Disclaimer
This talk is intended for educational value, and includes comments on unlicensed drugs. Please liaise with a specialist if you have a clinical query.

Cancer Immunotherapy – Future from the Past?

Dr Guy Faust
Consultant Medical Oncologist
Immunotherapy

- Understand the story so far...
- Define immunotherapy
- Perceive the future...
Immunotherapy: a brief history

- 1863: Virchow
- 1898: Treatment of Cancer with bacterial products by Coley
- 1957: Immunosurveillance hypothesis by Burnett
- 1973: Cross presentation discovered by Bevan
- 1974: MHC 1 restricted CD8+ T-cell recognition by Zinkernagel & Doherty
- 1976: Dendritic cell identified by Steinman
- 1977: BCG in bladder cancer first used
- 1957: 1st Allogeneic bone marrow transplantation
Immunotherapy a brief history

- 1973: First IL-2 Study
- 1983: First study with adoptive cell transfer in cancer
- 1985: First melanoma IFN-α study
- 1991: Human tumour-associated antigens characterised by Rosenberg & Boon
- 1992: IL-2 approved as cancer immunotherapy
- 1996: Human tumour-associated antigens characterised by Rosenberg & Boon
- 2002: Imiquimod used for VIN HPV Vaccination
- 2008: Future arrived....
Immunotherapy treatments

- Interferon/ Interleukins
- Vaccines
- Antibody therapies
- Ipilimumab
- Sipuluecel-T
- PD-1 / PD-1L inhibitors
- Future
Immune System

- **Innate:**
  - Immediate, rapid
  - Nphils, Macrophages
  - ‘Amnesic’, no memory

- **Adapative:**
  - Slower
  - Specific Antigen recognition
  - Memory to recall original antigen exposure
Humoral – production of antibodies by B cells & plasma cells

Cell-mediated immunity – helper & cytotoxic T-cells with various target cells
Immune System

- Cytokines – proteins allowing immune cell communication
  - Initiation
  - Perpetuation
  - Down-regulation
Immune System – cells

- Antigen presenting cells (macrophages, dendritic cells, B-cells, Langerhans cells)

- T-cells – multiple different classes defined by cytokine production
  - Th1 – cellular immune response
  - Th2 – enhance humoral activity with Ab release
Melanoma – the immunological cancer
IL–2 & others

- High dose IL–2
  Response rates of 16% duration of ~9mths
  Complete response ~4%
  Toxic +++ (hypotension, arrhythmias etc)

- Interferon–α
  ?adjuvant
Vaccination Success

- What’s the success story?
Human Papillomavirus (HPV)

Persistent infection causes virtually all cervix cancers & many anal, penile oropharyngeal cancers

2 vaccines
- Gardasil – HPV 6, 11, 16 & 18
- Cervarix – HPV 16 & 18

97% effective at preventing infection
Vaccination Success

- UK programme aged 12–13 yrs girls only
- Gardasil used (prevents genital warts as well)
- ? males
- ? young enough
Antibodies

- Target cell receptors
  - Induce antibody–dependant cell mediated cytotoxicity
  - Activate complement
  - Prevent cell–cell / receptor–ligand interaction
  - Deliver chemotherapy / radiotherapy

E.g. rituximab (CD–20) for NHL
     trastuzumab (Her–2) for breast cancer
     infliximab (TNF–α) for colitis, Rheumatoid arthritis etc
Immunotherapy in use
Ipilimumab

- Humanised IgG1 anti-CTLA-4 monoclonal antibody
- Blocks binding of CTLA-4 to its ligands CD80 & CD86
- Blocking CTLA-4
  - Reduces threshold for T-cell activation
  - Removes mechanism for T-cell down-regulation
T-cell activation

TCR
CD28
MHC
B7
APC

CTLA4
ipilimumab

T-cell activation

TCR
CD28
MHC
B7
APC
Types of response

- **Ipilimumab exposure**
- **T-cell activation**
- **Patterns of response**
  - PD
  - SD
  - PR
  - CR

Tumor volume can include immune-cell infiltrates and tumor cells.
Types of response

Current imaging cannot differentiate between tumour and T cell proliferation, thus apparent tumour growth in some studies with late response.
Toxicity

- Not straight forward
- Immune related – any autoimmune reaction...
  - Rash
  - Colitis
  - Dermatitis
  - Hepatitis
  - Endocrinopathy – hypopituitarism, adrenal insuff.
  - Neuropathy – Guillain–Barre, myasthenia gravis
Toxicity

- Management – as per autoimmune diseases?
- International guidance – consensus

- Early Steroids – 80–90% resolution
- Replacement of hormones (T_4 etc)
- More advanced treatments
  - Infliximab
  - Immunoglobulins
OS (ITT population)

Phase III Study MSX010–20
Sipuluecel-T (Provenge) Prostate Cancer

- Cultured own immune cells exposed to recombinant prostate specific antigen

Leukapheresis – cells harvested

Cells Exposed/ Incubated

Cells returned to patient
Sipuluecel-T (Provenge)

- Survival (%)
  - PROVENGE (n=341)
  - Control (n=171)

- Time From Randomization (Months)
  - 25.8 months
  - 21.7 months

- HR=0.775
  - 95% CI: 0.614, 0.979
  - P=0.032
The future, here now?
Programmed death 1
- T-cell membrane protein – negatively regulates T-cell receptor signals

Programmed death L1 & L2 – upregulated on macrophages & dendritic cells in response to PD-1
- PD-L1 – on almost all cancer cell lines
- PD-L2 – more restricted cancer but dendritic cells
http://www.cancer.gov/ncicancerbulletin
# PD–1 Pathway blocking mAbs in Clinical Testing

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<th>Pharma</th>
<th>PD–1</th>
<th>PD–L1</th>
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<tr>
<td>Bristol–Myers–Squibb</td>
<td>Nivolumab (Opdivo)</td>
<td>BMS–936559/ MDX–1105 (Human IgG4)</td>
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<td>CureTech</td>
<td>Pidilizumab/ CT–011 (Humanised IgG1)</td>
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<td>EMD Serono</td>
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<td>MSB0010718C (human IgG1)</td>
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<td>Roche</td>
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<td>MPDL3280A (Fc–modified human IgG1)</td>
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<td>AstraZeneca/ MedImmune</td>
<td>MEDI0680/ AMP–514</td>
<td>MEDI4736 (Fc–modified human IgG1)</td>
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<tr>
<td>Merck</td>
<td>Pembrolizumab (Keytruda)</td>
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ASCO 2014....
PD-1 / PD-Ligand 1 inhibitors

Skin cancer drug pembrolizumab hailed as 'miraculous' new treatment

'Miracle' skin cancer treatment to be made available to advanced melanoma sufferers, under deal struck between Therapeutic Goods Administration and Merck

- Doctors claim cancer fighting drug MK-3475 is a 'wonder drug'
- More effective than current melanoma treatment, little side effects
- Campaign to have it approved spearheaded by Ron Walker

By ADAM DUGGAN

A 'miracle' drug will be provided for free to Australia's sickest cancer patients, left with no other options, through a special access program by drug manufacturer Merck Sharp and Dohme.

The drug, known as MK-3475, has a positive response in about 60 per cent of patients taking it to treat advanced melanoma - compared with between 10 and 20 per cent for the current most effective treatment, Yervoy.
OS patients with melanoma treated with nivolumab
Pembrolizumab in treated & untreated melanoma patients

Maximum Percent Change from Baseline in Tumor Size\(^a\) (Central Review, RECIST v1.1)

- IPI-T
- IPI-N

\(^a\)In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317).
Percentage changes >100% were truncated at 100%.
Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas
Pembrolizumab in treated & untreated melanoma pts

Time to and Durability of Response (Central Review, RECIST v1.1)

- 88% of responses ongoing
- Median response duration not reached (range, 6+ to 76+ weeks)

*Ongoing response defined as alive, progression free, and without new antitumor therapy. Analysis cut-off date: October 16, 2013.

Presented by: Antoni Ribas
Pembrolizumab versus Ipilimumab in Advanced Melanoma
Ribas et al, NEJM 13th May 2015
# PFS at the First Interim Analysis (IA1)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 6 mo</th>
<th>HR (95% CI)</th>
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<td>Pembrolizumab Q2W</td>
<td>5.5 (3.4-6.9)</td>
<td>47.3%</td>
<td>0.58</td>
<td>&lt;0.00001</td>
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<tr>
<td>Pembrolizumab Q3W</td>
<td>4.1 (2.9-6.9)</td>
<td>46.4%</td>
<td>0.58</td>
<td>&lt;0.00001</td>
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<tr>
<td>Ipilimumab</td>
<td>2.8 (2.8-2.9)</td>
<td>26.5%</td>
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**No. at risk**

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Analysis cut-off date: September 3, 2014.
OS at the Second Interim Analysis (IA2)

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<td>(0.47-0.83)</td>
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<td>Pembrolizumab</td>
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<td>Q3W</td>
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<td>(0.52-0.90)</td>
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<tr>
<td>Ipilimumab</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
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No. at risk

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Analysis cut-off date: March 3, 2015.
Treatment-Related AEs With Incidence ≥10% at IA1

- **Fatigue**
- **Diarrhea**
- **Rash**
- **Pruritus**
- **Asthenia**
- **Nausea**
- **Arthralgia**
- **Vitiligo**

*Incidence not adjusted for duration of exposure.*
Analysis cut-off date: September 3, 2014.
AEs of Special Interest at IA1

- Pembrolizumab Q2W
- Pembrolizumab Q3W
- Ipilimumab

*Incidence not adjusted for duration of exposure.
Analysis cut-off date: September 3, 2014.
Combinations? Nivolumab + Ipilimumab

Overall Survival for Concurrent Therapy by Dose Cohort

1 Yr OS 94%  2 Yr OS 88%

1 Yr OS 57%  2 Yr OS 50%

Survival (%)
Vaccines (again)

- Multiple different vaccines injected directly into lesions

- Increasing evidence
  - When to use?
  - What to use?
  - Combinations?
Talimogene Laherparepvec (T-VEC)

T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

Local Effect: Virally-Induced Tumor Cell Lysis

- Selective viral replication in tumor tissue
- Talimogene Laherparepvec
- Cancer cells rupture for an oncolytic effect
- GM-CSF

Systemic Effect: Tumor-Specific Immune Response

- Systemic tumor-specific immune response
- Dendritic cell activated by GM-CSF
- CD4+ T cell (helper T cell)
- CD8+ T cell (cytotoxic T cell)
- Tumor-specific antigens
- Dying cancer cell
- Death of distant cancer cells

Presented by: Howard L. Kaufman, MD
Exploratory OS Subgroup Analysis By Disease Stage

Stage IIIB/C, IVM1a
Hazard Ratio: 0.57 (95% CI: 0.40, 0.80)
Log Rank: \( P < 0.001 \) (descriptive)

Stage IVM1b/c
Hazard Ratio: 1.57 (95% CI: 0.79, 3.22)
Log Rank: \( P = 0.71 \) (descriptive)
Future?

- More data
- Licensing of the PD-1 & PD-1L inhibitors
- More patients, better outcomes
Melanoma

Lung

Prostate

Breast

Bladder

Renal
Understand some of immunotherapy mechanisms

Current options

Aware of the potentials...

Brink of an immunotherapy revolution...?

In pipeline of almost every oncological pharmaceutical company

Costs....?

- Drug, capacity, toxicity managements...
What now?

- Other colleagues are starting to use...
- We are going to need increasingly specialised input from medical specialties

Ophthalmologists  Acute Medicine  Dermatologists
Respiratory Physicians  Hepatologists
Gastroenterologists  Cardiologists  Endocrinologists
Neurologists  Rheumatologists
A request...

- If you have an interest to help manage please contact me...

- Any questions?

- Key learning points on next slide
### Key Learning Points

#### Immunotherapy for cancer

- **Do not assume that a cancer patient has received chemotherapy, they may have had immunotherapy.**
- For acutely admitted cancer patients, consider Chemotherapy-associated Neutropenic sepsis & T cell-mediated autoimmune complications of immunotherapy.
- **COLITIS** is one of the main complications.

**Toxicities**

1. Require specific management protocols including steroid use
2. May occur after completion of treatments
3. Can be significant & potentially fatal