Lung Cancer Treatment

HIV, HCV and Cancer
Virus and Other Infection-associated Cancers
Research Program Retreat
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• Research grant from AstraZeneca
Lung cancer stage distribution and survival

Stage Distribution %

<table>
<thead>
<tr>
<th>Stage</th>
<th>2004-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>15 16 13</td>
</tr>
<tr>
<td>Regional</td>
<td>22 22 22</td>
</tr>
<tr>
<td>Distant</td>
<td>57 56 61</td>
</tr>
</tbody>
</table>

5 Year Survival %

<table>
<thead>
<tr>
<th>Stage</th>
<th>2004-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>54 55 46</td>
</tr>
<tr>
<td>Regional</td>
<td>27 27 24</td>
</tr>
<tr>
<td>Distant</td>
<td>4 4 4</td>
</tr>
<tr>
<td>All Stages</td>
<td>17 17 14</td>
</tr>
</tbody>
</table>

All Races, White, African American
Advanced Non-Small Cell Lung Cancer

- Chemotherapy improves survival for patients with advanced NSCLC
- Histology matters when choosing chemotherapy
- Median survival is ~1 year with chemotherapy alone
- Advances including adding bevacizumab or using maintenance chemotherapy have improved median survival by a few months
Overview of managing patients with HIV and lung cancer

• There are no specific recommendations in managing lung cancer in HIV-infected patients

• Caution with certain chemotherapies and targeted therapies – although very little clinical data exists

• Most data (although still very little) is with immunotherapy
<table>
<thead>
<tr>
<th>Chemotherapy or targeted therapy</th>
<th>Route of metabolism</th>
<th>Interaction</th>
<th>Effect on HIV therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKI</td>
<td>CYP3A4 inhibitor</td>
<td>Increased TKI toxicity $^{24,36}$</td>
<td>Dose reduction of ritonavir needed $^{65-68}$</td>
<td>Possible toxicities associated with higher doses of TKIs $^{65-68}$</td>
</tr>
<tr>
<td>TKI</td>
<td>CYP3A4 inhibitor</td>
<td>Reduced efficacy of TKIs when using with efavirenz (NNRTIs) $^{65-68}$</td>
<td>Potential less efficacy of HIV therapy $^{69}$</td>
<td>Unknown</td>
</tr>
<tr>
<td>Taxanes $^a$</td>
<td>CYP2C8, CYP3A4</td>
<td>May increase taxane concentration and increase myelosuppression and peripheral neuropathy $^{65-67}$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Antimetabolites $^b$ cisplatin, mito-mycin, and rituximab</td>
<td>Independent of CYP3A4 oxidation</td>
<td>Drug-drug interactions with PIs and NNRTIs unlikely $^{61,69}$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>VEGF inhibitors</td>
<td>CYP3A, CYP2B6</td>
<td>Potential interaction with abacavir, lamivudine, nevirapine $^{61,69}$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TKI, tyrosine kinase inhibitor; VEGF, vascular epithelial growth factor.

$^a$paclitaxel and docetaxel. $^b$methotrexate, fluorouridine, capecitabine, cytarabine.
Personalized Medicine in Lung Adenocarcinoma

n = 205
Median survival 1.5 vs 2.7 years

Targeted Therapy for Lung Adenocarcinoma

EGFR Sensitizing
- Gefitinib
- Erlotinib
- Afatinib
- Osimertinib
- Necitumumab
- Rociletinib

ALK
- Crizotinib
- Cabozantinib

MET
- Crizotinib
- Cabozantinib

HER2
- Trastuzumab emtansine
- Afatinib
- Dacomitinib

ROS1
- Crizotinib
- Cabozantinib
- Lorlatinib
- DS-6051b

BRAF
- Vemurafenib
- Dabrafenib

RET
- Cabozantinib
- Alectinib
- Apatinib
- Vandetanib
- Ponatinib
- Lenvatinib

NTRK1
- Entrectinib
- LOXO-101
- Cabozantinib
- DS-6051b

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

PIK3CA
- LY3023414
- PQR 309

Key
1. Phase I
2. Phase II
3. Phase III
4. Approved

Mutation status in HIV+ lung cancer patients

- Frequency of EGFR and KRAS mutations are similar between HIV+ and HIV- patients with lung adenocarcinoma
- Clinical outcomes did not appear to differ
- Caveat: A minority of these patients had EGFR (19 patients total) and no other actionable mutations were identified
Programmed Death Receptor 1 (PD1)/ B7-H1 Pathway

PD/1-PD-L1 inhibitors

- Anti-PD-1: Nivolumab, Pembrolizumab
- Anti-PD-L1: Atezolizumab, Durvalumab
Nivolumab in second-line treatment of advanced squamous NSCLC

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0–1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis
  \[ N = 272 \]

Randomize 1:1

Nivolumab
\[ 3 \text{ mg/kg IV Q2W until PD or unacceptable toxicity} \]
\[ n = 135 \]

Docetaxel
\[ 75 \text{ mg/m}^2 \text{ IV Q3W until PD or unacceptable toxicity} \]
\[ n = 137 \]

- Primary Endpoint:
  - OS

- Additional Endpoints:
  - Investigator-assessed ORR
  - Investigator-assessed PFS
  - Correlation between PD-L1 expression and efficacy
  - Safety
  - Quality of life (LCSS)

- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was \( P < 0.03 \)
Overall Survival with Nivolumab vs Docetaxel

Key End Points
Primary: PFS (RECIST v1.1 per blinded, independent central review)
Secondary: OS, ORR, safety
Exploratory: DOR

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.
First-Line Pembrolizumab versus Chemotherapy

Progression-Free Survival

Overall Survival

Hazard ratio for disease progression or death, 0.50 (95% CI, 0.37–0.68) 
P<0.001

Hazard ratio for death, 0.60 (95% CI, 0.41–0.89) 
P=0.005

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
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<td>Month</td>
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<tr>
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<td>104</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
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<td>70</td>
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<tr>
<td>9</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
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<td>9</td>
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<tr>
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<td>3</td>
<td>1</td>
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<tr>
<td>18</td>
<td>1</td>
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<td>2</td>
<td>1</td>
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<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Long-term outcomes with immunotherapy

Three Anti-PD-(L)1 Drugs for Advanced Lung Cancer – and one for Stage III Lung Cancer!

Advanced/Stage IV Lung Cancer:

• Pembrolizumab – Used for 1st or 2nd line treatment if tumor is PD-L1 +, or in combination with chemotherapy in 1st line
• Nivolumab – Used for 2nd line treatment after progression on chemotherapy
• Atezolizumab – Used for 2nd line treatment after progression on chemotherapy, or in combination with chemotherapy and VEFR inhibitor in 1st line

Locally Advanced/Stage III Lung Cancer:

• Durvalumab – Used after chemoradiation
Immunotherapy Toxicity

- Immune checkpoint inhibitors promote T-cell activity
- Activation of the immune system cannot be confined to antitumor effects
- Common Side Effects: fatigue, malaise, anorexia
- Immune system activation can lead to unrestrained T-cells attack on healthy tissue = auto-immunity
Patterns of IrAE Toxicity

**Neurologic-Muscular**
- Neuropathy
- Meningitis
- Guillane-Barre Syndrome
- Myalgias, Arthralgias
- Sarcoidosis

**Endocrine**
- Thyroiditis
- Hypothyroidism
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Adrenal Insufficiency

**Pulmonary**
- Pneumonitis
- Respiratory failure

**Gastrointestinal**
- Nausea, Emesis
- Diarrhea, Colitis
- Perforation;
- Pancreatitis

**Hematologic**
- Red Cell Aplasia
- Pancytopenia
- Autoimmune neutropenia

**Ocular**
- Iritis
- Uveitis
- Conjunctivitis

**Cardiac**
- Pericarditis
- Myocarditis
- Vasculitis

**Dermatologic**
- Mucositis
- Rash, Vitiligo

**Hepatic**
- Transaminitis
- Hepatitis

**Renal**
- Nephritis
- Renal Insufficiency

**Patterns of IrAE Toxicty**
Recognizing and managing immunotherapy toxicity

- Clinical suspicion is required in someone who has ever been on immunotherapy – any new symptoms should be considered auto-immune until proven otherwise.

- Endocrinopathies are usually treated with hormone replacement.

- Other toxicities may require steroids, especially if severe.

- High dose steroids or other immune suppressants are sometimes required in refractory cases.

- Taper steroids slowly to avoid relapse.
Pembrolizumab in patients with HIV and NSCLC

- Retrospective study of 7 patients treated with HIV and advanced lung cancer treated with pembrolizumab
- 3 partial responses, 2 stable disease, 2 progressed
- Grade 1-2 toxicities only
- 1 patient with decrease in CD4 count (423 to 307)
- 1 patient with increase in viral load (undetectable to 42)
- 1 patient with transient increase in viral load (undetectable to 115 to <30)

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| Case | Age | Sex | History of Tobacco Use | Histology | Driver Mutation | PD-L1 | Line/Drug BORa | Length of Time on PD-1 Therapy | Toxicities | ART Regimen | Baseline CD4 | Baseline HIV VL | Last Known CD4 | Last Known HIV VL | Concurrent Illnesses |
|------|-----|-----|------------------------|-----------|-----------------|-------|---------------|-------------------------------|------------|-------------|---------------|----------------|----------------|----------------|-------------------|----------------------|
| 1    | 53  | M   | 30 pk-yr               | Adeno     | KRAS G12C       | 90%   | 1stPembro    | SD                            | None       | Noc         | 423/μL        | 12,589         | 307/μL         | <20            | Kaposi sarcoma, latent syphilis |
| 2    | 52  | M   | 45 pk-yr               | Adeno     | None detected   | N/A   | 2ndNivo     | PD                            | Grade 1    | Abacavir/lamivudine, abacavir/dolutegravir/tenofovir disoproxil fumarate | 57/μL       | <20         | N/A           | <20            | None          | Chronic HCV genotype 1a |
| 3    | 59  | M   | 7.5 pk-yr              | Adeno     | KRAS G12C       | 90%   | 1stPembro    | PR                           | Grade 2    | Emtricitabine/tenofovir disoproxil fumarate, ritonavir and atazanavir | 1147/μL     | <20         | 1229/μL       | <20            | None          | None                      |
| 4    | 52  | M   | 23 pk-yr               | Adeno     | None detected   | N/A   | 2ndPembro   | PR                           | Grade 1    | Raltegravir, etravirine and darunavir | 435/μL      | <20         | 440/μL        | <20            | None          | None                      |
| 5    | 43  | M   | 30 pk-yr               | Adeno     | None detected   | N/A   | 3rdNivo     | SD                           | None       | Emtricitabine/tenofovir disoproxil fumarate and doravir | 233/μL       | <20         | 233/μL        | <20            | None          | None                      |
| 6    | 51  | M   | 30 pk-yr               | Adeno     | None detected   | N/A   | 1stPembro   | PR                           | Grade 2    | Emtricitabine/tenofovir alafenamide fumarate | 297/μL       | <20         | 305/μL        | <30g            | Chronic HBV | None                      |
| 7    | 47  | F   | 30 pk-yr               | Adeno     | KRAS G12V       | 20%   | 2ndPembro   | PD                           | None       | Yes         | Emtricitabine/tenofovir alafenamide fumarate and doravir | 36/μL        | <20         | N/A           | <20            | None          | None                      |
Pembrolizumab in patients with HIV and NSCLC

Case 3: Baseline vs. Pembrolizumab at 6 weeks

Case 6: Baseline vs. Pembrolizumab at 9 weeks
Immunotherapy in patients with HIV and cancer – efficacy and safety

Response Rate with immunotherapy

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>No. of Patients With Known Response</th>
<th>Patients With Previous Systemic Treatment, No. (%)</th>
<th>Response (No. of Patients)</th>
<th>ORR, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>23</td>
<td>19 (83)</td>
<td>CR (1), PR (6), stable disease (8), PD (8)</td>
<td>30</td>
</tr>
<tr>
<td>Melanoma</td>
<td>11</td>
<td>5 (45)</td>
<td>CR (1), PR (2), PD (8)</td>
<td>27</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>8</td>
<td>Unknownb</td>
<td>CR (1), PR (4), PD (3)</td>
<td>63</td>
</tr>
<tr>
<td>Classic Hodgkin lymphoma</td>
<td>2</td>
<td>2 (100)</td>
<td>CR (1), PR (1)</td>
<td>NA</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>1</td>
<td>1 (100)</td>
<td>CR (1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Summary of trials of immunotherapies for advanced cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Study Type</th>
<th>Tumor Type (No.)</th>
<th>ICI Therapy (No.)</th>
<th>Adverse Events (No.)</th>
<th>HIV Load</th>
<th>CD4 Cell Count</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslows-Garcia et al.2019</td>
<td>7</td>
<td>Retrospective case series</td>
<td>NSCLC (7)</td>
<td>Pembrolizumab (5), nivolumab (2)</td>
<td>Grade 1 arthralgia (1), grade 1 fatigue (1), grade 1 headache (1), grade 1 chest pain (1), grade 2 arthralgia (2)</td>
<td>Remained suppressedd</td>
<td>Stablef</td>
<td>Stable disease (2), PR (3), PD (2)</td>
</tr>
<tr>
<td>Samri et al.2017</td>
<td>12</td>
<td>Retrospective case series</td>
<td>NSCLC (12)</td>
<td>Nivolumab (12)</td>
<td>Grade 1 hepatitis (1), hyperesinophilia (1)</td>
<td>Remained suppressedd</td>
<td>Stable</td>
<td>Stable disease (4), PR (3), PD (5)</td>
</tr>
<tr>
<td>Heppt et al.17 2017</td>
<td>10</td>
<td>Retrospective case series</td>
<td>Melanoma (9), Merkel cell carcinoma (1)</td>
<td>Nivolumab (1), pembrolizumab (3), ipilimumab (1), ipilimumab plus nivolumab (3)</td>
<td>Grade 1 pneumonitis (1), grade 1 fatigue (1)</td>
<td>Remained suppressedd</td>
<td>Stable</td>
<td>PR (1), CR (2), PD (6), NR (1)</td>
</tr>
<tr>
<td>Park et al.27 2018</td>
<td>8</td>
<td>Retrospective case series</td>
<td>HNSCC (3), melanoma (2), cutaneous SCC (2), SCC (1)</td>
<td>Anti-PD-1 (7), ipilimumab plus nivolumab (1)</td>
<td>Anti-PD-1, grade 1 fatigue (4), grade 1 rash (2); ipilimumab plus nivolumab, grade 3 hepatitis (1)</td>
<td>Remained suppressed</td>
<td>Upward trendg</td>
<td>PR (4), CR (1), PD (2), NR (1)</td>
</tr>
<tr>
<td>Galanina et al.28 2018</td>
<td>8</td>
<td>Retrospective case series</td>
<td>Kaposi sarcoma (8)</td>
<td>Nivolumab (8)</td>
<td>No grade 2 toxic effects reportedh</td>
<td>Remained suppressed</td>
<td>Upward trend mean increase by 80.5 (μl)</td>
<td>PR (4), CR (1), stable disease (3)</td>
</tr>
<tr>
<td>Uldrick.29 2017</td>
<td>21</td>
<td>Prospective clinical trial</td>
<td>Primary effusion lymphoma (2), Kaposi sarcoma (1), diffuse large B-cell lymphoma (1), anal cancer (5), head and neck (5), SCC (1), NSCLC (2), HCC (1), transitional cell carcinoma (1), pancreatic cancer (1), cholangiocarcinoma (1)</td>
<td>Pembrolizumab (21)</td>
<td>Most treatment-emergent AEs were grades 1-2 (93%), immune-related AEs, grade 1 hypothyroidism (2), grade 1 ALT increase (1), grade 1 joint stiffness (1), grade 1 pneumonitis (1), grade 2 pneumonitis (2), grade 2 hypothyroidism (4), grade 3 ALT increase (1)</td>
<td>Remained suppressed</td>
<td>Upward trend</td>
<td>NR</td>
</tr>
</tbody>
</table>
Ongoing trials of immunotherapy in patients with HIV and cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT Trial No.</th>
<th>ICI Drug(s) Tested</th>
<th>Phase</th>
<th>Sample Size</th>
<th>Primary End Point</th>
<th>Tumor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy by Nivolumab After Prior Chemotherapy for HIV+ Patients With Advanced Non-small Cell Lung Cancer (NSCLC): IFCT-CHIVA2 Phase Ila Trial</td>
<td>NCT03304093</td>
<td>Nivolumab</td>
<td>2</td>
<td>30</td>
<td>Disease control rate</td>
<td>NSCLC (stage IIIb or metastatic)</td>
</tr>
<tr>
<td>A Phase II Exploratory Study of Durvalumab (Medi4736) in HIV-1 Patients With Advanced Solid Tumors</td>
<td>NCT03094286</td>
<td>Durvalumab</td>
<td>2</td>
<td>20</td>
<td>No. of HIV-infected patients who receive durvalumab at least 4 mo</td>
<td>Solid</td>
</tr>
<tr>
<td>Phase I Study of MK-3475 (Pembrolizumab) in Patients With Human Immunodeficiency Virus (HIV) and Relapsed/Refractory or Disseminated Malignant Neoplasm</td>
<td>NCT02595866</td>
<td>Pembrolizumab</td>
<td>1</td>
<td>60</td>
<td>Frequency of observed AEs</td>
<td>Refractory/recurrent</td>
</tr>
<tr>
<td>A Phase I Study of Ipilimumab and Nivolumab in Advanced HIV-Associated Solid Tumors With Expansion Cohorts in HIV-Associated Solid Tumors and a Cohort of HIV-Associated Classical Hodgkin Lymphoma</td>
<td>NCT02408861</td>
<td>Ipilimumab plus nivolumab</td>
<td>1</td>
<td>84</td>
<td>MTD and DLT</td>
<td>Refractory/recurrent</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer.
T-Cell Immune Checkpoints as Targets for Immunotherapy

Activating receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory receptors
- CTLA-4
- PD-1
- B7-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic antibodies

T cell stimulation

Blocking antibodies
Future Questions

• What are the molecular drivers of lung cancer in HIV+ patients that may allow the use of targeted therapies?
  – EGFR, ALK, ROS1, etc

• What is the full spectrum of safety and efficacy signals with single-agent immunotherapies in HIV+ patients?

• What about combination immunotherapies?
  – Will certain combinations be more toxic? More efficacious?

• Should trials be designed specifically for this patient population, or should HIV+ patients be included on other trials – or both?