NORTHWEST AIDS EDUCATION AND TRAINING CENTER

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On behalf of the Seattle AMC group
What is the AMC?

- The AIDS Malignancy Clinical Trials Consortium
- A National Cancer Institute-supported clinical trials group
- Founded in 1995
- To support innovative trials for AIDS-related cancers
- Composed of over 37 Clinical Trials Sites worldwide

http://pub.emmes.com/study/amc
AMC Local & International sites

International sites in:
- Africa
- South America
- Australia
- India

http://pub.emmes.com/study/amc
AMC composition

Working Groups

- Four of the working groups deal with the cancers that affect HIV-positive patients
  - Kaposi’s Sarcoma
  - Lymphoma
  - Human Papillomavirus-related Cancers (e.g., anal and cervical cancers)
  - Non-AIDS Defining Cancers (e.g., lung cancer, head and neck cancer, liver cancer)

- The behavioral research working group: Goal is to reduce health disparities (separate funding through the AMC)

- The Laboratory Working Group
  - Oversees the Central Laboratories of the AMC
  - Develops laboratory studies to answer important scientific questions related to cancer in HIV-positive patients

- Administrative Office
- Statistical Office
- Operations and Data Management Office

http://pub.emmes.com/study/amc/public/index.htm
Domestic Core Sites

Boston Clinical Core Site (Boston Medical Center, Beth Israel Deaconess Medical Center)
New York (Memorial Sloan Kettering Cancer, Laser Surgery Center, Cornell)
Albert Einstein – Montefiore Core Site
Pennsylvania Oncology
Johns Hopkins
Ohio State University
Wake Forest University
Northwestern University
Washington St Louis University
Louisiana State University
University of Texas at Houston
Dan L Duncan Cancer Center
UCLA-USC Core Site
UCSD Core Site
UCSF Core Site
UC Davis
University of Miami Core Site

Seattle Core Site
- Fred Hutchinson Cancer Research Center
- Harborview Medical Center
- Seattle Cancer Care Alliance
- Virginia Mason Medical Center
The Seattle AMC

Seattle AMC sites & PIs
- Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
  - Corey Casper, MD MPH
  - Ann Woolfrey, MD
  - Manoj Menon, MD

- Harborview Medical Center
  - Jeff Schouten, MD
  - Robert Harrington, MD
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- Virginia Mason Medical Center
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Current AMC Treatment Studies
HPV Protocols

- AMC-058: Companion protocol to evaluate anogenital HPV infection and anogenital squamous intraepithelial lesions (ASIL) in patients participating in AMC trials
- AMC-072: Protective effect of quadrivalent vaccine in young HIV+ MSM
- AMC-076: A randomized trial of infrared coagulation (IRC) ablation Vs expectant management of intra-anal high grade intraepithelial neoplasia (HGAIN) in HIV+ subjects (just closed to enrollment)
- AMC-081: Feasibility study of safety, toxicity, and compliance of concomitant chemoradiotherapy for HIV-associated locally-advanced cervical cancer
- AMC-084: Screening HIV+ women for anal cancer precursors
- AMC-088: 5-flurouricil, imiquimod or observation for high grade anal intraepithelial neoplasia
Kaposi Sarcoma Protocols

- AMC-063: Single-arm, dose-finding pilot trial of single-agent bortezomib in patients with relapsed/refractory AIDS-associated Kaposi sarcoma with correlative assessments of KSHV and HIV
- A5263/AMC-066: A randomized comparison of three regimens of chemotherapy with compatible ART for the treatment of advanced AIDS-KS in resource limited settings
- A5264/AMC-067: A randomized comparison of ART alone or with delayed chemotherapy Vs ART plus immediate chemotherapy if the treatment of AIDS-KS in resource limited settings
- AMC-070: Lenolidomide for patients with AIDS-associated KS not requiring systemic chemotherapy (study just completed)
Lymphoma Protocols

• AMC-053: Safety and efficacy pilot trial of the anti-viral and anti-tumor activity of Velcade combined with (R)ICE in subjects with EBV and/or HHV-8 positive relapsed/refractory AIDS-associated Non-Hodgkin’s Lymphoma

• AMC-075: A sequential phase 1, randomized phase 2 trial of Vorinostat and high risk adapted chemotherapy with Rituximab in HIV-related B-cell NHL

• BMT CTN 0803/AMC-080: Allogeneic Hematopoietic cell transplant for hematologic cancers and MDS in HIV+ patients

• AMC-085: A phase ½ study examining AVD plus Brentuximab vedotin in HIV+ patients with advanced stage Hodgkin’s lymphoma

• 9177/AMC-086: A phase 2 study of dose-adjusted EPOCH +/- Rituximab in adults with untreated Burkitt lymphoma, C-Myc + diffuse large B-cell lymphoma and plasmablastic lymphoma
Non-AIDS Defining Cancer Protocols

- AMC-078: A phase 1 study of **Vorinostat** in combination with Paclitaxel and Carboplatin in solid tumors (focus on upper aero-digestive cancers) in HIV+ patients
- AMC-087: A phase 1 trial of Cabozantinib for advanced solid tumors in HIV+ patients
- AMC-090: **Erlotinib** (a reversible tyrosine kinase inhibitor which acts on the epidermal growth factor receptor) for patients with lung cancer
AMC Treatment Studies Available in Seattle
HPV protocols
AMC 072: Protective Effect of the Quadrivalent HPV Vaccine in Young HIV-positive Males who have Sex with Males

Purpose
- This phase II trial is a study to protective effect of the quadrivalent vaccine (against HPV-6, 11, 16, 18) in preventing condyloma, HPV infection and disease in subjects naïve to these viruses at baseline compared to those not-naïve at baseline.

Major eligibility
- **Men aged 13-26 with a history of at least one male sexual partner**
- **HIV-1 infection; meets one of the following sets of criteria:**
  - Patients receiving HAART:
    - Receipt of antiretroviral therapy for at least 3 months prior to entry
    - No change in antiretroviral therapy within 30 days prior to entry
  - Patients not receiving HAART:
    - CD4-cell count ≥ 350 cells/mm³ within 90 days prior to study entry
    - No plans to start antiretroviral therapy prior to Week 28

- **Normal anal cytological result, LSIL/condyloma, or ASCUS result within 90 days prior to entry, and no HGAIN on biopsy:** REQUIRES ANAL PAP SMEAR AND BASELINE HRA (AND POSSIBLE BIOSPY) FOR ENROLLMENT
- **No current or history of anal or peri-anal carcinoma**
- **No anal cytological result of HSIL, atypical squamous cells suggestive of HSIL (ASC-H), or suggestive of invasive carcinoma at screening; or history of these results**
- **No presence of penile or scrotal condyloma, LGAIN (condyloma or AIN 1), HGAIN (e.g., AIN 2 or 3, or perianal intraepithelial neoplasia grade 2 or 3), or invasive carcinoma at pre-entry on biopsy**
- **No history of HGAIN**
AMC 072: Protective Effect of the Quadrivalent HPV Vaccine in Young HIV-positive Males who have Sex with Males

Study details

• Baseline evaluations includes physical exam, blood work, anal cytology, HRA with biopsy (if indicated), HPV shedding and serology

• Vaccination at day 1, week 8 and week 24

• Clinical evaluations at weeks 28, 52, 78 and 104 with physical exams, routine labs, HPV shedding, anal cytology, HRA with biopsy
AMC 076: A Randomized Trial of IRC Ablation Vs Expectant Management of HGAIN in HIV+ Adults

Purpose
• To determine the complete response rate at 3 months and 1 year of HIV+ patients with HGAIN treated with IRC Vs observation

Major eligibility criteria
• HIV+
• AIN 2 or 3 by biopsy
• No concurrent perianal AIN, perianal condyloma or lower vulvar intraepithelial neoplasia requiring treatment
• No prior HGAIN treated by IRC
• No concurrent cancer requiring therapy (KS of the skin allowed)
• No history of anal cancer
• No anticoagulants other than ASA and NSAIDs
• At least 3 months off of immunomodulating treatment (e.g. steroids, cytokines, interferon, imiquimod)

ClinicalTrials.gov Identifier: NCT01164722
AMC 076: A Randomized Trial of IRC Ablation Vs Expectant Management of HGAIN in HIV+ Adults

ClinicalTrials.gov Identifier: NCT01164722
Lymphoma protocols
AMC 053: Safety And Efficacy Trial Of The Anti-Viral And Anti-Tumor Activity Of Velcade Combined With (R) ICE In Subjects With Relapsed/Refractory AIDS-Associated Lymphoma

Purpose
• To evaluate the safety and response rate of bortezomib (velcade) in combination with ifosfamide, carboplatin, and etoposide with or without retixumab (R-ICE) in treating patients with relapsed or refractory AIDS-related NHL

Major eligibility
• Histologically or cytologically confirmed relapsed or refractory HIV-associated NHL
• Must have documented HIV seropositivity
• Must have documentation of EBV- and/or human HHV-8- positive infection within the lymphoma
• NONE of: neuropathy ≥ grade 2, symptomatic or grade 3-4 CHF, unstable angina, severe cardiac arrhythmias, ongoing active infections including OI requiring abx, serious psychiatric, medical or social condition that would interfere with study compliance, concurrent cancer (other than in situ cancers, non-melenotic skin cancers or Ks not requiring chemotherapy), active Hepatitis B that is not treated, CYP-3A4 inducers or inhibitors (other than HIV protease inhibitors)

ClinicalTrials.gov Identifier: NCT00598169
AMC 053: Safety And Efficacy Trial Of The Anti-Viral And Anti-Tumor Activity Of Velcade Combined With (R) ICE In Subjects With Relapsed/Refractory AIDS-Associated Lymphoma

- Velcade™ (bortezomib) is a small molecule proteasome inhibitor developed as a novel agent to treat human malignancies.

- Velcade is currently approved by the United States Food and Drug Administration (FDA) for the treatment of multiple myeloma (MM) and mantle cell lymphoma in subjects who have received at least one prior therapy.

**Mechanisms of action**
- Stabilization of cell-cycle reg proteins
- Inhibition of NF-κB activation
- Induction of apoptosis
- Anti-angiogenesis
- Weak MDR substrate
- Hypoxic cells are hypersensitive

Bortezomib blocks degradation of cyclin-B1: cell is stuck in mitosis
AMC 075: A Sequential Phase I/Randomized Phase II Trial of Vorinostat and Risk-Adapted Chemotherapy with Rituximab in HIV-Related B-cell Non-Hodgkin’s Lymphoma

Purpose
- A phase 1, 2 study to determine the dose, toxicity and effect of Vorinostat with Rituximab + dose-adjusted EPOCH (R-DA-EPOCH) in HIV associated aggressive CD-20+ NHL

Major eligibility
- 18 years and older
- Diffuse large B-cell lymphoma, other aggressive CD20+ non-Burkitt non-Hodgkin B-cell lymphoma variants and rare CD-20- lymphomas (e.g. plasmablastic lymphoma and PEL)
- Untreated patients or may have received a maximum of 1 cycle of chemotherapy at least 21 days prior to beginning treatment under this protocol
- Documentation of HIV infection
- If HBV chronic infection – on therapy
- If not on ART – must start after one cycle of chemotherapy
- CD4 count ≥ 50
- NONE of: second active tumor (other than in situ cancer, non-melanotic skin cancer or KS not requiring chemotherapy), CNS involvement of lymphoma, pregnant or nursing, expected survival < 2 months, KPS < 50%, serious ongoing non-malignant disease or infection, inability to comply with the protocol, MI in the last 6 months, ≥ class 2 CHF, ongoing angina or serious arrhythmia, valproic acid or other HDAC inhibitor in the previous 2 weeks

ClinicalTrials.gov Identifier: NCT01193842
Vorinostat

• An histone deacetylase (HDAC) inhibitor
• HDAC inhibitors are clinically active in both leukemias and solid tumors in combination with cytotoxic and other biological agents.
• Currently FDA approved for treatment of cutaneous T-cell lymphoma, under phase I/II RCT for elderly with refractory DLBCL

See protocol for details & references.
AMC 075: A Sequential Phase I/Randomized Phase II Trial of Vorinostat and Risk-Adapted Chemotherapy with Rituximab in HIV-Related B-cell Non-Hodgkin’s Lymphoma

Proposed mechanism of action

• **Blockage of histone deacetylation** → permits the accumulation of acetyl groups on histone lysine residues → chromatin de-condensation and expression on previously silenced (methylated) genes such as those encoding cell cycle regulators and tumor suppressors.

• **In vitro studies have demonstrated that HDAC inhibitors induce cell cycle arrest and/or apoptosis.**

• HDAC inhibitors can also activate the expression of latent viruses in host human cells, such as HIV and herpesviruses.

• Vorinostat, a proto-type of the newer and more potent HDAC inhibitors, can also activate HIV from latency.

• In preclinical lymphoma models, HDAC inhibitors also induced lytic expression of the gamma herpesviruses EBV and HHV-8 resulting in cell cycle arrest and apoptosis in transformed cells.

• In general, while vorinostat itself may result in increased NF-KB activity, the end result of this is tumor cell apoptosis, especially when combined with a protease inhibitor.
AMC 075: A Sequential Phase I/Randomized Phase II Trial of Vorinostat and Risk-Adapted Chemotherapy with Rituximab in HIV-Related B-cell Non-Hodgkin’s Lymphoma

ClinicalTrials.gov Identifier: NCT01193842
AMC 085: A Phase 1/2 Study Examining AVD and Brentuximab Vedotin in Patients with HIV and Advanced Stage Hodgkin Lymphoma

Purpose
• Phase 1,2 study to
  - Identify the maximum tolerated dose of Brentuximab vedotin when combined with doxorubicin, vinblastine and dacarbazine (AVD) = phase 1
  - Determine the 2yr progression-free survival of HIV+ patients with advanced HD treated with AVD + Brentuximab = phase 2

Major eligibility
• HIV-1 infection
• Histologic diagnosis of CD30-positive classical HD, stage 2, 3 or 4, not previously treated
• Normal baseline cardiac ejection fraction ≥ 50%
• CD4 ≥ 50
• NONE of: prior anthracycline therapy, pregnant or breast feeding, medical illness that would preclude treatment of HD (e.g. uncontrolled infections, recent MI, etc), prior malignancy within the last 5 years (other than in situ carcinoma, non-melanotic skin cancer, or KS not requiring treatment), grade 2 neuropathy, PML, CNS involvement of HD, cirrhosis

ClinicalTrials.gov Identifier: NCT01771107
Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components:
- Antibody cAC10, specific for human CD30
- Highly potent anti-microtubule agent, monomethyl auristatin E (MMAE)
- A protease-cleavable linker that covalently attaches MMAE to cAC10.

Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment.

Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage.

Binding of MMAE to tubulin prevents its polymerization, thus disrupting the microtubule network within the cell, inducing cell cycle arrest, and apoptotic death of the CD30-expressing tumor cell.

ClinicalTrials.gov Identifier: NCT01771107
AMC 085: A Phase 1/2 Study Examining AVD and Brentuximab Vedotin in Patients with HIV and Advanced Stage Hodgkin Lymphoma

Study details

• Baseline: Physical exam, imaging (FDG-PET/CT, CT), PFTs, Brain MRI, MUGA, BM bx, pathology review, routine labs, CD4 and VL, Hep serologies, HIV reservoir studies

• 6 cycles of therapy (each cycle 25 days with treatments given on day 1 and day 15)

• Post treatment: repeat imaging, BM bx, routine labs, CD4 and VL, HIV reservoir studies

ClinicalTrials.gov Identifier: NCT01771107
None-AIDS Defining Cancer Protocols
AMC 087: Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV Infection

Purpose
• Phase 1 study (of 3 starting doses of cabozantinib, depending on ART regimen) to determine the safety and tolerability of cabozantinib,
• Secondary objectives are to investigate pK interactions with ART, the effects on CD4 and VL and objective response rates of represented tumors

Major eligibility
• HIV infection
• Histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective
• Karnofsky > 60%
• CD4>50
• Women of child-bearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation
• Subjects must in the opinion of the investigator be capable of complying with this protocol
• NONE of: prior therapy with kinase inhibitors or hormonal treatment within 4 weeks, primary brain tumor, active brain or epidural metastases, full anticoagulation therapy, potent CYP3A4 inducers or inhibitors (other than ART), other significant, active medical conditions including cardiovascular, gastrointestinal, infectious disease or major surgery within 3 months, non-healing fractures or wounds, QTc > 500, previous organ Tx, pregnancy

ClinicalTrials.gov Identifier: NCT01822522
AMC 087: Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV Infection

Cabozantinib (XL184) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis.

The primary targets of cabozantinib are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2.

Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in vivo pharmacodynamic activity of cabozantinib against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

ClinicalTrials.gov Identifier: NCT01822522
AMC 087: Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV Infection

- Baseline: Physical exam, routine labs, ECG, imaging with tumor measurements, CD4 count
- 6 cycles (4 weeks each), exams and labs every 2-4 weeks and imaging every 8 weeks
- Dosing:

![protocol schema table]

* Cabozantinib (XL184) must be taken whole and on an empty stomach. Patients must fast for 2 hours before and 1 hour following each dose of cabozantinib (XL184). To permit pharmacokinetic sampling studies, AM dosing is required during the first cycle of therapy.

- Stratum A: Subjects taking either ritonavir-boosted or cobicistat-boosted ART regimens
- Stratum B: Subjects taking either efavirenz or stravine-based ART regimens
- Stratum C: Subjects taking any antiretrovirals not specified in Stratum A or B as of November 30, 2012, and subjects who are not taking an ART regimen

ClinicalTrials.gov Identifier: NCT01822522
AMC-A01: Anal Cancer/HSIL Outcomes Research (ANCHOR) Study

- Planned study of 5085 HIV+ men and women with anal HSIL
- Randomized to 1) Active monitoring (no treatment of anal HSIL) or 2) Treatment of anal HSIL
- Screening visit: anal Pap and HRA with biopsies
- Study procedures:
  - All patients: Every 6 months: anal Pap, HRA
  - Active monitoring group: annual biopsies
  - Treatment group: HSIL will be treated with either imiquimod, topical 5FU, 85% TCA, IRC, electocautery or surgery (surgery, if none of the other treatments are available)
  - $100 per visit paid to participants
  - Study duration: 5 years
Studies planned or in committee

- AMC-090: Erlotinib (a reversible tyrosine kinase inhibitor which acts on the epidermal growth factor receptor) for patients with lung cancer
- AMC-084: Anal cancer screening for HIV+ women
- AMC-088: 5-flurouricil, imiquimod or observation for high grade anal intraepithelial neoplasia