PEMBROLIZUMAB INDUCES HIV LATENCY REVERSAL IN HIV+ INDIVIDUALS ON ART WITH CANCER

Thomas S Uldrick, Steven P Fling, Scott V Adams, Ajantha Rhodes, Priscila H Gonçalves, Nicolas Chomont, Robert J Gorelick, Jeffrey D Lifson, Robert Yarchoan, Martin A Cheever, Frank Maldarelli, Steven G Deeks, Sharon R Lewin and the CITN12 and DARE Study Teams

Thomas S Uldrick, MD MS
Associate Member, VIDD and CRD
Fred Hutchinson Cancer Research Center
Associate Professor of Medicine, Division of Oncology
University of Washington

Conference on Retroviruses and Opportunistic Infections
March 5, 2019
Seattle, WA
Background: PD-1

- PD-1 is an inhibitory checkpoint molecule on T-cells that inhibits immune responses against cancers and viral infections.
- Monoclonal antibodies targeting PD-1 or PD-L1 are approved for a growing number of cancer indications.

Checkpoin Proteins Regulate T-cell Function

HIV infected CD4\(^+\) T-cells Enriched for PD-1

- PD-1 upregulated in HIV
- HIV DNA and unspliced RNA are enriched in PD-1+ cells in blood and lymph nodes in HIV+ individuals on ART
- We hypothesized anti-PD-1 would lead to latency reversal \textit{in vivo}

Cancer Immunotherapy Trials Network-12 (CITN-12)

- CITN-12 is a multicenter phase I study evaluating the monoclonal antibody, pembrolizumab, in participants with HIV and advanced cancers
- Participants on ART for ≥ 4 weeks with suppressed HIV
- Safety evaluated across a range of CD4 counts
  - Cohort 1: 100-199 CD4⁺ T cells/μL
  - Cohort 2: 200-350 CD4⁺ T cells/μL
  - Cohort 3: >350 CD4⁺ T cells/μL

Cockerham. *AIDS*, 2014
Measuring HIV Latency Reversal *in vivo*
Leveraging CITN-12 to Evaluate HIV Latency Reversal

Blood Sampling Schema

- Cell associated HIV DNA measured in peripheral CD4+ T-cells
- Cell associated unspliced HIV gag RNA measured in peripheral CD4+ T-cells
- Plasma HIV RNA measured in blood using PCR for HIV gag

* on day of administration: before and 2 hours after pembrolizumab

Statistical Analysis

- Kinetics of HIV plasma RNA, intracellular usRNA, usDNA, and usRNA/vDNA were evaluated by negative binomial regression.
- Pairwise correlation between assays were compared by Pearson’s correlation coefficient.
## Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Cohort 1 CD4+ 100-199 /µL</th>
<th>Cohort 2 CD4+ 200-350 /µL</th>
<th>Cohort 3 CD4+ &gt;350 /µL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>32</td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><em><em>Age (median, IQR</em>)</em>*</td>
<td>57 (49, 62)</td>
<td>53.5 (46, 61)</td>
<td>54.5 (49, 61)</td>
<td>58 (52, 64)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>29</td>
<td>7</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Black / African American</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Other / Unknown</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>HIV viral load (copies/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetected or &lt;20 copies/ml</td>
<td>28</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>≥20 copies/ml</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Baseline CD4 Count (median, IQR)</strong></td>
<td>272 (204, 477)</td>
<td>152 (119, 164)</td>
<td>239 (216, 289)</td>
<td>516 (425, 649)</td>
</tr>
<tr>
<td><strong>Baseline CD4/CD8 Ratio (median, IQR)</strong></td>
<td>0.5 (0.4, 0.9)</td>
<td>0.5 (0.4, 0.5)</td>
<td>0.4 (0.3, 0.7)</td>
<td>0.9 (0.5, 1.5)</td>
</tr>
</tbody>
</table>

*IQR: Intra-quartile range (25th and 75th percentiles)*
## Tumors

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 CD4+ 100-199 /µL</th>
<th>Cohort 2 CD4+ 200-350 /µL</th>
<th>Cohort 3 CD4+&gt;350 /µL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>12</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td><strong>AIDS-Defining</strong></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>DLBCL</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Non-AIDS Defining</strong></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma Skin</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tonsil</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adenocystic carcinoma</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prostate</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Baseline HIV Measures

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV plasma RNA (copies/ml)</td>
<td>1</td>
<td>(0.17 – 2.65)</td>
</tr>
<tr>
<td>HIV usRNA (copies/10^6 CD4^+ cells)</td>
<td>43</td>
<td>(15-133)</td>
</tr>
<tr>
<td>HIV vDNA (copies/10^6 CD4^+ cells)</td>
<td>76</td>
<td>(55 - 149)</td>
</tr>
</tbody>
</table>

- No correlation between assays (all P>0.05)
Waterfall Plots of Fold Change HIV RNA

Unspliced Intracellular HIV RNA
- Day 2
- Day 8
- Day 22

Plasma HIV RNA
- Day 2
- Day 8
- Day 22
HIV RNA After Pembrolizumab

Unspliced Intracellular HIV RNA

Plasma HIV RNA

P=0.008

P=0.11
Fold Change HIV DNA and usRNA/DNA

Intracellular HIV DNA

Day 2 | Day 8 | Day 22

Intracellular HIV usRNA/DNA

Day 2 | Day 8 | Day 22
HIV DNA and usRNA/DNA after Pembrolizumab

**Intracellular HIV DNA**

**Intracellular unspliced RNA / DNA**

- **Pembrolizumab**
  - **P=0.02**
  - **P=0.004**
Conclusions

- In CITN-12, pembrolizumab led to transient increase in HIV transcription in CD4\(^+\) T-cells \textit{in vivo} in individuals on ART, consistent with latency reversal
- Early decrease in HIV DNA was observed after pembrolizumab
- Evaluation of the longer term effects pembrolizumab on HIV persistence and HIV specific immunity are ongoing
- Further evaluation of monoclonal antibodies against PD-1 or PD-L1 as a strategy for HIV cure is warranted
Acknowledgements

CITN
Mac Cheever
Holbrook Kohrt
Steve Fling
Alisia Claeyse
Lisa Lundgren
Betty Bertoli
Judy Kaiser
Andreaanne Lacroix

Fred Hutch
Scott Adams

DARE
Doherty Institute,
University of Melbourne
Sharon Lewin
Ajantha Rhodes
UCSF
Steve Deeks
University of Montreal
Nicholas Chomant
Case Western
Rafick Sekaly

NCI–Frederick
Frank Maldarelli
Jeff Lifson
Rob Gorelick

CTEP
Elad Sharon
Sherry Ansher
Richard Little
William Merritt

CITN Investigators:
Louisiana State Univ.
Chris Parsons
NCI – HIV & AIDS
Malignancy Branch
Bob Yarchoan
Priscila Gonçalves
Kate Lurain
Matt Lindsley
Ramya Ramaswami
NYU
Maher Abdul-Hay
Steve Lee
Roswell Park
Marc Ernstoff
UCSF
Jackie Wang
Lawrence Fong
Yale
Brinda Emu
Mario Sznol
CURES START HERE
THANK YOU