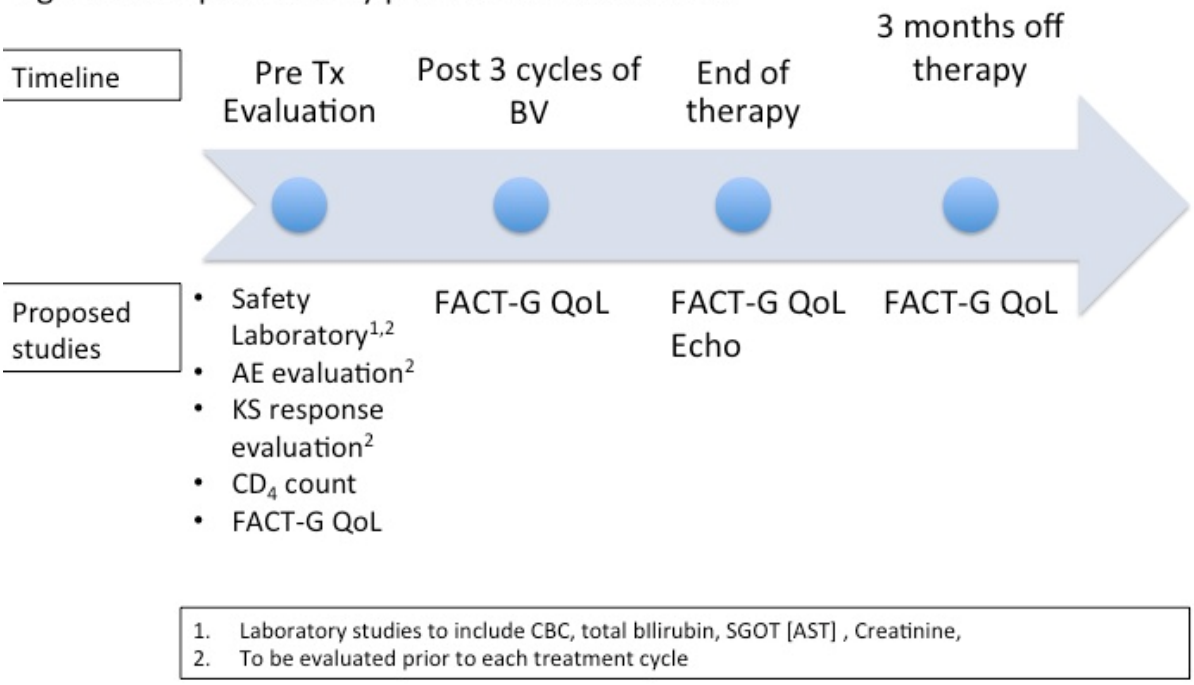
PROTOCOL SCHEMA

Figure 1. Proposed study procedure and timeline



1. Laboratory studies to include CBC, total bllirubin, SGOT [AST] , Creatinine,
2. To be evaluated prior to each treatment cycle

ICH	International Conference on Harmonisation
IDB	Investigational Drug Branch
IEC	institutional ethics committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
KPS	Karnofsky performance status
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma-associated herpesvirus
LFT	liver function test
LLN	lower limit of normal
MDS	myelodysplastic syndrome
MOP	manual of procedures
NCI	National Cancer Institute
NIMR	National Institute for Medical Research
NRTI	nucleoside reverse transcriptase inhibitor
ODMC	Operations and Data Management Center
OHAM	Office of HIV and AIDS Malignancy
OTC	over the counter
PCP	*Pneumocystis jirovecii* pneumonia
PD	progressive disease
PI	principal investigator
PIO	Protocol Information Office
PLD	pegylated liposomal doxorubicin
PN	peripheral neuropathy
PR	partial response
prn	pro re nata (as needed)
QOL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
ULN	upper limit of normal
WHO	World Health Organization

2.0 BACKGROUND

2.1 Study Disease

Kaposi sarcoma (KS) is a vascular inflammatory tumor of endothelial origin caused by Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8).[1] HIV infection and immunosuppression dramatically increase the risk of KS among people infected with KSHV.

KS is the most common malignancy seen in patients with human immunodeficiency virus infection. The incidence of HIV associated KS remains high in parts of Africa where rates of both HIV and HHV-8 infection are high, but treatment options are often limited. In high resource countries, treatment for advanced AIDS-associated KS, in addition to antiretroviral treatment, typically includes chemotherapy.[2-8] While chemotherapy has been shown to reduce the burden of disease, it has not been shown to alter survival outcomes. The goal of treatment is palliation and improvement in quality of life (QOL). However, in low resource countries, such as Tanzania, the optimal treatment and the effect of treatment on quality of life is unknown.

2.2 Treatment Regimen

2.2.1 Bleomycin and vincristine

This study will only use standard of care drugs for the treatment of KS. The selection of bleomycin and vincristine sulfate (BV), and its choice over another regimen available in Tanzania, adriamycin, bleomycin, and vincristine (ABV), was based on several considerations. First, the large, randomized, controlled trials of liposomal anthracyclines versus BV or ABV were all conducted pre-highly active antiretroviral therapy (HAART). For example, in the randomized trial that compared pegylated liposomal doxorubicin (PLD) and BV reported by Stewart *et al.*, only half of the patients in each arm of the study were receiving any antiretroviral therapy (ART), and ART was confined to single or combination nucleoside reverse transcriptase inhibitors (NRTIs).[2]

In studies that have used rigorous response criteria, there was no evidence that BV was inferior to ABV with respect to objective, strictly defined response rates.[2-4] On the other hand, there was good evidence that BV had a superior toxicity profile compared to ABV, which was associated with a higher rate of hematologic toxicity and treatment delays for neutropenia and infection and also presents the risk of serious cardiotoxicity. In addition, as noted by Stewart *et al.,*[2] BV was also associated with considerably less myelosuppression than PLD, which may be particularly important in locales where hematopoietic growth factors like granulocyte-colony stimulating factor (G-CSF) are not available and where access to blood component transfusion is limited.

2.3 Study Design and Rationale

HIV seroprevalence among Tanzanians age 15-49 is estimated at 5.1%,[9] resulting in approximately 2.2 million HIV-positive persons within the country. Little is known about either the rate of objective response of KS to standard chemotherapy in this setting or its influence on QOL. Bugando Medical Centre (BMC) is a provisional AMC site and the current proposal is exploratory and intended to develop clinical research and database

management capacity. Additionally, knowledge of both the objective response rate to the current standard therapy and its influence on QOL, using a standardized questionnaire validated in Swahili, would be useful before embarking on clinical trials of other treatments for KS conducted with the AMC.

This is a prospective observational study to evaluate the quality of life of participants receiving BV for HIV-associated KS at a single institution in Tanzania. All participants presenting for care of HIV-associated KS at BMC during a 1-year study period will be approached for enrollment.

At enrollment, KS stage, clinical symptoms, CD4 count, complete blood count (CBC), liver, and renal function labs, and history of opportunistic infection will be recorded. The extent of KS will be evaluated at baseline and after each cycle of treatment, and response assessed using standard AMC criteria. The Functional Assessment of Cancer Therapy-General (FACT-G) QOL questionnaire has been used successfully in HIV-associated clinical trials to collect data in 4 categories: physical, emotional, functional, and social wellbeing. A Swahili version has been validated and will be used in the current proposal.[5] This questionnaire will be completed at four time points: prior to initiating treatment, after 3 cycles, at the end of therapy, and 3 months off therapy.

Participants will receive institutional standard of care treatment with BV, administered on day one of each 21-day chemotherapy cycle. Vincristine sulfate will be administered at a dose of 2 mg (fixed dose) over 1 minute into the sidearm of a rapidly flowing intravenous infusion every 3 weeks. The vincristine infusion will be followed by bleomycin administered at a dose of 15 units/m^2 over 10 minutes every 3 weeks.

Treatment with BV will continue for six cycles or until toxicity requiring discontinuation of chemotherapy, or the local physician determines that alternative therapy is required, whichever occurs first.

Institutional standard pre-treatment staging evaluation includes chest X-ray and physical history and exam. Complete blood cell counts, and serum liver/ renal function analysis will be required at each pretreatment visit. Other clinical or laboratory evaluations will be performed as deemed necessary by the medical provider. Clinical benefit, objective tumor response, and toxicity will be assessed every 3 weeks, prior to initiating each new chemotherapy cycle.

probable, or definite).

This includes the following:

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

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

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

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

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

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

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

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

6.2.6 Unexpected adverse event: Any AE that is not listed in available sources including

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

6.3.3 Expedited reporting guidelines

Investigators must report ALL SAEs (as defined in Section 6.2.3) that occur from enrollment through 30 days following protocol treatment discontinuation to the AMC and IRBs as required. The investigator's initial report to the AMC will be made using the Adverse Event form in Advantage eClinical within 24 hours of awareness of the event, followed by a completed SAE form within the following timelines.

- Grade 3 SAEs: complete SAE form within 10 calendar days of investigator awareness
- Grade 4 or 5 SAEs: complete SAE form within 5 calendar days of investigator awareness

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

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

6.3.4 Expedited reporting for pregnancy

Female participants who become pregnant or initiate breastfeeding while on protocol treatment must immediately discontinue protocol treatment. Participants will continue to be followed for the remainder of the study visit schedule and procedures. AMC-S007 will not provide perinatal care for women. Women who become pregnant will be referred to local clinics and/or other research studies for prenatal and postpartum care.

Pregnancy reporting and outcomes will be documented by completion of the appropriate CRFs, including the Adverse Event form, using the appropriate term in the system organ class (SOC) for Pregnancy, puerperium and perinatal conditions.

6.3.5 Expedited reporting to regulatory authorities

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

As this trial will not be conducted in the U.S., and will not support a marketing application or change in labeling or advertising for the drug, the trial is exempt from the requirement for an IND. No serious adverse event reporting to FDA is required.

6.4 Routine Adverse Event Reporting

With the exception of the cases noted below, selected adverse events that occur within

timeframes defined in protocol Section 6.4.3 **must** be reported in routine study data submissions.

6.4.1 Additional protocol-specific routine adverse event reporting exclusions

All grade 1 adverse events are not required to be reported in the Adverse Event Form in Advantage eClinical. These adverse events must be recorded in the source documents only.

6.4.2 Timeline for routine adverse event reporting

AEs will be recorded in the source and assessed for routine reporting requirements from receipt of the first dose of BV through the treatment discontinuation evaluation. Following treatment discontinuation, only SAEs that are possibly, probably, or definitely attributed to treatment, or grade 5 SAEs will be reported in the AE form.

6.5 Secondary Malignancy

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

All secondary malignancies that occur following treatment with standard treatment on this protocol will be reported expeditiously via Advantage eClinical. Three options are available to describe the event:

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

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

6.6 Second Malignancy

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

Appendix IV) at 4 time points: prior to initiating treatment, cycle 4 prior to chemotherapy, completion of treatment and final study visit. Results recorded on the CRFs. Trained site personnel are defined as site pharmacist, nursing staff, clinician, or other trained clinical personnel (e.g., adherence counselors, social workers). It is estimated that this assessment will take 10-15 minutes to complete.

8.3 Treatment Discontinuation Evaluations

8.3.1 All participants will have the following evaluations and laboratory tests within three weeks of the last dose of protocol treatment, regardless of the reason for discontinuation:

- Physical examination including vitals, weight, and performance status
- Toxicity evaluation
- Tumor response evaluation, including radiologic evaluation for participants that had visceral KS at baseline or those who have symptoms suggestive of visceral KS at treatment discontinuation
- CBC with differentials and platelets
- Liver and renal function labs as defined in Section 8.1.5
- Oxygen saturation level
- FACT-G questionnaire

8.4 Final Evaluations, Off Study

In addition to the evaluations listed below, the Off-Study Summary Form should be completed in Advantage eClinical.

8.4.1 All participants will have the following evaluations and laboratory tests within three months of the last dose of protocol treatment, regardless of the reason for discontinuation:

- Physical examination including vitals, weight, and performance status
- Toxicity evaluation
- Tumor response evaluation, including radiologic evaluation for participants that had visceral KS at baseline or those who have symptoms suggestive of visceral KS at treatment discontinuation
- CBC with differentials and platelets
- Liver and renal function labs as defined in Section 8.1.5
- Oxygen saturation level
- FACT-G questionnaire

9.0 MEASUREMENT OF EFFECT

All participants will be evaluated for KS response by physical examination as described in the AMC KS Tumor Assessment Manual of Procedures (MOP) within 3 days prior to the first day of every cycle. See Appendix I for the KS Tumor Assessment schedule.

9.1 Definition of Response

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

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

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

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

- A 50% or greater decrease in the number of all lesions present at entry (either total body or in the representative areas) lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesions become macules, either total body or in the representative areas) present at entry lasting for at least 4 weeks; OR
- A 50% or greater decrease in the area of the cutaneous marker lesions compared with entry lasting for at least 4 weeks; OR
- A 50% or greater decrease in the number or size of all measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions; OR
- Complete disappearance of non-measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions.

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

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

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

9.1.4 Progressive disease (PD) is defined as follows:

For participants with ≤50 cutaneous lesions

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

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

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

For participants with >50 cutaneous lesions

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

- ≥ 25% increase in the area of the cutaneous marker lesions compared to entry or best response;
- ≥ 25% increase in the total number of lesions in the prospectively defined anatomic sites containing representative lesions;
- a total of five new lesions in anatomic sites that were previously documented as having no evidence of cutaneous disease,
- ≥ 25% increase in the number of raised lesions in the prospectively defined anatomic sites containing representative lesions (minimum of five raised lesions if there are very few raised lesions, for example < 8) whichever is greater. Photographic documentation of "gross" or significant progression, particularly in areas that were not being followed, will be of particular value.

9.1.5 Noncutaneous progression (PD): Noncutaneous PD includes new oral or visceral sites of involvement or progression of oral or visceral disease or the development of new or increasing tumor-associated edema or effusion that interferes with the participant's normal activities lasting for at least two consecutive evaluations.

11.0 ROLE OF DATA MANAGEMENT

11.1 CRF Instructions

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

11.2 Data Quality

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

11.3 Data Monitoring

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

APPENDIX II: PERFORMANCE STATUS SCALES

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

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad……	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
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

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)….	0	1	2	3	4
GF2	My work (include 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

ABBREVIATIONS LIST

ABV	adriamycin, bleomycin, and vincristine
AE	adverse event
AERS	Adverse Event Reporting System
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AMC	AIDS Malignancy Consortium
AML	acute myelocytic leukemia
ANC	absolute neutrophil count
ART	antiretroviral therapy
AST	aspartate aminotransferase
BIP	bleomycin-induced pneumonitis
BMC	Bugando Medical Centre
BV	bleomycin and vincristine sulfate
cART	combined antiretroviral therapy
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Monitoring Service
CXR	chest x-ray
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy-General
FCBP	female of childbearing potential
FDA	Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
HAART	highly active antiretroviral therapy
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the longitudinal quality of life of participants with HIV-associated KS during treatment with bleomycin and vincristine at a single institution in East Africa.

1.2 Secondary Objective

To explore baseline and time-dependent correlates of improvements in quality of life (QOL).

1.3 Exploratory Objective

To assess quality control (completeness and accuracy) in data capture of adverse events, clinical benefit, and objective response for site evaluation and training purposes.

3.0 PARTICIPANT SELECTION

A CTEP-registered investigator (Dr. Nestory Masalu or Dr. Kristin Schroeder) will document that each protocol participant meets all stated eligibility criteria. Satisfaction of eligibility requirement will be documented prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

NOTE: Institutions may use this section of the protocol as an eligibility checklist for source documentation if it has been reviewed, signed, and dated before registration/randomization by the study investigator. If used as source documentation, this checklist must be printed, the investigator must check each item to document their assessment that the participant meets each eligibility criterion, and the completed checklist must be maintained in the participant's chart.

Participant ID Number: S007- ___ ___ ___ - ___ ___ ___ ___ ___

Patient's Initials (L, F, M): ___ ___ ___

3.1 Eligibility Criteria

____ 3.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term "licensed" refers to a U.S. FDA-approved kit or for sites located in countries other than the U.S., a kit that has been certified or licensed by an oversight body within that country and validated internally.

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

____ 3.1.2 Participants must have pathologically confirmed Kaposi sarcoma.

____ 3.1.3 Participants should not have had prior therapy for their Kaposi sarcoma.

____ 3.1.4 All participants must be on stable antiretroviral therapy (ART) for a minimum of 12 weeks prior to study entry with an acceptable regimen that adheres to national guidelines for treatment of HIV infection.

____ 3.1.5 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of BV in participants <18 years of age, children are excluded from this study.

____ 3.1.6 ECOG performance status ≤ 2 (Karnofsky performance status ≥ 50%, see Appendix II).

the package insert, the Investigator's Brochure, or the protocol, or is not consistent with the severity or specificity of the risk information described in the available sources, or is not consistent with the severity or specificity of the risk information described in the available sources.

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

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

Table 6-C: Attribution

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to treatment/intervention	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to treatment/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

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

6.3 Expedited Adverse Event Reporting

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

A 24-hour notification is to be made to the AMC ODMC by telephone at +1 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into Advantage eClinical by the original submitter at the site.

7.0 PHARMACEUTICAL INFORMATION

No medications will be provided by the study. The site will source medications from its usual commercial pharmacy per institutional policy, and administer these drugs in accordance with the approved package inserts.

7.1 Study Product Preparation

7.1.1 Bleomycin

Description

Bleomycin is an antibiotic complex produced by fermentation from *Streptomyces verticillus*. It causes single- and double-strand DNA breaks through formation of an intermediate iron complex. DNA synthesis, and to a lesser degree, RNA and protein synthesis are inhibited. Bleomycin is cell cycle phase-specific. Please refer to the approved package insert for complete prescribing and toxicity information.

Reconstitution of Lyophilized Product

The locally-available formulations of bleomycin are packaged as 15 units of bleomycin sulphate powder per vial. Instructions for reconstitution described for the Zuvius Lifescience product should be followed: Zuvius's formulation of bleomycin is packaged as 15 units of bleomycin sulphate powder per vial. Using aseptic technique, reconstitute each vial with 5 mL of 0.9% sodium chloride for injection to yield 3 Units/mL (15 Units/ 5 mL) solution. If these reconstitution and preparation instructions are not in accordance with the package insert of the locally-sourced bleomycin, then the site should must the package insert and proposed preparation instructions to the protocol team for review and approval prior to use.

Withdraw study participant's calculated dose of bleomycin in mL from the reconstituted bleomycin vial(s) into a syringe and inject it into a 50 mL 0.9% sodium chloride for injection IV bag.

Administer the prepared bleomycin in 50 mL 0.9% sodium chloride for injection IV bag by IV infusion over 10 minutes.

Bleomycin prepared in 50 mL 0.9% sodium chloride IV bag for infusion should be stored as directed by the manufacturer in the package insert.

Do not use if a precipitate, foreign matter, or discoloration is present.

Bleomycin for injection should not be reconstituted or diluted with 5% dextrose for injection or other dextrose-containing diluents, as loss of potency can occur.

Do not mix bleomycin with other drugs or solutions, as compatibility is unknown.

Caution should be exercised in handling bleomycin. The use of gloves and gown is recommended. If bleomycin comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.

Administration

Reconstitute with 5-10mL normal saline.

Progressive oral or visceral disease, for measurable and evaluable disease, should be analogous to cutaneous KS response criteria.

Progressive edema is defined as the following:

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

9.1.6 Recurrent disease

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

9.1.7 Time to response

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

9.1.8 Time to progression

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

9.1.9 Response duration

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

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

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

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

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

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

12.2 Changes to the Protocol

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

12.3 Women and Minorities

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

APPENDIX III: AMC DATA AND SAFETY MONITORING PLAN

(Version 6.0 • March 17, 2017)

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (http://ctep.cancer.gov/guidelines/index.html). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS; expedited reporting via AdvantageEDC/Advantage eClinical may be permitted for select commercial agent studies per protocol requirements. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met. For phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the Protocol Chair, AMC Medical Monitor, and

FACT-G (Version 4), SWAHILI

Hapa chini kuna orodha ya kauli ambazo watu wengine wenye ugonjwa wako wamesema ni muhimu. **Tafadhali chagua nambari moja katika kila mstari na kuichorea duara ili kuonyesha kadiri kila kauli ilivyokuwa na ukweli kwako wakati wa <u>siku 7 zilizopita.</u>**

	<u>HALI YA KIMWILI</u>	**Hata kidogo**	**Kidogo**	**Wastani**	**Zaidi ya wastani**	**Sana**
GP1	Nina upungufu wa nguvu.....	0	1	2	3	4
GP2	Nina kichefuchefu…….	0	1	2	3	4
GP3	Kutokana na hali yangu ya kimwili nina matatizo ya kukidhi mahitaji ya familia yangu……..	0	1	2	3	4
GP4	Nina maumivu.....	0	1	2	3	4
GP5	Ninasumbuliwa na athari mbaya za matibabu……	0	1	2	3	4
GP6	Ninajisikia mgonjwa.....	0	1	2	3	4
GP7	Ninalazimika kukaa kitandani…..	0	1	2	3	4

	<u>HALI YA JAMII/FAMILIA</u>	**Hata kidogo**	**Kidogo**	**Wastani**	**Zaidi ya wastani**	**Sana**
GS1	Najisikia karibu na marafiki zangu…….	0	1	2	3	4
GS2	Ninapata msaada moyoni kutoka kwa familia yangu…….	0	1	2	3	4
GS3	Ninapata msaada kutoka kwa rafiki zangu……	0	1	2	3	4
GS4	Familia yangu imeukubali ugonjwa wangu.....	0	1	2	3	4
GS5	Nimeridhika na mawasiliano ya familia yangu kuhusu ugonjwa wangu.....	0	1	2	3	4