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Chelsea and Westminster Hospital, London
Cancer immunotherapy & HIV

Disclosures: None
Lessons for oncology from HIV

• Awareness and advocacy
• Activism
• Rational drug design
• Prescribing based on target drug resistance
Awareness and advocacy
Activism

ACT UP
AIDS Coalition to Unleash Power

ACT UP FOR LIFE!!

JOIN THE FIGHT FOR WOMEN’S SURVIVAL
CANCER RESEARCH UK
Rational drug design based on identified targets

Targets identified from HIV life cycle:
Reverse Transcriptase (NRTIs false bases)
Protease (Analogues of the phenylalanine-proline sequence)
Integrase

Crystallographic structure of RT (NNRTIs)
Drug discovery in oncology

Mustard Gas, an alkylating agent
First used as chemical warfare on 12 July 1917 at Ypres

\[ \text{Cl-S-Cl} \]
Rational drug design (CML)

The first $1$ billion drug

CML
Philadelphia chromosome

BCR-ABL gene in Philadelphia chromosome

BCR-ABL hybrid fusion peptide

BCR-ABL structure & imatinib
Prescribing based on target sensitivity in HIV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptibility</th>
<th>Fold change in IC\textsubscript{50} (Cut-off for normal susceptible range)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Trade name</td>
<td>Generic name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrovir®</td>
<td>Zidovudine</td>
<td></td>
<td>0.7</td>
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<tr>
<td>Epivir®</td>
<td>Lamivudine</td>
<td></td>
<td>0.2</td>
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<tr>
<td>Videx®</td>
<td>Didanosine</td>
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<td>0.3</td>
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<tr>
<td>Hiivid®</td>
<td>Zalcitabine</td>
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<td>0.6</td>
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<tr>
<td>Zerit®</td>
<td>Stavudine</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Ziagen®</td>
<td>Abacavir</td>
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<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viramune®</td>
<td>Nevirapine</td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Rescriptor®</td>
<td>Delavirdine</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>Sustiva®/Stocrin®</td>
<td>Efavirenz</td>
<td></td>
<td>7.3</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crixivan®</td>
<td>Indinavir</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonavir</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>Viracept®</td>
<td>Nelfinavir</td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>Imivirase®/Fortovase®</td>
<td>Saquinavir</td>
<td></td>
<td>7.0</td>
</tr>
<tr>
<td>A component of Kaletra®</td>
<td>Lopinavir</td>
<td></td>
<td>4.7</td>
</tr>
</tbody>
</table>

1. Sample within normal susceptible range
2. Fold change in IC\textsubscript{50} relative to reference virus (log\textsubscript{10})
Cancer treatments based on tumour biology “personalised medicine”

Breast cancer HER-2 expression is target for trastuzumab (Herceptin)

Non-small cell lung cancer mutations are targets for therapy
New lessons from oncology for HIV?

• Only HIV patient ever cured by haemato-oncologists....
• CART-T
• Immune checkpoint inhibition
CCR5 Δ32/Δ32 Allograft

Patient No More
Timothy Brown—a.k.a. “the Berlin Patient”—is the Man Who Once Had HIV.
Two HIV+ patients with MDS
CCR5 Δ32/Δ32 Allograft with RIC (reduced intensity conditioning)
Both non-chimeric (repopulated with host own haematopetic cells)
CAR-T therapy
Chimeric antigen receptor (CAR)

Combines target specificity chosen by monoclonal antibody with T cell effector function of T-cell receptor
Making autologous targeted CAR-T cells

FDA approval for anti-CD19 CAR-T therapy in ALL (Tisagenlecleucel) and NHL (Axicabtagene ciloleucel)
HIV reservoirs.. A target for CAR-T?
Anti-CD4 CAR-T *in vitro*

Planned trials in T-cell lymphoma
Immune checkpoint inhibition
Cellular immune response to cancer

**Antigen priming of T-cells**

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

**Effector phase**
Antigen priming of T-cells

1. Dendritic cells present antigens via the major histocompatibility complex (MHC) to T-cell receptor (TCR)

2. A second signal is delivered by B7: Bind CD28 activates T-cell
Bind CTLA-4 inhibits T-cell

CTLA-4 = Cytotoxic T-lymphocyte–associated antigen
Effector phase of adaptive immune system

Primed T-cell recognizes the cancer antigen and kills the tumour cell

This is stopped if PD-1 (on T-cell) binds PD-L1 on cancer cell
Checks and balance at the Immunological Synapse (negative feedback loops)

**Nivolumab**
**Pembrolizumab**

Inhibits effector phase

**Ipilimumab**
Blocks antigen priming
CTLA-4 therapy (to enhance T-cell priming) in refractory metastatic melanoma

- 2nd line, advanced melanoma
- \( n=676 \)

No therapy is approved beyond the first-line therapy for metastatic melanoma, and enrollment in clinical trials is the standard of care. No therapy has been shown in a phase 3, randomized, controlled trial to improve overall survival in patients with metastatic melanoma.6-9

Hodi et al., N Eng J Med (2010); 363:711-23
PD-1 antibody Pembrolizumab for relapsed NSCLC

**PD-L1 >50%**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>HR* (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>0.54 (0.38-0.77)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>0.50 (0.36-0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
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</tr>
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</table>

2 vs 10 mg/kg: HR 1.12, 95% CI 0.77-1.62

28% of ITT population

Herbst et al., Lancet (2016); 387: 1540-50

March 2016

July 2016
The principal PD-1/PD-L1 checkpoint inhibitors currently approved and in clinical development.

<table>
<thead>
<tr>
<th>Target</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
<th>Pidilizumab</th>
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<tbody>
<tr>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
<td>PD-L1</td>
<td>PD-1</td>
</tr>
<tr>
<td>Fully human IgG4</td>
<td>Humanised IgG4k</td>
<td>Humanised IgG1</td>
<td>Engineered IgG1k</td>
<td>Fully human IgG1</td>
<td>Humanised IgG1k</td>
<td></td>
</tr>
<tr>
<td>Stage of clinical development</td>
<td>FDA approved Phase III</td>
<td>FDA approved Phase III</td>
<td>FDA approved Phase III</td>
<td>FDA approved Phase III</td>
<td>FDA approved Phase III</td>
<td>FDA approved Phase II</td>
</tr>
</tbody>
</table>
Not without toxicity....

**Immune-Related AEs With Immunotherapy**

- **Skin**
  - Dermatitis exfoliative
  - Erythema multiforme
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Vitiligo
  - Alopecia

- **Eye**
  - Uveitis
  - Iritis

- **Endocrine**
  - Hypothyroidism
  - Hyperthyroidism
  - Adrenal insufficiency
  - Hypophysitis

- **Pulmonary**
  - Pneumonitis
  - Interstitial lung disease
  - Acute interstitial pneumonitis

- **Hepatic**
  - Hepatitis, autoimmune

- **Gastrointestinal**
  - Colitis
  - Enterocolitis
  - Necrotizing colitis
  - GI perforation

- **Renal**
  - Nephritis, autoimmune
  - Renal failure

- **Neurologic**
  - Autoimmune neuropathy
  - Demyelinating Polyneuropathy
  - Guillain-Barre
  - Myasthenia gravis-like syndrome

*If not vigilant, may result in more serious immune-related AEs*
What about HIV?
2009

Increased expression of PD-1 and PDL-1 on CD4 & CD8 cells in PLWH

Blocking PD-1 or PDL-1 with mouse mAbs increased anti-HIV gag specific responses
Do immune-checkpoints contribute to KS resistance to cART?

10 HIV+ MSM with progressive KS despite cART and plasma HIV VL<20 copies/mL
Immune-checkpoints contribute to KS resistance to cART

50% had KS spindle cells expressing PDL-1
KS expressing PDL-1 had denser tumour infiltrating CD8 lymphocytes
KS expressing PDL-1 had more infiltrating macrophages and these macrophages also expressed PDL-1
Programmed death ligand 1 (PD-L1) expression influences the immune-tolerogenic microenvironment in antiretroviral therapy-refractory Kaposi’s sarcoma: A pilot study

Salvinia Mletzko a, David J. Pinato a, Rebecca C. Robey a, Alessia Dalla Pria b, Peter Benson a, Nesrina Imami a, and Mark Bowen a

aImperial College London, London, UK; bChelsea and Westminster Hospital, London, UK; cLabCorp Clinical Trials, MN, USA

ABSTRACT

Upregulation of programmed death ligand 1 (PD-L1) is a mechanism of immune escape utilized by a
Nivolumab in HIV+ KS

8 HIV+ Patients
75% had CD4 count >200 and undetectable HIV viral load
Median follow up 3.5 months
Response rate 63% (5/8)
No rebound in viral load
PD-L1 & PD-L2 expression in NSCLC in PLWH

24 HIV-associated NSCLC
45% PD-L1+ & 33% PD-L2+

Same as matched HIV-ve NSCLC controls (p=0.12 & P=0.20)
Nivolumab (anti-PD-1) for relapsed lung cancer.

During treatment:

1. Plasma HIV RNA level increased from <20 copies/mL to 101 copies/mL (viral blip)
2. Expansion of HIV-specific CD8 cells
3. Total HIV DNA level fell from 369 to 30 copies/million cells
Decline in total HIV DNA on Nivolumab

- **HIV-DNA** (copies/10^6 cells)
- **HIV-RNA** (copies/ml)
- **CD4/mm^3**
- **CD8/mm^3**
- **IL-6*10 (pg/ml)**

**Plasma HIV RNA blip**

Nivolumab
But...previously no effects

Ipilimumab (anti-CTLA-4)
Transient rise in HIV RNA but no effect on HIV reservoirs

Nivolumab (anti PD-1)
Increase in HIV-specific T cells but no effect on HIV reservoirs

AIDS 2017; 31(7): 1048–1051.
CWH patients on Nivolumab (3months)
CWH patients on Nivolumab (3months)

Integrated HIV DNA

Copy/10^6 PBMCT

Before
After

Integrated HIV DNA

Copy/10^6 CD4

Before
After

MH1
NET
NSCLC

Centre for Immunology and Vaccinology

Imperial College London
Conclusions

New approaches in cancer immunotherapy
CAR-T & Immune checkpoint inhibitors

Very promising results in cancer

Potential for HIV latent reservoir eradication?