Clinical Trial Design Considerations: Leveraging Cancer Immunotherapy Studies to Evaluate HIV Endpoints

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Cancer in People with HIV

US Prevalence Diagnosed HIV by Age 2008 - 2014

US: ~7760 cases of cancer in PLWHIV in 2010

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Standard Incidence Ratio (HIV only / AIDS)</th>
<th>Estimated % of all cancers in HIV 2010</th>
<th>Estimated US Cases in HIV+ 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIDS-Defining Malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>10-15 / 30-60</td>
<td>19%</td>
<td>1493</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>250 / 1,020</td>
<td>2%</td>
<td>157</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>1,300 / 3,640</td>
<td>12%</td>
<td>910</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>2.9 / 5.3</td>
<td>1%</td>
<td>80</td>
</tr>
<tr>
<td><strong>Non-AIDS Defining Malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2.6 / 2.6</td>
<td>11%</td>
<td>840</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>9.2 / 20</td>
<td>10%</td>
<td>760</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2.7 / 3.3</td>
<td>5%</td>
<td>390</td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td>5.6 / 14</td>
<td>4%</td>
<td>320</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>1.7 / 2.1</td>
<td>4%</td>
<td>280</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>68%</td>
<td>5230</td>
</tr>
</tbody>
</table>

Adapted from: Left, CDC Surveillance Data
Biology of Cancer in the Setting of HIV

**Immune Dysregulation**
- CD4+ Deficits
- Chronic Immune Activation

**Chronic Viral Infections**
- EBV, KSHV
- High Risk HPV
- HBV, HCV
- Merkel Cell Polyomavirus

**Smoking**
- DNA adducts/mutations
- Epigenetic changes
- Inflammation

**Other Risk Factors**

**Chronic Viral Infections**

**Immune Dysregulation**
Increasing Inclusion of Participants with HIV In Cancer Studies

- Most oncology studies of novel agents exclude people with HIV
- Delay of experience of novel agents in this patient population
  - Phase I – Approval: Median 6.8 years (2.3, 19.7)
  - NDA Study to approval: Median 3.9 years (1, 7.6)
  - Phase I to HIV Specific Study: Median 6.3 years (3.5, 11.7)
- U.S Food & Drug Administration, American Society of Cancer Research, and Friends of Cancer Research have identified modernizing eligibility criteria to allow for appropriate inclusion of HIV-infected participants as important for goal for accelerating drug development
- Increased education and community Involvement is required for implementation of recommendations

Cancer Immunotherapy Trials Network (CITN)-12: Study Design

- Multicenter study to evaluate safety of pembrolizumab, a humanized monoclonal antibody targeting PD-1 in patients with HIV and relapsed/refractory cancers across a range of CD4\(^+\) counts
- 3 Cohorts
  - 100-199 CD4\(^+\) T cells/\(\mu\)L
  - 200-350 CD4\(^+\) T cells/\(\mu\)L
  - >350 CD4\(^+\) T cells/\(\mu\)L
- Pembrolizumab 200 mg IV every 3 weeks with concurrent ART
- Treat continued if therapeutic benefit for up to 2 years
- Evaluate HIV Cure Biomarkers
Leveraging CITN-12 for HIV Cure Endpoints

**Latency Reversal**
- ART
- Latency Reversal
  - Latently Infected CD4+ T-cell

**HIV-Specific Immunity**
- Pembrolizumab
- HIV Specific CD8+ T-cell

**Effect on HIV Reservoir**
- HIV DNA
- HIV RNA
- HIV
- PD1
- Pembrolizumab
## Schema for CITN-12 HIV Correlatives

### Cycle 1
- **Latency Reversal** (Lewin, Maldarelli)
- **Mass Cytometry** (Lewin)
- **mRNA** (Sekaly)
- **TILDA** (Chomont)
- **Anti-HIV** (Connors)
- **Flow Cytometry** (Fling)

### Cycle 2
- **Latency Reversal**
- **Mass Cytometry**
- **mRNA**
- **TILDA**
- **Anti-HIV**
- **Flow Cytometry**

### Cycle 3
- **Latency Reversal**
- **Mass Cytometry**
- **mRNA**
- **TILDA**
- **Anti-HIV**
- **Flow Cytometry**

### Cycle 4
- **Latency Reversal**
- **Mass Cytometry**
- **mRNA**
- **TILDA**
- **Anti-HIV**
- **Flow Cytometry**

### Cycle 6 or End
- **Latency Reversal**
- **Mass Cytometry**
- **mRNA**
- **TILDA**
- **Anti-HIV**
- **Flow Cytometry**

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**Notes:**
- Latency Reversal: Day 1 and Day 2
- Mass Cytometry: Day 8
- mRNA: Day 1 and Day 2
- TILDA: Day 1
- Anti-HIV: Day 1
- Flow Cytometry: Day 1

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**References:**
- Lewin, Maldarelli
- Sekaly
- Chomont
- Connors
- Fling
HIV & Cancer: Study Design Considerations

- Evaluation of safety in participants with HIV is feasible
- Therapeutic index may allow for more prolonged dosing than HIV specific studies

For Approved Agents
- HIV & Cancer Specific Studies
- Cohort Studies Across Agents in patient with HIV and Cancer
- HIV Specific Studies

Consider Patient Heterogeneity