case that ten evaluable HIV negative subjects have not yet been accrued at the time that accrual of evaluable HIV positive subjects reaches fifteen. In the

event that 16 to 18 HIV positive patients are enrolled, 4 or more responders will still be needed to be considered sufficiently positive for further investigation.

Response rates will be estimated for pomalidomide. Survival analysis will be performed using Kaplan-Meier methods. Progression-free survival will be defined as the time from Day 1 of a given intervention until progression *requiring a change in therapy*. Event-free survival will be defined as the time from Day 1 of a given intervention until progression *requiring a change in therapy* or death as a result of any cause. All results will be carefully reported in the context of the limited size of the study.

For those subjects who obtain a clinical complete or partial response or clinical benefit from initial treatment with pomalidomide, and subsequently again manifest KS requiring therapy while not receiving pomalidomide, an additional course of treatment with pomalidomide may be offered as described in Section **3.1.6**. Based on responses seen at the time of this amendment (January 2013) and our experience with treatment of KS, it is anticipated that approximately 3-6 subjects will potentially be eligible for and receive an additional course of therapy, but this estimate will be refined as further subjects are enrolled and become assessable for response. The scientific objective of this cohort will be to explore the safety and tolerability of a second course of pomalidomide in patients who had previously benefited from the agent: this exploration will comprise a secondary objective for the protocol overall. As a further objective, tumor response rates in this cohort will also be evaluated with exploratory intent; and virologic and immunologic correlative studies will be performed for comparison with those obtained during the first treatment course. For those subjects treated with this additional course, a new tumor baseline will be taken, and the subsequent response to treatment from this baseline will be determined. The fraction of the patients who receive the extra course who respond to treatment (complete responders plus partial responders) will be determined and estimated along with a 95% confidence interval. The results obtained following this subsequent treatment will be presented separately from those for the initial treatment.

Each of the correlative analyses will be evaluated with exploratory intent, using non-parametric methods generally, and without formal adjustment for multiple tests performed. Results will be presented in the context of a hypothesis generating study.

## 11 COLLABORATIVE AGREEMENTS

Pomalidomide will be provided to the investigators under a Co-operative Research and Development Agreement (CRADA) between Celgene Corporation and the National Cancer Institute; CRADA #2719. Therefore, the following obligations apply to the use of pomalidomide in this study, and to the data generated herein.

Pomalidomide may not be used outside the scope of the CRADA, nor can pomalidomide be transferred or licensed to any party not participating in activities specified in the CRADA.

Celgene data regarding pomalidomide are confidential and proprietary to Celgene and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or a patient's family member, the individual should sign a confidentiality agreement.

For data generated from the CRADA, the producing Party will retain sole ownership of and title to all copies of CRADA Data produced solely by its employee(s). The Parties agree to exchange all data and materials generated from the study.

The CRADA Parties are encouraged to make publicly available the results of their research and development activities. Before either Party submits a paper or abstract for publication or otherwise intends to publicly disclose information about a CRADA Subject Invention, CRADA Data, or CRADA Materials, the other Party will have thirty (30) days to review proposed manuscripts and three (3) days to review proposed abstracts to assure that Confidential Information is protected. Either Party may request in writing that the proposed publication or other disclosure be delayed for up to thirty (30) additional days as necessary to file a Patent Application.

# 12 HUMAN SUBJECTS PROTECTIONS

## 12.1 RATIONALE FOR SUBJECT SELECTION

The protocol is designed for analysis of adult subjects with measurable KS. KSHV infection in the US is associated with certain ethnic and behavioral groups, including African immigrants and men who have sex with men (MSM)([154-157]); most of the women who have participated in previous HAMB studies of KSHV-associated diseases have been immigrants from Africa. KS and other KSHV-associated diseases are much more common in subjects with intercurrent immunodeficiencies, including HIV, and it is anticipated that the majority of study participants will be drawn from these groups. Including both HIV-infected and HIV-uninfected individuals may enable a greater understanding of the similarities and differences of pomalidomide safety, toxicity and response in these groups.

Strategies for recruitment will include announcements on www.clinicaltrials.gov, letters to referring physicians, targeting HIV providers and those who provide primary care to the African immigrant community, and AIDS treatment bulletins.

## 12.2 PARTICIPATION OF CHILDREN

As noted in Section **10.2**, KSHV-associated disease is extremely rare in children in North America. It is also known that KS may have a markedly different presentation and natural history in pediatric populations, perhaps representing biologically distinct disease variants. Furthermore, as approved therapies are available for KS and the proposed therapies have uncertain efficacy, and the risk to a vulnerable population appears excessive in the absence of preliminary estimates of benefit. For these reasons, subjects <18 years old will be excluded from the study. If the therapy appears beneficial, a risk/benefit assessment will be made for the potential enrollment of children, and if it appears reasonable to do so, consideration for amending the protocol to allow enrollment of children will be made.

## 12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will remain in the study because there is a prospect of direct benefit. All subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on

the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see Section **12.6.1** for consent procedure.

## 12.4 Evaluation of Benefits and Risks/Discomforts

The investigational nature and objectives of this study, the procedures and treatments involved and their attendant risks and discomforts, potential benefits, and potential alternative therapies will be carefully explained to the patient or the patient's surrogate, and a signed informed consent document will be obtained.

While the study is performed based on background data suggesting that pomalidomide may be of benefit to patients with KS, there is no assurance that this will be the case and it is quite possible that there may be no direct benefit to the patient volunteers on this study. The potential benefit is that the protocol therapy may result in control of KS and resolution of symptoms in those patients to whom it is administered.

The potential risk for patients receiving treatment is that the protocol therapy may be toxic, ineffective, or both. In addition, the study requires multiple, sometimes invasive, evaluations. The time commitment and potential morbidity associated with tumor biopsy and blood sampling is a potential risk and discomfort to study participants.

Biopsies are an important part of this study. Up to three optional, sequential biopsies will be obtained from each patient over the course of protocol participation. The material obtained will be used to evaluate for the correlative endpoints, and may be used to guide future studies in this disease. Refusal to undergo biopsy will not result in removal from study.

### *12.4.1 Risks to Study Procedures*

12.4.1.1 Blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.4.1.2 Medical photography

No physical risks are associated with these procedures.

## 12.5 Risks and Benefits Analysis

The risks to individual study subjects are reasonable in relation to the anticipated benefits. This protocol explores an agent with a strong preclinical rationale in KS, and which is a derivative of another agent (thalidomide) that was shown to have promising clinical activity in our prior study in KS. Pomalidomide has an acceptable toxicity profile at similar or higher doses to that used here in studies in other solid tumors (and a better toxicity profile than thalidomide when directly compared), and promising clinical activity in other solid tumors and hematologic malignancies. Potential therapeutic benefits include limitation of cumulative anthracycline dosing, more rapid tumor regression, and additional therapeutic options for patients for difficult to manage and chronic KS. The risks include potential toxicities of pomalidomide alone or in combination with HIV and its therapies and additional studies associated with participation in a clinical study. The

major alternative for patients with limited KS is to receive FDA approved agents outside of a clinical study, or not to receive any KS-directed therapy. The comparative risks and benefits are acceptable for an early phase clinical study, when compared to the alternatives for patients with limited KS.

## 12.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here.

### *12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation*

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

# 13 REGULATORY AND OPERATIONAL CONSIDERATIONS

## 13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

## 13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## 13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the

design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

### 13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

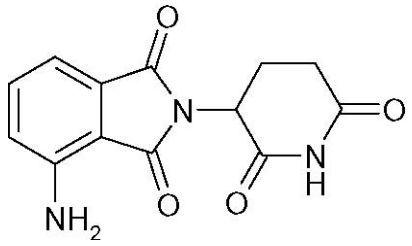
## 14 PHARMACEUTICAL INFORMATION

### 14.1 POMALIDOMIDE

#### *Description*

Pomalidomide, 4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1'-one)-1,3-dione, belongs to the IMiDs class of compounds. The Chemical Abstract Service (CAS) registry number for CC-4047

is 19171-19-8. The chemical structure of the active pharmaceutical ingredient (API) is as follows:




Pomalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S (-) and R (+). Pomalidomide is being developed as a racemate.

***Mechanism of Action***

Pomalidomide is a novel member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs). It shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide, but it is a more potent anti-proliferative immunomodulating agent than either drug. The pharmacodynamic properties of pomalidomide are of potential therapeutic benefit in the treatment of several human tumors.

***Supply***

Celgene Corporation will supply POMALYST® (pomalidomide) through Celgene's Pomalidomide Risk Evaluation and Mitigation Strategy (POMALYST REMS™).

***Dosage Form***

Pomalidomide will be supplied as 1.0 mg, 2.0 mg, 3.0 mg and 4.0 mg capsules for oral administration.

***Packaging***

Pomalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for one cycle of dosing. Study drug must be dispensed in the original packaging with the label clearly visible.

***Labeling***

Pomalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. Pomalidomide should not be handled by FCBP unless wearing gloves.
The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

***Receipt of Study Drug***

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

***Storage***

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

***Unused Study Drug Supplies***

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return any unused capsules to the study site.

***Drug Dispensing Requirements***

Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard **POMALYST REMS™** program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the **POMALYST REMS™** program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies.

**Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ program.**

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# 16 APPENDICES

## 16.1 APPENDIX 1: POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

**Risks Associated with Pregnancy**
Pomalidomide was found to be teratogenic in a developmental study in rabbits. 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 may cause birth defects or death to an unborn baby.

**Criteria for females 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).

**Counseling**
For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should 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 the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male patients taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- 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 female of childbearing potential.

**Contraception**
Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

Highly effective methods:
- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:
- Male condom
- Diaphragm
- Cervical Cap

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 patients with neutropenia.

**Pregnancy testing**
Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

**Before starting study drug**

**Female Patients:**
FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 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 patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

**Male Patients:**

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

**During study participation and for 28 days following study drug discontinuation**

**Female Patients:**

- FCBP 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 on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- 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 study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

**Male Patients:**

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide 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 study patient during study participation, the investigator must be notified immediately.

**Additional precautions**

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- **Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.**

## 16.2 APPENDIX 2: POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT

To be completed prior to each dispensing of study drug.

**Protocol Number:** _____

**Patient Name (Print):** _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female ☐

If female, check one:

☐ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) 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 during the preceding 24 consecutive months)

☐ NOT FCBP

Male ☐

**Do not dispense study drug if:**

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) at least 28 days prior to therapy, during therapy and during dose interruption.**

**FCBP:**

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
    - Potential risk of fetal exposure to pomalidomide: 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. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
    - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy , during dose interruption and 28 days after discontinuation of study drug].
    - That even if she has amenorrhea she must comply with advice on contraception
    - Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
    - Highly effective methods:
        - Intrauterine device (IUD)
        - Hormonal (birth control pills, injections, implants)

    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
  - Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
  - Frequency of pregnancy tests to be done:
    - **Every week** during the first 28 days of this study and a pregnancy test **every 28 days** during the patient's participation in this study if menstrual cycles are regular or **every 14 days if cycles are irregular**.
    - If the patient missed a period or has unusual menstrual bleeding.
    - When the patient is discontinued from the study and at day 28 after study drug discontinuation 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 study drug discontinuation.
  - Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
  - NEVER share study drug with anyone else.
  - Do not donate blood while taking study drug and for 28 days after stopping study drug.
  - Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
  - Do not break, chew, or open study drug capsules.
  - Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

**FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):**

1. I counseled the female NOT of childbearing potential regarding the following:
   - Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules
   - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

**MALE:**

1. I counseled the Male patient regarding the following:
    - Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
    - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
    - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
    - NEVER share study drug with anyone else.
    - Do not donate blood while taking study drug and for 28 days after stopping study drug.
    - Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
    - Do not break, chew, or open study drug capsules.
    - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(circle applicable)

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

## 16.3 APPENDIX 3: 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, since there may be new information. 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?***

**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 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**

- for 28 days before starting pomalidomide
- while taking pomalidomide
- during dose interruptions of pomalidomide
- for 28 days after stopping pomalidomide

**Stop taking pomalidomide if you become pregnant during pomalidomide treatment**

**Do not breastfeed while taking pomalidomide**

**You must have pregnancy testing done at the following times:**

- within 10 – 14 days and again 24 hours prior to the first dose of pomalidomide
- weekly for the first 28 days
- every 28 days after the first month or every 14 days if you have irregular menstrual periods
- 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)

**You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**

- for 28 days before starting pomalidomide
- while taking pomalidomide
- during dose interruptions of pomalidomide
- and for 28 days after stopping pomalidomide

The study doctor will be able to advise you where to get additional advice on contraception.

If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.

**If you are a female not of childbearing potential:**
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 the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

Male patients must either **not have any sexual relations with a female who can become pregnant or a pregnant female or must use a condom during sexual intercourse with a pregnant female or a female that can become pregnant** (including those who have had a vasectomy):

- While you are taking pomalidomide
- During dose interruptions of pomalidomide
- For 28 days after you stop taking pomalidomide

**Male patients should not donate sperm or semen** while taking pomalidomide and for 28 days after stopping pomalidomide.

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 Celgene Corporation.

**Pomalidomide restrictions in sharing pomalidomide and donating blood:**

- **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.
- **Do not give blood** while you take pomalidomide and for 28 days after stopping pomalidomide.
- **Do not break, chew, or open pomalidomide capsules.**
- You will be supplied with no more than one cycle of pomalidomide
- 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.

## 16.4 APPENDIX 4: PERFORMANCE STATUS SCALES

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

## 16.5 APPENDIX 5: HAMB KS RESPONSE FLOWSHEET

**HAMB KAPOSI SARCOMA MEASUREMENT AND RESPONSE SUMMARY**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| INITIALS | | DATE | | STUDY | | CYCLE | | PHOTOS | |
| BASELINE TIS | | T: | I: | S: | | REASON T1: | | | |

KEEP IN RESEARCH RECORD ONLY

| LESION | DESCRIPTION | FLAT OR NODULAR | DIMENSIONS | PRODUCT |
|---|---|---|---|---|
| ONE | | | | |
| TWO | | | | |
| THREE | | | | |
| FOUR | | | | |
| FIVE | | | | |
| | | | TOTAL PRODUCT | |

| | | |
|---|---|---|
| TOTAL LESIONS | OVER 50_____<br>UNDER 50*_____ | *FOR PATIENTS WITH UNDER 50 LESIONS, WRITE 'TOTAL BODY' FOR AREA AND USE LEFT COLUMN |

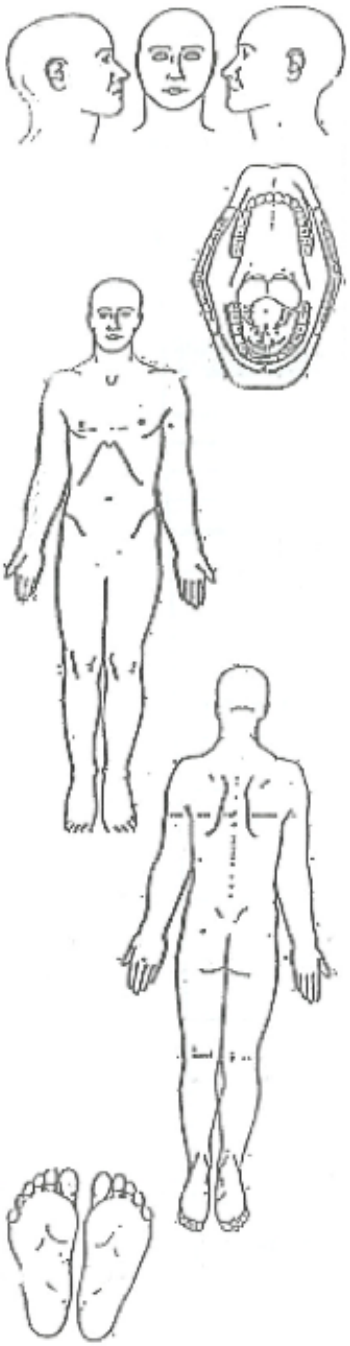
| | | | | | | |
|---|---|---|---|---|---|---|
| AREA | | | AREA | | | |
| NUMBER FLAT | | | NUMBER FLAT | | | |
| NUMBER NODULAR | | | NUMBER NODULAR | | | |
| TOTALS | ALL | | NODULAR | | FLAT | |

| | | | | | | |
|---|---|---|---|---|---|---|
| ORAL LESIONS | PRESENT | | NONE | | NO EVAL. | |
| DESCRIPTION IF PRESENT | | | | | | |
| VISCERAL LESIONS | PRESENT | | NONE | | NO EVAL. | |
| DESCRIPTION IF PRESENT | | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| RESPONSE THRESHOLDS FROM: _____ | | | | RESPONSE FROM BASELINE | |
| PARTIAL RESPONSE | | PROGRESSIVE DISEASE | | RESPONSE BASED ON | |
| TOTAL | | TOTAL | | RESPONSE FROM _____ | |
| NODULAR | | NODULAR | | RESPONSE BASED ON | |
| PRODUCT | | PRODUCT | | RESPONSE CONFIRMED BY | |

| | |
|---|---|
| RECORDER | SIGNATURE |

**HAMB KAPOSI SARCOMA MEASUREMENT AND RESPONSE SUMMARY**

| REGIONS | LESION COUNT |
|---|---|
|  | |

| TUMOR EDEMA | | | | | |
|---|---|---|---|---|---|
| LEFT | | | RIGHT | | |
| LEVEL | DIST. | DIAM. | LEVEL | DIST. | DIAM. |
| ANKLE | 0cm | | ANKLE | 0cm | |
| KNEE | | | KNEE | | |
| THIGH | | | THIGH | | |
| PELVIS | | | PELVIS | | |

## 16.6 APPENDIX 6: FUNCTIONAL ASSESSMENT OF QUALITY OF LIFE (V.4) ASSESSMENT TOOL (ENGLISH VERSION)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the *past 7 days.***

### 1. PHYSICAL WELL-BEING

| | | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |
| B1 | I have been short of breath | 0 | 1 | 2 | 3 | 4 |
| B8 | I am bothered by a change in weight | 0 | 1 | 2 | 3 | 4 |
| BMT6 | I get tired easily | 0 | 1 | 2 | 3 | 4 |
| HI7 | I feel fatigued | 0 | 1 | 2 | 3 | 4 |
| HI12 | I feel weak all over | 0 | 1 | 2 | 3 | 4 |
| L2 | I have been coughing | 0 | 1 | 2 | 3 | 4 |

## 2. EMOTIONAL WELL-BEING/LIVING WITH HIV

| | | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |
| HI1 | I am unhappy with my appearance | 0 | 1 | 2 | 3 | 4 |
| HI2 | It is hard to tell other people about my infection | 0 | 1 | 2 | 3 | 4 |
| HI4 | I worry about spreading my infection | 0 | 1 | 2 | 3 | 4 |
| HI5 | I am concerned about what the future holds for me | 0 | 1 | 2 | 3 | 4 |
| B7 | I worry about the effects of stress on my illness | 0 | 1 | 2 | 3 | 4 |
| HI10 | I am embarrassed by my illness | 0 | 1 | 2 | 3 | 4 |

## 3. LIVING WITH KS

| | | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| HKS1 | Pain has interfered with my normal work or activities | 0 | 1 | 2 | 3 | 4 |
| HKS2 | I am satisfied with my physical appearance | 0 | 1 | 2 | 3 | 4 |
| HKS3 | I have had swelling in my face, arms, or legs | 0 | 1 | 2 | 3 | 4 |

## 4. FUNCTIONAL AND GLOBAL WELL-BEING

| | | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (including work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (including work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| B4 | I feel sexually attractive | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| HI6 | I feel motivated to do things | 0 | 1 | 2 | 3 | 4 |
| HI11 | I am hopeful about the future | 0 | 1 | 2 | 3 | 4 |

## 5. SOCIAL WELL-BEING

| | | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with my family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| HI3 | I have people to help me if I need it | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question.*<br>*If you prefer not to answer it, please mark this box ☐ and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

## 6. COGNITIVE FUNCTIONING

| | | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| L1 | My thinking is clear | 0 | 1 | 2 | 3 | 4 |
| HI8 | I have trouble concentrating | 0 | 1 | 2 | 3 | 4 |
| HI9 | I have trouble remembering things | 0 | 1 | 2 | 3 | 4 |

## 16.7 APPENDIX 7: FUNCTIONAL ASSESSMENT OF QUALITY OF LIFE (V.4) ASSESSMENT TOOL (SPANISH VERSION)

A continuación encontrará una lista de afirmaciones que otras personas con su misma enfermedad consideran importantes. **Marque un solo número por línea para indicar la respuesta que corresponde *a los últimos 7 días.***

### 1. ESTADO FÍSICO GENERAL DE SALUD

| | | **Nada** | **Un poco** | **Algo** | **Mucho** | **Much-ísimo** |
|---|---|---|---|---|---|---|
| GP1 | Me falta energía | 0 | 1 | 2 | 3 | 4 |
| GP2 | Tengo náuseas | 0 | 1 | 2 | 3 | 4 |
| GP3 | Debido a mi estado físico, tengo dificultad para atender a las necesidades de mi familia | 0 | 1 | 2 | 3 | 4 |
| GP4 | Tengo dolor | 0 | 1 | 2 | 3 | 4 |
| GP5 | Me molestan los efectos secundarios del tratamiento | 0 | 1 | 2 | 3 | 4 |
| GP6 | Me siento enfermo(a) | 0 | 1 | 2 | 3 | 4 |
| GP7 | Tengo que pasar tiempo acostado(a) | 0 | 1 | 2 | 3 | 4 |
| B1 | Me ha faltado el aire para respirar | 0 | 1 | 2 | 3 | 4 |
| B8 | Me molestan los cambios de peso | 0 | 1 | 2 | 3 | 4 |
| BMT6 | Me canso fácilmente | 0 | 1 | 2 | 3 | 4 |
| HI7 | Me siento agotado(a) | 0 | 1 | 2 | 3 | 4 |
| HI12 | Siento debilidad en todo el cuerpo | 0 | 1 | 2 | 3 | 4 |
| L2 | He estado tosiendo | 0 | 1 | 2 | 3 | 4 |

## 2. ESTADO EMOCIONAL/VIVIENDO CON VIH

| | | **Nada** | **Un poco** | **Algo** | **Mucho** | **Much-ísimo** |
|---|---|---|---|---|---|---|
| GE1 | Me siento triste | 0 | 1 | 2 | 3 | 4 |
| GE4 | Me siento nervioso(a) | 0 | 1 | 2 | 3 | 4 |
| GE5 | Me preocupa morir | 0 | 1 | 2 | 3 | 4 |
| GE6 | Me preocupa que mi enfermedad empeore | 0 | 1 | 2 | 3 | 4 |
| HI1 | Estoy descontento(a) con mi apariencia personal | 0 | 1 | 2 | 3 | 4 |
| HI2 | Me cuesta trabajo hablar de mi enfermedad con otras personas | 0 | 1 | 2 | 3 | 4 |
| HI4 | Temo contagiar mi enfermedad a otras personas | 0 | 1 | 2 | 3 | 4 |
| HI5 | Estoy preocupado(a) por lo que me pueda pasar | 0 | 1 | 2 | 3 | 4 |
| B7 | Me preocupan las consecuencias del estrés (la tensión) en mi enfermedad | 0 | 1 | 2 | 3 | 4 |
| HI10 | Mi enfermedad me da vergüenza | 0 | 1 | 2 | 3 | 4 |

## 3. VIVIENDO CON KS

| | | **Nada** | **Un poco** | **Algo** | **Mucho** | **Much-ísimo** |
|---|---|---|---|---|---|---|
| HKS1 | El dolor interfiere con mi trabajo normal y mis actividades | 0 | 1 | 2 | 3 | 4 |
| HKS2 | Estoy satisfecho con mi apariencia fisica | 0 | 1 | 2 | 3 | 4 |
| HKS3 | He tenido inchazon en la cara, brazos o piernas | 0 | 1 | 2 | 3 | 4 |

## 4. ESTADO GENERAL DE FUNCIONAMIENTO

| | | **Nada** | **Un poco** | **Algo** | **Mucho** | **Much-ísimo** |
|---|---|---|---|---|---|---|
| GF1 | Puedo trabajar (incluya trabajo en el hogar) | 0 | 1 | 2 | 3 | 4 |
| GF2 | Me satisface mi trabajo (incluya trabajo en el hogar) | 0 | 1 | 2 | 3 | 4 |
| GF3 | Puedo disfrutar de la vida | 0 | 1 | 2 | 3 | 4 |
| GF4 | He aceptado mi enfermedad | 0 | 1 | 2 | 3 | 4 |
| GF5 | Duermo bien | 0 | 1 | 2 | 3 | 4 |
| GF6 | Disfruto con mis pasatiempos de siempre | 0 | 1 | 2 | 3 | 4 |
| GF7 | Estoy satisfecho(a) con mi calidad de vida actual | 0 | 1 | 2 | 3 | 4 |
| GE2 | Estoy satisfecho(a) de cómo estoy enfrentando mi enfermedad | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| GE3 | Estoy perdiendo las esperanzas en la lucha contra mi enfermedad | 0 | 1 | 2 | 3 | 4 |
| B4 | Me siento físicamente atractivo(a) | 0 | 1 | 2 | 3 | 4 |
| C6 | Tengo buen apetito | 0 | 1 | 2 | 3 | 4 |
| HI6 | Me siento motivado(a) para hacer cosas | 0 | 1 | 2 | 3 | 4 |
| HI11 | Tengo esperanzas para el futuro | 0 | 1 | 2 | 3 | 4 |

## 5. AMBIENTE SOCIAL

| | | **Nada** | **Un poco** | **Algo** | **Mucho** | **Much-ísimo** |
|---|---|---|---|---|---|---|
| GS1 | Me siento cercano(a) a mis amistades | 0 | 1 | 2 | 3 | 4 |
| GS2 | Recibo apoyo emocional por parte de mi familia | 0 | 1 | 2 | 3 | 4 |
| GS3 | Recibo apoyo por parte de mis amistades | 0 | 1 | 2 | 3 | 4 |
| GS4 | Mi familia ha aceptado mi enfermedad | 0 | 1 | 2 | 3 | 4 |
| GS5 | Estoy satisfecho(a) con la manera en que se comunica mi familia acerca de mi enfermedad | 0 | 1 | 2 | 3 | 4 |
| GS6 | Me siento cercano(a) a mi pareja (o a la persona que es mi principal fuente de apoyo) | 0 | 1 | 2 | 3 | 4 |
| HI3 | Tengo quien me ayude, si lo necesito | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Q1 | *Sin importar su nivel actual de actividad sexual, conteste a la siguiente pregunta. Si prefiere no contestarla, marque esta casilla ☐ y continúe con la siguiente sección.* | | | | | |
| GS7 | Estoy satisfecho(a) con mi vida sexual | 0 | 1 | 2 | 3 | 4 |

## 6. ACTIVIDAD MENTAL

| | | **Nada** | **Un poco** | **Algo** | **Mucho** | **Much-ísimo** |
|---|---|---|---|---|---|---|
| L1 | Pienso con claridad | 0 | 1 | 2 | 3 | 4 |
| HI8 | Tengo dificultad para concentrarme | 0 | 1 | 2 | 3 | 4 |
| HI9 | Tengo dificultad para recordar las cosas | 0 | 1 | 2 | 3 | 4 |

## 16.8 APPENDIX 8: PATIENT DRUG ADMINISTRATION DIARY

**Patient Name _____ Study ID _____**

**Please complete this form and return to the research nurse or doctor every cycle**

You will take: **Pomalidomide** Dose: _____

| DAY | DATE | TIME TAKEN | COMMENTS (side effects or missed doses) |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
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| 23 | | Rest Day | |
| 24 | | Rest Day | |
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| 26 | | Rest Day | |
| 27 | | Rest Day | |
| 28 | | Rest Day | |

**Patient Signature:_____**

## 16.9 APPENDIX 9: CALCULATION OF CREATININE CLEARANCE

**1. Calculation: Cockcroft-Gault formula for creatinine clearance estimation:**

**Males:** CrCl (estimated) =(140-age) * (weight)/(sCr * 72)

**Females:** CrCl (estimated) =(140-age) * (weight * 0.85)/(sCr * 72)

**Notes:** CrCl (estimated): estimated creatinine clearance rate in mL/min

Age in years

Weight in kilograms (lean or actual body weight, whichever is less)

sCr:serum creatinine in mg/dl

Estimated creatinine clearance should not be used in the following circumstances:

-altered protein intake (vegetarian diet, creatine supplements)

-altered muscle mass (malnutrition, wasting, amputation)

-in such cases, a 24-hour urine collection for measured creatinine clearance should be obtained

**2. Calculation: 24 hour Creatinine Clearance**

**Males and Females:** CrCl=(uCr * uV) / (sCr *1440)

**Notes:** CrCl: Creatinine clearance in ml/min

sCr: serum creatinine in mg/dl

uCr: urine creatinine in mg/dl

uV: 24 hour urine volume in ml

1440: number of minutes in 24 hours

**3. Calculation: Lean Body Weight**

Males: Lean Body Weight = (1.10 x Weight(kg)) - 128 ( $Weight^2/(100 \times Height(m))^2$)

Females: Lean Body Weight= (1.07 x Weight(kg)) - 148 ( $Weight^2/(100 \times Height(m))^2$)