SUMMARY OF CHANGES

Clinical and Genomic Factors for Prognosis of AIDS Primary Effusion Lymphoma (Version 3.0)

NCI Protocol #: AMC-S004
Local Protocol #: AMC-S004

NCI Version Date: DDJUL2019
Protocol Date: DDJUL2019

I. Administrative and Editiorial Changes by Principal Investigator:

#	Section	Comments
1.	Global	The protocol date and version have been updated to 23AUG2019 and version 3.0.
2.	Global	The AMC operations page URL has been updated.
3.	Protocol Roster	The protocol roster has been updated to reflect current contacts.
4.	3.0	Template language has been added to indicate that an AMC rostered investigator must establish eligibility.
5.	4.2	Appendix numbers have been updated for consistency with current protocol.
6.	7.5	The AMC name has been updated.
7.	Appendix I	The AMC Data and Safety Monitoring Plan has been updated to the current version, v6.0

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL # S004:

CLINICAL AND GENOMIC FACTORS FOR PROGNOSIS OF AIDS PRIMARY EFFUSION LYMPHOMA

A TRIAL OF THE AIDS MALIGNANCY CONSORTIUM (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT02823327
Protocol Chair:	Erin Gourley Reid, MD
Protocol Co-Chair:	William Wachsman, MD, PhD

Version 3.0, August 23, 2019
NCI Version Date: August 23, 2019

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol # S004 – Clinical and Genomic Factors for Prognosis of Primary Effusion Lymphoma (Version 3.0, 23AUG2019**), as written according to AMC, NCI, and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (mm/dd/yyyy)

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PROTOCOL ROSTER

AMC Protocol # S004

Clinical and Genomic Factors for Prognosis of Primary Effusion Lymphoma

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PROTOCOL SYNOPSIS

Title:	Clinical and Genomic Factors for Prognosis of Primary Effusion Lymphoma
Phase of Study:	Retrospective case series
Participating Institutions:	This study will be open to participation at all AMC and member institutions
Accrual Target:	80 participants
Population:	Participants diagnosed with primary effusion lymphoma (HIV seropositive or negative) on or after January 1, 1998 and on whom survival status at 2 years post diagnosis is available.
Duration:	Record review and data collection will occur for up to 2 year after the protocol is activated for enrollment of eligible cases.
Primary Objective:	Objective 1 (Primary clinical objective): Identify baseline clinical characteristics and treatment strategies in patients with AIDS-associated primary effusion lymphoma (PEL) that correlate with long-term survival (≥ 2 years). Objective 2 (Primary genomic objective): Identify differentially expressed genes in PEL that are associated with long-term survival (≥ 2 years).

1.0 OBJECTIVES

1.1 Hypothesis

We hypothesize that there will be a sub-set of PEL clinical characteristics and differentially expressed genes in PEL cells that will be predictive of long-term survival (≥ 2 years), when data from long-term and short-term survivors of the disease are compared.

1.2 Primary Objectives

1.1.1 Primary clinical objective:

Identify baseline clinical characteristics and treatment strategies in patients with AIDS-associated primary effusion lymphoma (PEL) that correlate with long-term survival (≥ 2 years).

1.1.2 Primary genomic objective:

Identify differentially expressed genes in PEL that are associated with long-term survival (≥ 2 years).

2.0 BACKGROUND

2.1 Study Disease

Primary effusion lymphoma (PEL) is a rare type of non-Hodgkin lymphoma (NHL) that presents with predominately body cavity involvement and is nearly universally associated with Kaposi's sarcoma herpesvirus (KSHV), with Epstein Barr virus (EBV) also present in a fraction of cases[1]. PEL is typically associated with a poor prognosis with a median survival of 6 months[2]. A solid variant has also been described and carries a similarly poor prognosis[3]. PEL typically arises in the context of HIV infection, where it accounts for approximately 2-3% of AIDS-NHL[2].

Data supporting optimal treatment strategies of PEL are limited given the rarity of the disease. There are rare reports of remissions in PEL occurring with the introduction of HAART therapy in HIV patients, who are not on highly active antiretroviral therapy (HAART) at the time of diagnosis. However, HAART is not sufficient for adequate treatment in the vast majority of AIDS-PEL cases. Therefore, combined chemotherapy regimens and other anti-viral treatments are now routinely used for AIDS-PEL treatment. In addition to classic CHOP-based chemotherapy, clinicians and investigators have employed one or more of the following: (a) infusional chemotherapy regimens (EPOCH); (b) methotrexate (after chemotherapeutic debulking or drainage of effusions); (c) VEGF inhibition, aggressive effusion drainage; (d) taken advantage of latent gamma herpes virus tumor infection using bortezomib as an inducer of lytic viral replication and an inhibitor of NF-kB[4]; and (e) cidofovir or valganciclovir as inhibitors of KSHV replication, with or without interferon[5]. Auto- and allo-geneic hematopoietic stem cell transplant is also reported in the salvage setting with variable success. Long-term AIDS-PEL survivors have been reported[2], some of whom are being followed at UCSD as well as by collaborators at other institutions within the AMC.

Most of the literature on AIDS-PEL is in the form of single or small case reports, with the largest series including 28 participants reported from a French cohort in 2005[2]. This series explored baseline clinical factors associated with poor survival and identified ECOG performance status > 2 and lack of HAART use at time of diagnosis as independent predictors of shorter survival. A recent review of case in the literature identified the number of body cavity sites as predictive of survival[6].

An initial genomic evaluation of 9 PEL cases was published by Klein et al., in 2003 and reported PEL as having a distinct profile from other NHLs – including those from immunocompetent and HIV-seropositive hosts – with features of both immunoblasts and plasma cells[7]. Although distinct, AIDS-PEL had a profile most similar to EBV+ immunoblastic diffuse large B cell lymphoma. Despite the limited sample size, they were able to identify 51 genes differentially expressed between PEL cells and normal B cells as well as NHL, including AIDS-NHL.

Past work on gene expression profiling of AIDS-PEL determined that it was quite different from other types of non-HIV and AIDS-related non-Hodgkin's lymphoma[7] and discerned sub-types of PEL that were primarily associated with the presence, or absence of either KSHV or EBV[8]. In the first study, 9 cases of fresh AIDS-PEL specimens, in the form of cell blocks prepared from cytospins of the PEL fluid, were expression profiled on the Affymetrix U95 GeneChip. Although distinct, AIDS-PEL had a profile most similar to

EBV+ immunoblastic diffuse large B cell lymphoma. Despite the limited sample size, they were able to identify 51 genes differentially expressed between PEL cells and normal B cells as well as NHL, including AIDS-NHL. In the second study, 3 cases of freshly obtained AIDS-PEL mononuclear cells were expression profiled on the Affymetrix U133 GeneChip. In contrast, the intent of this project is to identify genes in PEL, whose expression is associated with long-term survival (≥ 2 years).

Currently, little is known about factors of prognostic importance in PEL. We hypothesize that there will be a sub-set of PEL clinical characteristics and differentially expressed genes in PEL cells that will be of prognostic value for this disease, when data from long-term and short-term survivors of the disease are compared.

2.2 Study Design and Rationale

This is a retrospective analysis to determine the baseline characteristics, treatment patterns and gene expression associated with of long-term survival in HIV-seropositive and negative patients with PEL diagnosed on or after January 1, 1998, a time period during which use of HAART has been widespread in the United States. Due to the rare nature of this disease, data supporting optimal treatment strategies are limited. The AMC is interested in studying this disease because of the disproportional prevalence among people with HIV infection. Information gathered from this retrospective study might serve to initiate future prospective studies in the AMC.

In this study, patient, disease, and treatment information will be obtained from multiple centers within the AMC. Archived biopsy specimens of PEL will also be collected when available for genomics portion of the analysis. The AMC Operations and Data Management Center (AMC ODMC) will provide an electronic clinical research form (CRF) to all participating sites via the AMC AdvantageEDC^{SM} Internet Data Entry System. Each participating AMC center will perform chart reviews after obtaining an Institutional Review Board (IRB) waiver or approval to conduct the study, as determined by the local IRB. All case data will be entered in AdvantageEDC in a de-identified manner, and protected health information (PHI) collected will be limited to information necessary to determine participant eligibility and to address the research questions. Data will be provided to Jeannette Lee, Ph.D., at the AMC Statistical Center at the University of Arkansas for Medical Sciences for statistical analysis via secure electronic transfer. The data set will only be accessible by the registered investigators, Dr. Reid and Dr. Wachsman, the statistician, Dr. Lee, and the AMC ODMC for the purposes of data monitoring and analysis.

3.0 PARTICIPANT SELECTION

Protocol participants must meet all stated eligibility criteria. A rostered AMC investigator must document that each protocol participant meets all stated eligibility criteria Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted in any circumstance.

3.1 Eligibility Criteria

Patients diagnosed with primary effusion lymphoma (HIV seropositive or negative) on or after January 1, 1998 on whom survival status at 2 years post PEL diagnosis is available.

Participants may be enrolled to *either or both* the clinical or genomic portions of the study.

The minimum data required to be able to include a participant for analysis of **clinical prognostic factors** are:

a. HIV status, and for HIV-positive participants, include CD4 count, HIV viral load within one year prior PEL diagnosis (or within 3 months after PEL diagnosis)

b. Age at PEL diagnosis

c. Gender

d. Stage at PEL diagnosis

e. Treatment of PEL

f. Response to PEL treatment

g. Survival status at 2 years post diagnosis

h. Pathology slides (or paraffin block) for central review

i. Year of PEL diagnosis

The minimum data required to be able to include a participant for analysis of **genomic prognostic factors** are:

a. Availability of a pathologic specimen of PEL that will be submitted for genomic analysis

b. Survival status at 2 years post diagnosis

3.2 Exclusion Criteria

Patients who do not fulfill the criteria as listed in Section 3.1 above are ineligible.

3.3 Number of Participants to be Enrolled

A survey of investigators participating in the AMC consortium regarding the number of PEL patients seen at their site in the last 5 years reported 23 participants from 11 responding sites. By including the last 13 years (HAART era), it is reasonable to expect approximately 80 participants especially considering new sites added to the AMC.

3.3.1 Proposed Sample Size

The enrollment goal is 80 participants with a minimum of 20 participants in the genomics portion of the study.

3.3.2 Accrual Rate

An average of 4 participants per month anticipated.

3.3.3 Replacement of Participants in the Genomics Portion of the Study

A participant in the genomics portion of the study will be replaced if insufficient specimens are received (see Section 4.2.1.2 for required specimens), or if insufficient genetic material is retrieved (see Section 4.3.1). However, the participant may still participate in the clinical portion of the study if the eligibility criteria are met (see Section 3.1).

3.4 Participant Enrollment Procedures

This is a retrospective review. Enrollment is expected to occur over a two-year period. The medical records of participants who meet the inclusion/exclusion criteria will be reviewed. For participants enrolled into the genomics portion of the study, archived pathologic specimens will be obtained. Sites must obtain approval from their Institutional Review Boards (IRB) to waive the requirement for informed consent for this study, or conduct informed consent if required by the local IRB, and register with the AMC ODMC before enrolling participants.

After the investigator at the site has determined that a patient case is eligible for inclusion in this retrospective analysis, the participant will be registered for the protocol on-line via the AMC AdvantageEDC^{SM} Internet Data Entry System. After successful registration, the participant will be assigned a system-generated ten-digit participant ID. Once the eligibility checklist is submitted, a system-generated confirmation email will be sent to the enroller upon successful completion of participant enrollment. If the online system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

4.0 RESEARCH METHODS

4.1 Overview

Once an eligible case is enrolled on the protocol, the Primary Effusion Lymphoma Retrospective Analysis Forms will be available for data entry in the disease-specific Participant Assessment Form will be available for entry. The case report form will collect information regarding the participant's HIV/AIDS medical history, staging of AIDS related malignancy and type of treatment. Sites are to complete forms based on the participant's cancer diagnosis.

4.2 Study Plan

4.2.1 Data, Documents, Records, or Specimen Identification:

4.2.1.1 The following data will be collected for participants enrolled into the clinical portion of the study:

- HIV status, and for HIV-positive participants, include CD4 count, HIV viral load within one year prior PEL diagnosis (or within 3 months after PEL diagnosis)
- Age at PEL diagnosis
- Gender
- Stage at PEL diagnosis
- Treatment of PEL
- Best response to PEL treatment
- Survival status at 2 years post diagnosis
- Pathology slides for central review (See Appendix II for specimen preparation and shipping)
- Year of PEL diagnosis

4.2.1.2 The following will be collected for participants enrolled into the genomics portion of the study:

- Pathology slides for central review (if unavailable, paraffin block may be submitted)
- Pathologic specimen that will be submitted for genomic analysis:
  - Frozen specimens, formalin-fixed and paraffin-embedded (FFPE) demonstrating PEL including cytospins as well as any mass/nodal biopsies are acceptable (See Appendix II for specimen preparation and shipping)
- Survival status at 2 years post diagnosis

4.2.1.3 The following is a list of additional data that is highly desirable for inclusion whenever available for participants enrolled in either the clinical and/or genomics portion of the study:

- Race and ethnicity
- For participants with HIV: HIV treatment history (which HAART drugs has participant received prior to PEL diagnosis, after PEL diagnosis), baseline HIV characteristics (i.e., CD4 count and HIV viral load closest

to time of PEL diagnosis, history of opportunistic infections)

- Presence or history of other human herpesvirus-8 (HHV-8)-related diseases (i.e., Kaposi's sarcoma, Multicentric Castleman's Disease), and other malignancies)
- Lymphoma baseline disease characteristics (immunophenotype, Epstein-Barr virus (EBV) and Kaposi sarcoma herpes virus (KSHV) status, sites of extranodal involvement), and either IPI or data required for calculation of International Prognostic Index (IPI)
- Lymphoma treatment: type, number of treatment regimens, use of therapeutic effusion drainage
- Best response to PEL treatment, best response duration
- Survival status at time of enrollment and duration of survival in months from PEL diagnosis

4.3 Genomics Methods

4.3.1 RNA Extraction and Quality Assessment

The vast majority of specimens are in the form of archived blocks of cells prepared from cytospin of PEL fluid that are formalin-fixed and paraffin-embedded (FFPE). Each specimen will be centrally reviewed for morphology and immunophenotype to confirm the diagnosis of PEL and to ascertain the percentage of tumor cells in the tissue block. Only samples containing > 95% PEL cells will be further profiled. It should be noted that PEL effusions are typically quite homogeneous, such that all 9 of the specimens assessed by Klein et al. met this criteria[7]. Thus, we expect that nearly all of the FFPE PEL specimens received for this study should be able to move forward for expression profiling. Based on our experience and feedback from outside AMC investigators, we expect that 25-40% of the PEL samples will be from patients who are long-term survivors (20-32 of the 80 total PEL specimens).

Total RNA will be extracted from FFPE PEL sections using a method that enables preparation of RNA for use in both microarray and RNA-Seq assay protocols (i.e., Prelude FFPE Isolation Module (NuGen Inc.)). Some 5 x 20 micron sections of the trimmed FFPE blocks will be extracted by column purification following deparaffinization and lysate preparation. RNA quantity will be measured by OD 260/280/320 assay on a NanoDrop spectrophotometer. Although we anticipate the RNA to be variably degraded, we will still assess its quality by determining a RIN score following Bioanalyzer assay. This will permit us to determine whether a very poor RIN metric (i.e., < 7) was instrumental in the outcome of an expression assay and enable better comparison of the results. We will use enough of each PEL specimen to prepare approximately 400 ng of total RNA. The RNA will be stored at -80ºC.

4.3.2 RNA-Seq and Microarray Analysis of RNA

4.3.2.1 RNA-Seq Analysis

For RNA-Seq assays we will use Illumina's TruSeq RNA Access Library Prep Kit to generate RNA libraries. This reagent kit, which focuses on transcriptome coding regions, can be performed with as little as 20ng of

degraded total RNA isolated from FFPE specimens. RNA libraries will be multiplexed and, following cluster generation, sequenced with 100 basepair (bp) single end (SE) reads to a depth of approximately 45 million reads per sample on an Illumina HiSeq2000 instrument. To mitigate assay noise we will perform RNA-Seq on each PEL RNA sample in triplicate, using an independently generated library for each RNA-Seq assay. Each sample will be barcoded and sequenced as part of a single pool with up to 30 samples loaded onto an 8-lane flow cell.

The general approach to RNA-Seq data analyses is as follows: Multiplexed RNA-Seq data will be deconvoluted to separate each of the samples, after which, sequencing adapters and poly-A/T tails will be trimmed using cutadapt software. Sequencing reads of length less than 20 base pairs will be removed. Reads will be aligned to the human genome using STAR software. Aligned reads will be realigned using GATK's IndelRealigner. Gene Expression: STAR genomic alignments will be filtered to remove any reads that align outside of Gencode exons. Remaining reads will be realigned to the Gencode transcriptome using bowtie2 and transcriptome alignments passed to eXpress for expression estimation. Gene expression will be calculated by summing the FPKM estimates for each of the gene's transcripts. Genes with expression greater than zero FPKM will be considered expressed. All of the RNA-Seq data that pass these quality metrics will then be normalized and then subjected to supervised analysis to identify genes differentially expressed between PEL treatment responders vs non-responders. This supervised analysis will be performed by means of t-test with multi-testing correction (Westfall & Young Permutation method)[11] ($p < 0.05$, $FDR < 0.05$). Based on past experience[10], we expect that fewer than 500 genes will be found to be differentially expressed between treatment responders and non-responders. Lastly, we will take advantage of bioinformatic approaches to examine genes that are found to be differentially expressed between the sample groups. Bioinformatic software, such as Ingenuity Pathways (**http://www.ingenuity.com**), focus on the analysis of genetic networks and pathways and help place such genes, which may have prognostic significance, into biologic context.

Following quantification and quality assessment of the RNA, RNA-Seq analyses, as described above will be performed on 20 PEL specimens, 10 of which are from long-term survivors and 10 from non-long-term survivors. The resulting data will be assessed for quality and adequacy: the total number of reads compatible with a transcript on the RNA-Seq assay.

4.3.2.2 Microarray Analysis

For microarray-based assays, we will follow an approach that we have successfully used in our past work[10] with modifications to incorporate updates to the Affymetrix GeneChip technology. Total RNA (50-100 ng) will be amplified using the SensationPlus FFPE Amplification kit (Affymetrix, Inc.) with QC to assess the quantity and quality of the final

amplified product. We will use the Affymetrix GeneChip Human Transcriptome Array 2.0 for performing gene expression profiling of the PEL RNA. Following amplification of the RNA specimen, the sample will be hybridized, labeled with the WT Labeling Kit (Affymetrix, Inc.), washed, and scanned as per the Affymetrix protocol. Spike-in hybridization controls will facilitate data normalization between specimens. Normalization of array CEL files will be carried out using the gcrma software from the Bioconductor suite (http://www.bioconductor.org). The percent present calls and 3'/5' ratio of GAPDH will be determined for each sample. Samples with less than 25% presents calls will be considered technical failures. This methodology is specifically meant for GeneChip assay of small amounts of partially degraded RNA from clinical samples.

4.3.2.3 Analytic Strategy

RNA-Seq assay of PEL is the preferred approach because it has a better linear dynamic range than does a GeneChip assay and may provide insights about PEL genomics that are not possible to be discerned by GeneChip-based expression profiling (i.e., novel splice junctions and transcripts, viral RNAs, etc.). However, because of the high likelihood of very substantial RNA degradation in these FFPE samples, we are concerned about the potential for poor quality RNA-Seq data. RNA-Seq will be the primary method for genomic analysis of the PEL specimens, if it satisfies QC metrics for read number and data quality (i.e., 30 million pair-end reads of length > 30 nucleotides, of which 20-25 million may be mapped to the genome or known transcriptome; R^2 (Pearson) correlation between technical replicates of the same sample of > 0.9). If the QC metrics are not met, GeneChip assay will be performed instead, as these should yield higher quality data. In summary, GeneChip assay is planned as a backup in the event that RNA-Seq QC is inadequate.

5.0 STATISTICAL CONSIDERATIONS

5.1 Study Design/Endpoints

5.1.1 Analysis/Statistics

Survival will be estimated using the Kaplan Meier method and Cox proportional hazards model will be used to assess differences between treatment groups and categorical baseline variables. Response rates will be reported with 95% confidence intervals (binomial distribution). Descriptive statistics will be used to summarize baseline clinical, histological, and viral characteristics.

We will perform either RNA-Seq or GeneChip assays, as described in Section 4.3, expression profiling on a total of up to 80 AIDS-PEL specimens. We are already aware of at least 10 long -term AIDS-PEL survivors within the AMC. Resultant data will be assessed for quality, normalized, and then analyzed for differential gene expression. We will use standard algorithms in both GeneSpring and Bioconductor for this purpose, with which we have considerable experience (see Preliminary Studies above). In particular, the RNA-Seq data will be analyzed by the DESeq algorithm in Bioconductor[1]. Lastly, we will take advantage of bioinformatic analysis approaches to help make sense of possible biological links between the genes found to be differentially expressed between the sample groups that may be of prognostic significance. These bioinformatic approaches, such as Ingenuity Pathways (http://www.ingenuity.com), focus on the analysis of genetic networks and pathways and help place genes identified as differentially expressed into biologic context.

5.2 Sample Size/Accrual Rate

We expect to obtain clinical data and pathology specimens on 80 participants from sites throughout the AIDS Malignancy Consortium. It is estimated that 15-25% of these participants will be long-term survivors.

6.0 ROLE OF DATA MANAGEMENT

6.1 Records to Be Kept

CRFs will be provided for each participant via the AMC AdvantageEDC^{SM} Internet Data Entry System upon enrollment. Participants must be identified by participant ID number only on all study documents. Data will be recorded on the CRFs using the unique participant identification number assigned at registration. Sample CRFs will be available on the AMC Operations Center web site (www.AIDSCancer.org).

6.2 Source Documentation

Source documents are defined as the first place where data are recorded. For purposes of this study, medical records, chart notes that are signed and dated, and reports received from a local or central laboratory (e.g., Western blot, HIV-1 RNA) are considered source materials for this study.

6.3 Role of Data Management

Instructions concerning the recording of study data on CRFs will be provided by the AMC Operations Center. The AMC Internet Data Entry System User's Guide can be found on the AMC Operations Center web site (www.AIDSCancer.org). Each site is responsible for keying the data in and submitting the forms according to the target submission dates set forth by the AdvantageEDC^{SM} system.

It is the responsibility of the AMC Operations Center to assure the quality of computerized data for each AMC study (See Appendix I, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study databases.

6.4 Clinical Site Monitoring and Record Availability

This protocol will follow the AMC Data and Safety Monitoring Plan (see Appendix I).

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.

7.0 ETHICAL AND REGULATORY CONSIDERATIONS

7.1 Institutional Review Board (IRB) Review 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 must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB, which specifically approves the protocol, before participant enrollment. The IRBC 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 subject 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.

A request to waive the requirement to obtain informed consent is being requested for this retrospective chart data collection and analysis. A model informed consent document is available if the IRB at a participating site denies waiver of consent. The investigator believes this study meets the following requirements for this request per 46 CFR 46.117(c):

- The research involves no more than minimal risk to the participants. *The only risk is the loss of patient confidentiality, which will be minimized as described in the confidentiality section* (Section 7.3).
- The waiver or alteration will not adversely affect the rights and welfare of the participants. *There will be no contact with the participants and no documentation of this study in their medical records.*
- The research could not practicably be carried out without the waiver or alteration. *As described above, this disease is very rare, and patients with retrospective cases of PEL may be deceased or unavailable to contact for consent; therefore, it would not be practical to recruit prospectively.*
- The project could not practicably be conducted without the use of PHI. *PHI collected will be limited to dates, such as the year of diagnosis, treatment, response, and diagnosis. Collection of select dates is necessary to obtain data elements that are required to determine participant eligibility and are important to the question being studied. The AMC also requires collection of demographic data (participant initials, birth date, and zip code) in standard forms for the purpose of required demographic reporting to the NCI.*
- An adequate plan to protect identifiers from improper use and disclosure is included in the research proposal. *Only authorized study personnel have access to this information in AdvantageEDC, which is secured from unauthorized access with login/password controls. Participant initials are encrypted in the AdvantageEDC data entry system*

and in the study database, and can only be viewed in AdvantageEDC by the clinical site staff.

- An adequate plan to destroy the identifiers at the earliest opportunity, or justification for retaining identifiers, is included in the research proposal. *The PHI collected is a component of standard AMC data entry forms for compliance with NCI demographic reporting requirements, and is also required for data analysis. Protections for this information will be applied as stated above.*
- The project plan includes written assurances that PHI will not be reused or disclosed for other purposes. *Data access will be restricted to the parties listed in Section 7.3, and will not be reused or disclosed for any other purpose. No PHI, including dates, will be included in any study publications.*
- *The AMC routinely provides study summaries for participants on its website.*

A waiver of HIPAA Authorization is being requested for this study. As described above, the use or disclosure of PHI involves no more than minimal risk; granting of the waiver will not adversely affect privacy rights or the welfare of the individuals whose records will be used; the project could not practicably be conducted without a waiver; and the project could not practicably be conducted without use of PHI. Further, the privacy risks are reasonable relative to the anticipated benefits of research, as the importance of the knowledge that may reasonably be expected to result outweighs the minimal risk posed to participants. PHI will not be re-used or disclosed for other purposes and, whenever appropriate, the participants will be provided with additional pertinent information after participation. In accordance with Good Clinical Practice and the retention of records under 45 CFR 46.115, study records will not be destroyed until at least three years after the completion of the research. Only de-identified data will be retained.

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

7.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Protocol Chair before implementation. All protocol amendments require approval by the IRB of each participating institution. A copy of the written approval of the IRB must be provided to the AMC ODMC.

7.3 Participant Confidentiality

Confidentiality of a participant's protected health information will be maintained by the following methods. Each participant will be assigned a separate study number that will be used as the main form of identification. The participant identification number will be linked to the medical record number in the participating site's study records, but this information will be known only to the primary investigators at each site. Thus, there will be no direct link between confidential medical information, the medical record number, or the participant identification number in AdvantageEDC. Data submitted by AMC sites will be identified only by the study number and not by the participant's name or medical record number. The information will be stored in a password-protected database for data analysis. The data set will provided to the AMC Statistical Center at UAMS for data analysis via secure electronic transfer and will only be accessible by the registered investigator, Dr.

Erin Reid, the AMC Biostatistician, Dr. Jeannette Lee, and the AMC ODMC, as necessary for data monitoring and analysis.

Furthermore, study-specific records containing PHI, and copies of study-related medical records, will be maintained in compliance with existing local standards for data security and confidentiality to prevent unauthorized access to confidential patient information. In accordance with the AMC's Certificate of Confidentiality, clinical information will not be released without the written permission of the participant, except as necessary for monitoring by the AMC ODMC, the IRB, the NCI, the OHRP, or designee.

7.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCI, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

7.5 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 and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	4	=	6
Not Hispanic or Latino	4	+	70	=	74
Ethnic Category: Total of all participants	6	+	74	=	80
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	1	+	2	=	3
Black or African American	1	+	34	=	35
Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	2	+	36	=	38
Racial Category: Total of all participants	6	+	74	=	80
	(A1 = A2)		(B1 = B2)		(C1 = C2)

8.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the AMC's Standard Operating Procedures for Publication Policy.

9.0 REFERENCES

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APPENDIX I: 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 pilot or 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 Group Statistician determine whether these criteria have been met.

For phase III trials and other select studies requiring additional oversight, the AMC has formed an independent Data and Safety Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the protocol statistician, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The DSMB reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB Charter. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the Group Chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMB are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMB Chair, and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying

and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site audits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDC/Advantage eClinical (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, AMC Medical Monitor, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC Medical Monitor review reported adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

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

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For phase I and II trials, the Protocol Chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into AdvantageEDC/Advantage eClinical. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. AMC ODMC staff routinely interacts with site staff to resolve any data problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventive action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX II: SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

BACKGROUND AND PROCEDURES

The following specimens are required for participation in the genomics portion of the study:

- Paraffin embedded tissue or cytology block or frozen tissue specimen (latter preferred if available).
- Pathology slides and a pathology report for central pathology review. If slides are not available, the site must provide a paraffin block for review, which if adequate, will also be used for genomic studies. The participant can be included in the clinical portion of the trial if the material submitted is only sufficient for pathology review.
- If neither slides nor adequate paraffin block is available, the participant will be considered ineligible.

For participants in the clinical portion, pathology slides and a pathology report are required for central pathology review.

Slides and/or tissue blocks will be returned to the site once all studies are complete.

Details regarding specimen shipment are provided in the protocol Manual of Procedures.

Technical questions regarding tissue specimens should be directed to Dr. Wachsman (see Protocol Roster).

The AMC Biorepository will ship pathology slides and tissue specimens to UCSD and Cornell for central pathology review. Specimens for genomic analysis will be sent to UCSD.