Exciting Advances in Immunotherapy

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2013 Breakthrough of the Year

Cancer Immunotherapy
T cells on the attack
Immunotherapy: The Old and the New
The Questions We Hear:

- What is inflammation? Is it good or bad?
- How can I boost my immune system to fight my cancer?
- What immunotherapies are available for me?
Microbial pathogens
Environmental exposure
Dietary lifestyle
Therapy induced

Chronic inflammation

Tumor development

Cell transformation
Primary growth
Metastasis

Source: Immunotherapy © 2011 Future Medicine Ltd.
The effect of low-dose aspirin on risks of cancer, heart and circulatory problems, and bleeding

- Cancers
- Major heart and circulatory problems
- Internal Bleeding

Relative Risk

- At start
- 0 to 2.9 years
- 3 to 4.9 years
- Greater than 5 years

Length of time
Inflammation: Good or Bad?

- 2011: Meta-analysis of 8 randomized trials: Risk of cancer death 20% lower for people who took aspirin for 4 years
  - Especially colorectal cancer, but also in lung, prostate, breast cancers.

- Evidence mounting for prevention of certain cancers

- Several large aspirin studies are ongoing
  - ASPREE=19,000 healthy people, results in 2018
    Does aspirin prevent cancers (and other diseases) in healthy people over 70?
  - ASCOLT=1,200 people with colorectal cancer
  - ABC= 3,000 women with breast cancer, $10 million DOD grant
T cells killing a tumor cell
Anti-Tumor Immunity: A Balancing Act

B cell activation
T cell activation
Antigenic Targets
Innate immunity

Inflammation
Immune evasion
T cell Dysfunction
Cytokine Dysregulation

- B7.1/CD80
- B7.2/CD86
- CD40
- 4-1BB
- OX40
- MICA, MICB
- Toll-like receptors
- TNF-a
- Regulatory T cells
- FoxP3
- CTLA-4
- B7-H1/PD-L1
- B7-H4
- IDO
- TGF-β
- Interleukin-10
- FasL/CD95L
Which Cancers Respond to Immunotherapy

- Lung Cancer
- Colon Cancer
- Breast Cancer
- Prostate Cancer
- Bladder Cancer
- Head and Neck Cancer
- Melanoma
- Renal Cell Cancer
- Glioblastoma
- Multiple Myeloma
- Leukemia
- Lymphoma
The Adaptive Immune System

Sees foreign proteins
Has “memory”

Consists of:

T cells

B cells
Why do we need T cells?
How we see “Self”: HLA proteins
What is Checkpoint Blockade (and Other Targets?)?

<table>
<thead>
<tr>
<th>Antigen Presenting Cell</th>
<th>T cell</th>
<th>Tumor cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-12</td>
<td>CTLA-4</td>
<td>MAGE</td>
</tr>
<tr>
<td>Gm-CSF</td>
<td>PD-1</td>
<td>NY-ESO</td>
</tr>
<tr>
<td>KLH</td>
<td>PD-L1</td>
<td>MUC</td>
</tr>
<tr>
<td>Poly I:C</td>
<td></td>
<td>WT-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NY-BR-1</td>
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<td>hTERT</td>
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Ernst and Anderson Curr. Oncol Report. 2015
Checkpoint Blockade Immunotherapy

Ipilimumab (anti-CTLA-4, BMS; Yervoy)
  Approved in 2011 for malignant melanoma
  Associated with autoimmune toxicity

Pembrolizumab (anti-PD-1, Merck; Keytruda)
  Approved in 2014 for malignant melanoma, lung cancer, head and neck cancer

Nivolumab (anti-PD-1, BMS; Opdivo)
  Approved in for malignant melanoma

Efficacy in other cancers:
  bladder cancer, renal cell cancer, lung cancer
  many more being tested.

New targets coming:
  GITR, OX40, TIM-3, LAG-3
Early Pseudoprogression in KEYNOTE-001

Best Overall Response by irRC

- 7 of 192 patients (3.6%) showed ≥25% increase of tumor burden at week 12 that was not confirmed as irRC PD at the next assessment.

Analysis cut-off date: October 18, 2013.

Presented by: F. Stephen Hodi
KEYNOTE-023—Efficacy of Pembrolizumab + Len/Dex in R/R MM

R/R MM pts with ≥ 2 prior treatments including a PI and IMiD

- **Dose Determination**: 3 + 3 (n = 9)
- **Dose Confirmation TPI Algorithm**: (n = 8)
- **Dose Expansion**: (n = 33)

**Primary endpoints**: Safety, Tolerability (on all pts)
**Secondary endpoints**: ORR, DoR, PFS, OS (on pts in first 2 stages only)

**Final MTD**: Pembrolizumab 200 mg* IV Q2W Lenalidomide 25 mg Dexamethasone 40 mg

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Response-Evaluable Pts (n = 17)</th>
<th>Lenalidomide-Refractory Pts (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>13 (76)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>• VGPR</td>
<td>4 (24)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>• PR</td>
<td>9 (53)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Disease control rate, n (%)</td>
<td>15 (88)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Median time to first response, mos (range)</td>
<td>1.2 (1.0-6.5)</td>
<td></td>
</tr>
<tr>
<td>M-protein reduction ≥ 50% from baseline, %</td>
<td>76.5</td>
<td></td>
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<tr>
<td>Median DoR, mos</td>
<td>9.7</td>
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Maximum Change from Baseline in M Protein or Free Light Chains (Efficacy Population)

35/40 (88%) of patients with a decrease

Data cutoff: April 11, 2016
The Opportunity: Targeting Immunomodulators

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

Inhibitory Receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Optimal cancer immunotherapy combinations

What is a Chimeric Antigen Receptor?

The tumor-specific portion can be:
- An antibody
- A T cell receptor

The signaling portion is a modified portion of the T cell receptor and activation domains.
Adoptive T Cell Therapy/ CAR-T cells (Chimeric Antigen Receptors)

- Genetically engineer cancer-specific T-cells
- Fragmentation of tumour sample and isolation of tumour infiltrating lymphocytes
- Activation and expansion
- Transfusion into recipient
Regression of Glioblastoma after Chimeric Antigen receptor T cell Therapy

Brown et al, NEJM 2016
Conclusions

- The immune system naturally reacts to cancer
- Antibodies to cancer proteins are now widely used for cancer treatment
- Adoptive Cell Therapy/CAR-T cells are being developed for leukemias and solid cancers
- Vaccines are in the future....
I AM MY OWN SECRET WEAPON.

The battle against cancer is hard fought and hard won, and often treatments are as devastating as the disease itself. But inside each of us is the power to fight cancer: our immune system. Stand Up To Cancer and the Cancer Research Institute have joined forces in one of the most promising new research areas, using the science of immunology to tap our bodies' own natural defenses to fight the disease. Immunotherapy has the potential to significantly change the treatment of cancer as we know it. Stand Up with us. Together, we can impact millions of lives.
Acknowledgements

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• Our patients

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