RFA Reissuance Request

AIDS Malignancy Consortium

Office of HIV and AIDS Malignancy (OHAM)

Cooperative Agreement
5 Years Funding
$24,000,000 year 1
$113,730,523 total over 5 years
Background - HIV Epidemic

Approximately 36.7 million people live with HIV worldwide, and there are ~1.8 million new infections per year:

- **United States**
  - ~1.1 million people live with HIV
  - ~40,000 new infections per year

- **Sub Saharan Africa (SSA)**
  - ~19 million People live with HIV
  - ~960,000 new infections per year

- **Latin America**
  - ~2.3 million people live with HIV
  - ~100,000 new infections per year

*Cancer has been a prominent manifestation of HIV/AIDS since the beginning of the epidemic and is a leading cause of morbidity and mortality in HIV-infected people*
### Estimates of the Incidence and Burden of Selected AIDS-Related Cancers in USA

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Incidence per 100,000 person years</th>
<th>Number of cases/year in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIDS Defining</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>194</td>
<td>1650</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>110</td>
<td>910</td>
</tr>
<tr>
<td>Cervix</td>
<td>47</td>
<td>80</td>
</tr>
<tr>
<td><strong>Non-AIDS Defining</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>78</td>
<td>840</td>
</tr>
<tr>
<td>Anus</td>
<td>59</td>
<td>760</td>
</tr>
<tr>
<td>Liver</td>
<td>32</td>
<td>390</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>22</td>
<td>320</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
<td>13</td>
<td>290</td>
</tr>
</tbody>
</table>

Robbins et al., 2014, 2015, Shiels & Engels, 2017
Burden of HIV/AIDS, Cervical Cancer and Kaposi Sarcoma in Sub Saharan Africa (SSA)

HIV Incidence
- Incidence per 1000 persons
- ~90% in low- and middle-income countries (LMICs)

Kaposi Sarcoma Incidence
- Incidence per 100,000 persons
- ~90% in low- and middle-income countries (LMICs)

Cervical Cancer Incidence
- Incidence per 100,000 women
- 1st/2nd most common cancers in women in many LMICs
AMC Mission

- Develop and evaluate clinical interventions for the treatment and prevention of malignancies in people with HIV

- Conduct Phase I, II and III clinical trials of HIV-related malignancies

- Investigate the biology of these malignancies in the context of clinical trials

- Contribute specimens and clinical data to the AIDS and Cancer Specimen Resource (ACSR)
Some Performance Parameters

- Developed 15 protocols so far in this grant cycle (the past 36 months).
- 14 protocols completed enrollment.
- 2887 patients accrued (2350 ANCHOR + 537 non-ANCHOR). (Excluding survey, laboratory and quality of life studies)
- 14 protocols actively accruing patients.
- Approximately 63% of accrued US participants are of African-American or Hispanic origin.
- In the last 3 years, published approximately 39 papers in peer-reviewed journals.
Anal Cancer HSIL Outcomes Research (ANCHOR) Study

• A randomized controlled trial to establish whether treatment of anal high grade squamous intraepithelial lesions (HSIL) is an effective strategy to prevent anal cancer.
• It will thus evaluate whether screening for HSIL is warranted.
• 5058 patients with HSIL will be randomized to treatment vs. active monitoring.
• To date, >7000 screened and >2804 randomized.
• The study will establish a bank of blood, anal swab and tissue specimens to study molecular pathogenesis of progression from HSIL to cancer.
AMC Overall Accrual and Demographics

AMC Patient Accrual (2011-2018)

AMC Patient Population by Race and Ethnicity

- White: 35%
- African American: 11%
- Hispanics: 1%
- American Indians/Alaskans: 52%
AMC Accomplishments this Grant Cycle

- Evaluated immunotherapy approaches to solid tumors in HIV patients: e.g. use of ipilimumab and nivolumab in advanced solid tumors, and brentuximab vedotin, or nivolumab for Hodgkin lymphoma.

- Development and assessment of new approaches for the front-line treatment of AIDS lymphoma: e.g. ibrutinib and R-DA-EPOCH; vorinostat and R-DA-EPOCH.

- Investigated treatments with novel mechanisms of action for KS (e.g. bortezomib, lenalidomide, sEphB4-HAS).

- Conducted KS international trials that defined standard of care in limited resource settings.
AMC Accomplishments (Cont.)

- Provided evidence for efficacy of the HPV vaccine in preventing HSIL among HIV-infected individuals naïve to the vaccine type.
- Assessment of a therapeutic vaccine directed to E6 and E7 HPV 16/18 genes using electroporation.
- Established a network of clinicians trained in high resolution anoscopy and treating anal HSIL. These treatments and platform are being used for the conduct of the ANCHOR Study.
- Completed a feasibility study in Africa of the safety, toxicity, and compliance of concomitant chemotherapy and radiotherapy for HIV-associated locally-advanced cervical cancer.
- Examined pharmacokinetic interactions of antiretroviral agents and novel anti-cancer agents (e.g. sunitinib, cabozentnib) in HIV subjects with solid tumors.
AMC Practice-Changing Accomplishments

- Established the standards for chemotherapy in aggressive CD20+ AIDS-related lymphomas, including use of combination anti-retroviral therapy (cART) with rituximab-CHOP;

- Helped establish treatment standard for drug-resistant severe Kaposi Sarcoma (paclitaxel) and assessed the relative merits of the 2 most efficacious drugs (paclitaxel vs. liposomal doxorubicin);

- Established infrared coagulation as the leading method of treatment of anal high grade squamous intraepithelial lesions (HSIL);

- Established the superiority of paclitaxel over etoposide or bleomycin/vincristine (the previous standard of care) for treating KS in Africa;

- Demonstrated that HIV-associated aggressive lymphoma patients who meet standard eligibility criteria for autologous or allogeneic stem cell transplant respond well to transplantation – as a result, this is now standard of care;

- Development and initiation of the ANCHOR trial (N=5058), which will likely define standard for anal cancer screening. The study is more than half accrued.
Current Scientific Needs

▪ Cancer continues to be among the leading causes of death among HIV-infected patients in the U.S., and in some studies is the leading cause.
▪ The standards of care for progressive KS and NHL have not been optimized.
▪ Non-AIDS-defining cancers (especially lung, liver, head & neck, anal) are increasing in areas where cART is widely available.
▪ The impact of AIDS and cART on anti-cancer chemotherapy, on toxicity profiles, and on response to treatment are not sufficiently studied.
▪ Need to optimize treatment in resource-limited countries.
AMC Mid-Cycle Evaluation

- Uniquely positioned to carry forward the NCI clinical agenda in HIV-associated malignancies;
- Well-elaborated succession plan;
- Expanded their international agenda and had effected the development and capacity building of their international sites;
- Promoted young investigators in leadership roles in AMC activities;
- Increased engagement of community representatives in AMC activities;
- Outstanding record of the disease Working Groups to complete ongoing trials and to develop new trials, and the renewed focus in cutting-edge immunotherapy-based clinical trials.
Review - Recommendations

▪ To give more attention to increase accrual;
▪ To consider development of cancer prevention intervention trials and strategies, other than ANCHOR trial;
▪ To expand to areas of cancer survivorship;
▪ To expand genomic studies in domestic and international trials; and
▪ To develop a structured strategic plan relative to prioritization of research-related areas of emphasis.
AMC Plans for Increasing Domestic Enrollment

- Open new sites in geographical areas with high HIV disease burden (including ANCHOR Sites).
- Streamline the protocol development process and make the protocols more “user friendly”.
- Plan to restructure the current domestic Clinical Sites compensation model to be more incentive-dependent.
- Recruitment of an Executive Officer to oversee the protocol development. Work closely with the protocol chairs and operations to facilitate the process.
Proposed AMC Budget Year One

Two components: AMC base $9,975,000
ANCHOR $14,025,000
Total: $24,000,000

Current Year 5 Budget: AMC base $9,175,000
ANCHOR $14,025,000
Total: $23,200,000

Difference: $800,000
Rationale:
- Increased costs related to foreign trials
  - Costs for drug sourcing, storage, distribution
  - Operations center, site monitoring, clinical trials insurance
- Increased costs related to moving to central IRB
Total AMC Budget

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC Base</td>
<td>9,975,000</td>
<td>10,274,250</td>
<td>10,582,478</td>
<td>10,899,952</td>
<td>11,226,952</td>
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<tr>
<td>ANCHOR</td>
<td>14,025,000</td>
<td>14,025,000</td>
<td>11,375,000</td>
<td>10,643,210</td>
<td>10,703,681</td>
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<tr>
<td>Total</td>
<td>24,000,000</td>
<td>24,299,250</td>
<td>21,957,478</td>
<td>21,543,162</td>
<td>21,930,633</td>
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</tbody>
</table>

Total cost for 5 years: $113,730,523

Source of Funds: NCI AIDS funds, including a $5.6 million yearly increase to AIDS base from the OAR for ANCHOR
AMC Patient Costs

Core structure + patient care $16,655,000
Cost per patient $12,000

Minimum 1400 patients
25 domestic sites + 7-9 non-AMC ANCHOR Sites
11 International sites in SSA & Latin America
New AMC Group Chair

• Dr. Joseph Sparano, is the next AMC Group Chair, from Montefiore Medical Center, Bronx, NY.

• Vice Chair of the AMC since 2009

• Vice Chair, ECOG-ACRIN Research Group, May, 2013-present

• Served as the Group Chair of the New York Cancer Consortium (2005-2011)

• Well recognized nationally and internationally
Some Areas Where the AMC Can Make Unique Contributions

- Only group with expertise and focus on HIV/AIDS-associated cancers.
- Poised to evaluate immunotherapy approaches for malignancies in HIV-infected patients.
- Conducts preventive and therapeutic trials for Kaposi sarcoma and HPV-related precancers and cancers in HIV patients.
- Only NCI-supported clinical trial network to conduct interventional trials for HIV malignancies in LMIC.
- Investigation of pharmacokinetic interactions between novel anticancer drugs and antiretroviral drugs - will facilitate the inclusion of HIV patients on larger CTEP studies.
- Has established a network of clinicians trained in high resolution anoscopy and treating anal HSIL. In addition to ANCHOR, this resource can be used for other key studies in this area.
Questions
Adults and children estimated to be living with HIV, 2017

- 2.1 million new cases/year
- ~50% women
- ~90% in low- and middle-income countries (LMICs)
- 1.1 Million deaths/year

Total: 36.9 (31.1 – 43.9) million
Incidence of HIV Infection in the US

Rates of Persons Living with Diagnosed HIV, by County, 2014 per 100,000 person-years
A Brief History of the AMC

- Prior to 1995 AIDS-related cancer trials were the charge of the Oncology Committee of the NIAID-sponsored AIDS Clinical Trials Group (ACTG).

- In 1994-5, AIDS-related cancer trials were transferred to the NCI. The AMC was created as a group of 15 semi-autonomous clinical trial sites with multiple PIs and three scientific working groups - KS, NHL, HPV.

- In 2006, the AMC was restructured to a cooperative group structure with a single PI.

- AMC is now comprised of 25 domestic clinical sites and 11 international sites and a network laboratory.
AMC Patient Accrual

ANCHOR Cumulative Accrual

- Randomized
- Screened

Non-ANCHOR AMC Accrual
- Domestic
- International
- QOL, Lab & Survey
Some Aspects of the AMC that Affect Cost and Enrollment

- Simultaneous treatment of two life threatening diseases
- Majority of patients are indigent, lack insurance and are from socioeconomically disadvantaged areas both domestically and internationally
- Rarity of events requires a wider network of U.S. sites to enroll meaningful numbers
- Patient numbers prevent economy of scale
- Diversity of cancers require wider expertise
- Due to the rarity of the events, there is no vested interest from Pharma, and the Government is just about the only viable source of support.
International studies are critical but require capacity building as the regions with heavy disease burden have never been traditional NCI partners.

Dedicated full time personnel are needed for international sites.

The AMC pays for costs of drug procurement, storage and distribution for international studies.

Monitoring and site inspection for international sites.

The grant pays for standard of care costs for international studies including pathology and imaging.

The AMC conducts its own study monitoring, auditing, and performance evaluation through a subcontract paid by the grant.
Cancer is the Most Frequent Cause of Death in HIV-Infected Patients in the HAART Era

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>2000</th>
<th>2005</th>
<th>2010</th>
</tr>
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<tbody>
<tr>
<td>Cancer (all)</td>
<td>29%</td>
<td>33%</td>
<td>36%</td>
</tr>
<tr>
<td>Cancer – AIDS Defining</td>
<td>16%</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Cancer – non-AIDS defining</td>
<td>13%</td>
<td>21%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Mortalité 2000, 2005, and 2010 Studies:
C. Lewden et al., *Cancer* 2014; *CID* 2009, and M. Phillippe et al., *AIDS* 2014.
Collaborations with other Groups

- **ACTG**: AIDS KS protocols; HPV vaccine studies.
- **BMT-CTN**: Development of autologous and allogeneic stem cell transplant protocols.
- **CCR/Cooperative Groups**: Dose adjusted EPOCH+/- Rituximab in adults with Burkitt lymphoma, plasmablastic lymphoma and c-Myc positive DLBCL.
- **ACSR**: Contributing tumor and other specimens and working with development of international pathology capability in resource limited countries.
- **ATN (Adolescent HIV-positive Treatment Network)**: Protective effects of the HPV quadrivalent vaccine in young HIV-positive Males who have sex with males.