Cancer Immunotherapy Review: Oncology Perspective

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Speaker Disclosures

- Consultant and speaker for Dendreon
- Consultant for Bayer
- Consultant and speaker for Sanofi-Aventis
- Research support from Prometheus
- Consultant for Genentech

Cancers that are known to have responded to immunotherapy > 20 and counting

- NSCL
- Melanoma
- Renal
- Head and Neck
- Merkel cell
- Prostate
- Bladder
- Colon – mismatch repair deficient
- Hodgkin lymphoma
- Non Hodgkin lymphoma
AACR April 2016

- SCC of Head and neck – platinum treated
  - Maura Gillison
  - Nivolumab doubles 1 year OS in Head and Neck 36 vs 16 % in patients (CheckMate-141)
  - Median OS 7.5 vs 5.1 months

AACR April 2016

- Melanoma update
- James Allison “Get that tail up”.
  - Ipilimumab long term survivors ~22%.
- Stephen Hodi update on longest f/u on Nivo survivors
  - Nivolumab. At 5 years the OS rate for patients with pre-treated metastatic melanoma is 34%! (107 pt study –CA209-003)
  - Suggestion that upfront treatment will be better
  - Nivo + Ipi vs Ipi (2yr OS 64% vs 54%)
    - >50% had grade 3-4 toxicity; 37% discontinued combination therapy
  - Median survival with Nivo 17 -20 months

For context: historical median survival metastatic melanoma is 11mo

Learning Objectives

- Review the evidence supporting the immune system’s role in cancer and the characteristics of an immune response
- Describe several mechanisms of immunotherapy
- Discuss treatment considerations for cancer immunotherapy
Talk Outline

**Immune System's Role in Cancer**

- Immunotherapy Landscape
- Clinical Considerations of Immunotherapy
- State of Immunotherapy

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**Cancer Pathogenesis: Formerly Characterized by 6 Hallmarks**

- Sustaining proliferative signaling
- Resisting cell death
- Inducing angiogenesis
- Activating invasion and metastasis
- Enabling replicative immortality
- Resisting cell death


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**Cancer Pathogenesis: Immune Evasion Now Recognized as a Hallmark**

- Avoiding immune destruction
- Evading growth suppression
- Resisting cell death
- Inducing angiogenesis
- Activating invasion and metastasis
- Enabling replicative immortality

**Hallmarks of Cancer Pathogenesis (2011)**

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Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems.1-4

Tumor risk in transplant patients compared to general population1-3

Testicular cancer
Breast cancer
Ovarian cancer
Pancreatic cancer
Esophageal cancer
Stomach cancer
Prostate cancer
Lung cancer
Colon cancer
Bladder cancer
Leukemia
Hepatobiliary cancer
Cervical cancer
Vulvovaginal cancer
Melanoma
Kidney cancer
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Non-melanoma skin cancer


Fold-increase in tumor/cancer risk
2-fold
3-fold
5-fold
8-fold
15-fold
20-fold and beyond

Immune Cells Within Tumors Predicts Overall Survival

- T-cell infiltration within tumors is associated with overall survival (OS) in patients with different cancers.1,2

Kaplan-Meier Curve for OS in Advanced Ovarian Cancer

- Intratumoral T cells at 102: Median OS = 30.3 months
- No intratumoral T cells: Median OS = 18 months

P < 0.001

P < 0.001

Adapted with permission from Zhang L, Coukos G, et al.

Immunotherapy Proven Effective in Cancer

- Therapies that engage the immune system have been shown to improve patient survival in randomized, phase 3 cancer trials.1-3
- Immunotherapies (cytokines, checkpoint inhibitors, therapeutic vaccines, monoclonal antibodies) have been approved by the FDA to treat certain cancers.4

Dynamics Between Cancer and the Immune System

- In a dynamic process, the immune system can either
  - Block tumor growth, development, and survival
  - Allow tumor outgrowth

Dynamic Process Described by 3 Phases

- The 3 E’s
  - Elimination
  - Equilibrium
  - Escape

Elimination: Immune System Eradicates Cancer Cells

- A natural process involved with early disease

 Adapted from Dunn GP, Schreiber RD, et al.1


Equilibrium: Immune System Controls Cancer Cells

- Occurs with later stage tumors
- Represents a balanced “dynamic” between the immune system and cancer

![Diagram showing immune cells and abnormal cells/tissue outgrowth controlled]

Adapted from Dunn GP, Schreiber RD, et al.

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Escape: Cancer Cells Evade Immune System

- Tumor cell variants grow, resulting in progressive disease

![Diagram showing immune cells and abnormal cells/tissue continuing to replicate]

Adapted from Dunn GP, Schreiber RD, et al.

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Key Components Involved in the Immune Response

- **Antigens**
  - Molecules produced by microbes or foreign agents that bind to T cells and antibodies
- **Antigen presenting cells (APCs)**
  - Identify and uptake foreign antigens
  - Present them to T cells
- **T cells**
  - Activated by APCs
  - Recognize and destroy cells containing foreign antigen
- **B cells**
  - Produce antibodies specific to foreign antigens

Adams AK, Lichtman AH. Basic Immunology. 3rd ed. 2011.
Initiation of Immune Response: Key Components

Adapted from Abbas AK, Lichtman AH.

Features of an Effective Immune Response

- Specificity
- Trafficking
- Adaptability
- Target elimination
- Durability (immune memory)

Immune Response: Specificity

- Ability of immune cells to identify and target a specific antigen

In type 1 diabetes, T cells recognize and destroy only β cells

Pancreatic islets of Langerhans (normal)

Pancreatic islets of Langerhans (type 1 diabetes)

α cells (black)
β cells (brown)

T cell infiltration

Reprinted with permission from Irene Woldin, MD.

Immune Response: Trafficking

- Ability of activated immune system cells to migrate to particular antigens throughout the body\(^1\)\(^-\)\(^3\)
- In this example, activated T cells were mobilized to areas containing antigen\(^1\)

\[\text{Injection of naive T cells} \rightarrow \text{Injection of activated T cells} \]

Immune Response: Adaptability

- Allows for a broader immune response\(^1\)
  (eg, immune response to additional antigens\(^2\))

\[\text{Tumor} \rightarrow \text{Activated T cell} \rightarrow \text{Adaptation Galley, Jr., New Vision (2015): 1-9.}\]

Immune Response: Target Elimination

- Ability of immune cells to destroy their target (eg, cancer cells)\(^1\)\(^-\)\(^2\)
  - Usually via induction of apoptosis\(^3\)

\[\text{Target cell death}\(^1\)\]


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\[\text{Target cell death}\(^1\)\]


Immune Response: Durability (Immune Memory)

- Ability of immune system to recognize an antigen to which it has previously been exposed and provide long-lasting protection against it.
- Shown is the durable virus-specific T-cell response after smallpox vaccination.

![Graph showing the percentage of volunteers with CD4+ T-cell memory after smallpox vaccination.]

Program Agenda

- Immune System's Role in Cancer
- Immunotherapy Landscape
- Clinical Considerations of Immunotherapy
- State of Immunotherapy

Immunotherapy

**Definition**

- Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases

**Examples in cancer**

- Monoclonal antibodies
- Cytokines
- Checkpoint inhibitors
- Therapeutic vaccines

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The Renaissance of Immunotherapy

<table>
<thead>
<tr>
<th>Enthusiasm Phase</th>
<th>Skepticism Phase</th>
<th>Renaissance Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-1985</td>
<td>1985-1997</td>
<td>1997-</td>
</tr>
<tr>
<td>1st study with BCG in bladder CA</td>
<td>1993 IFN-α approved for CA</td>
<td>1st cellular immunotherapy approved for CA</td>
</tr>
<tr>
<td>1985 1st study with adoptive T-cell transfer in CA</td>
<td>1995 1st mAb approved for CA</td>
<td>2011 1st checkpoint inhibitor approved for CA</td>
</tr>
<tr>
<td>1978 Discovery of the dendritic cell (Steinman)</td>
<td>1990s Discovery of role of checkpoint inhibitors in CA</td>
<td>1997</td>
</tr>
<tr>
<td>1890s 1st CA vaccine developed (Coley)</td>
<td>1986 IFN-α (cytokine) approved for CA</td>
<td>2010 1st cellular immunotherapy approved for CA</td>
</tr>
<tr>
<td>1973 Discovery of the dendritic cell (Steinman)</td>
<td>1992 IL-2 (cytokine) approved for CA</td>
<td>2011 1st checkpoint inhibitor approved for CA</td>
</tr>
</tbody>
</table>

Types of Immunotherapy

- Cytokines
- Monoclonal antibodies
- Checkpoint inhibitors
- Therapeutic cancer vaccines

Cytokines

- Proteins that are naturally secreted by immune system cells
- Mechanism of action
  - Interleukin-2 (IL-2) stimulates T-cell proliferation
- Examples
  - Interleukins, interferons
- Efficacy
  - High dose IL-2 administration resulted in long term disease-free survival in patients with melanoma and renal cell carcinoma

Cytokines

- Interferon-α (IFN-α): "the control"
  - Median PFS: 4.7 mo
  - Median OS: 13 mo
- High dose Interleukin (IL-2)
  - Response rate: 15-20%
  - 5-7% durable CRs
  - NCI 1986-2006

Median Overall Survival
CR: Not reached
PR: 39.1 mo
No response: 15.1 mo

Monoclonal Antibodies (mABs)

- Mechanism of action1,2
  - Differs between agents
  - Bind to their specific target antigen ultimately causing cell death
- Efficacy3-7
  - Improved overall and progression-free survival (PFS) in randomized, phase 3 clinical trials in breast cancer, colorectal cancer, leukemia, and head and neck cancer

FDA approved cancer antibodies

- trastuzumab
- trastuzumab emtansine
- pertuzumab
- bevacizumab
- cetuximab
- panitumumab
- Ipilimumab
- ramucirumab
- pembrolizumab
- nivolumab
- rituximab
- alemtuzumab
- ofatumumab
- gemtuzumab ozogamicin
- brentuximab vedotin
- 90Y-labelled ibritumomab
- 131I-labelled tositumomab

Toxicity!


Potential mechanisms of mABs in cancer

Tumor cell death


Tumor
Drug-mAb
Cytokine-mAb
Toxin-mAb
Receptor

HER2 targeted therapy

- Breast cancer historically not considered immune responsive cancer
  - HER2+ and TNBC may be exceptions
  - Immune-related gene expression signatures
  - Prognostic value of TILs
- High levels of TILs are associated with benefit to trastuzumab and chemotherapy
- "Immunologic factors were highly significant predictors of therapy response (pCR)...particularly in patients treated with neoadjuvant carboplatin...” (stromal TIL not tumoral)

Loi et al, 2013
Mahmoud et al, JCO 2011
Denkart, C. et al JCO 2015

Checkpoint Inhibitors

- **Mechanism of action**1,2
  - Block immune checkpoints that regulate T cell activation/function
- **Examples**1,2
  - CTLA-4 and PD1
- **Efficacy**3-6
  - Extends overall survival in certain metastatic diseases
  - A significant effect on PFS not consistently observed

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**Figure 1** Targets of immune modulatory drugs for cancer therapy

Gangadhar, T. C. & Vonderheide, R. H. (2014) Mitigating the toxic effects of anticancer immunotherapy
Anti CTLA therapy. Ipilimumab in melanoma


Melanoma

- pembrolizumab (Keytruda, MK-3475)
  - First PD-1 FDA approved (September 2014) 2mg/kg q2W
  - Advanced melanoma (post Ipilimumab and BRAFi if BRAF mutant)
  - Relatively well tolerated (fatigue, pruritis and rash, 2 patients with hepatitis, hypophysitis)
- Nivolumab
- Ipilimumab + Nivolumab

nivolumab in untreated melanoma w/o BRAF mutation
Bladder Cancer: MPDL3280a (anti PD-L1)

<table>
<thead>
<tr>
<th>PD-L1 tumor infiltrating immune cells</th>
<th>ORR % (95% CI)</th>
<th>Dx+ vs Dx- ORR % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n=10)</td>
<td>50% (22-78)</td>
<td>43% (26-63)</td>
</tr>
<tr>
<td>IHC 2 (n = 20)</td>
<td>40% (21-64)</td>
<td></td>
</tr>
<tr>
<td>IHC 1 (n=23)</td>
<td>13% (4-32)</td>
<td>11%(4-26)</td>
</tr>
<tr>
<td>IHC 0 (n=12)</td>
<td>8% (0.4 -35)</td>
<td></td>
</tr>
</tbody>
</table>

- 2 CRs (1 IHC 2, 1 IHC 3)
- 16 of 17 responding pts had ongoing responses at time of data cutoff
- ORR = 52% (95% CI, 32-70) for Dx+ with ≥ 12 weeks of f/u

Breakthrough therapy designation by FDA phase II started phase III planned (also NSCLC) [Roche]

Kidney Phase I Nivo + Ipi

Nivolumab: Hodgkins
Cellular Therapy

- **Heme**. Chimeric antigen receptor (CAR) Modified T-Cells
  - Targeting CD 19 (CLL, NHL, ALL, and others)
  - Leukopheresis, expose T cells to lentivirus...
- Nearly 50% RR in heavily treated patients
- Toxicity relatively well tolerated
  - Reversible hepatotoxicity, renal toxicity
  - Reversible tumor lysis syndrome
  - B cell aplasia (toxicity or efficacy?)
    - Supported with IVIG
    - No excessive or frequent infections
  - Cytokine release syndrome

Therapeutic Cancer Vaccines

- **Mechanism of action**
  - Activation of T cells to seek out and destroy target cancer cells
- **Efficacy**
  - Extended overall survival in certain metastatic diseases without an effect on PFS

Preventive vs Therapeutic Vaccines

"Cancer treatment vaccines are designed to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment."

- NCI (2011)

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**David Porter**

**Therapeutic Cancer Vaccines**


**Preventive vs Therapeutic Vaccines**

Cancer Vaccine

- Sipuleucel-T (Dendreon)
- Autologous process
- "antigen" is PAP

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Tumor vaccine: sipuleucel - T

Update 349 vs 331 deaths
HR 0.759 (95% CI: 0.606, 0.951)
P = 0.017 (Cox model)
Median survival remains

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Characteristics of Immunotherapy

<table>
<thead>
<tr>
<th>ACTIVE</th>
<th>PASSIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engages immune system</td>
<td>Enhances pre-existing immune response</td>
</tr>
<tr>
<td>Durable</td>
<td>Short-lived</td>
</tr>
<tr>
<td>Some examples: therapeutic cancer vaccines</td>
<td>Some examples: mAbS, cytokines</td>
</tr>
</tbody>
</table>

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Oncology Nursing Society 41st Annual Congress
April 28–May 1, 2016
Program Agenda

- Immune System's Role in Cancer
- Immunotherapy Landscape
- Clinical Considerations of Immunotherapy
- State of Immunotherapy

Immunotherapy: Treatment Considerations

- Relative efficacy of immunotherapy may be greater with lower tumor burden1-2
- Patient given immunotherapy earlier in disease course might have a better outcome3

![Graph showing tumor growth rate and tumor burden over time.]


Immunotherapy: Treatment Considerations

- Standard practice in oncology is the use of combination agents with different mechanisms of action1-3
  - Chemotherapy and mABs
  - Radiation and chemotherapy
  - Multiple chemotherapy regimens
- Immunotherapy offers potential for synergy with other therapies1-6

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Immunotherapy: An Established Treatment Strategy

- More than a dozen different immunotherapy agents have been approved*, with the majority over the last decade1-5
- Immunotherapy agents currently approved target >10 different cancer types1-5

<table>
<thead>
<tr>
<th>FDA-Approved Immunotherapiesa</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Approve</td>
</tr>
<tr>
<td>Checkpoint inhibitor</td>
<td>2011, 2014</td>
</tr>
<tr>
<td>Therapeutic vaccine</td>
<td>2010</td>
</tr>
</tbody>
</table>

*Not inclusive of all immunotherapy classes


Immunotherapy: Future Promise

- Rapid increase in immunotherapy clinical research
  - Doubling of abstracts at major conferences from 2009 to 2012
  - Approximately 800 clinical trials in various phases ongoing
  - eg, breast, colon, head and neck, kidney
- Trials utilize agents alone and in combination with conventional therapies2

*Not inclusive of all immunotherapy classes

Summary

- The immune system plays a critical role in controlling cancer.
- Key features of an effective immune response include:
  - Specificity
  - Adaptability
  - Durability (immune memory)
- Future clinical considerations:
  - May elicit better immune system response if used earlier in disease.
  - Potential for durable clinical effects and synergy with subsequent therapies.

References:

Toxicities

Balance

Toxicity Management options

- Mild
  - Hold agent (Ipi)
  - Consider lower dose steroids if no improvement
- Moderate to severe
  - Permanently discontinue
  - High dose steroids with careful wean when symptoms improve

References:

### Toxicities: Gastrointestinal

- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Ileus

### Toxicities: Liver

- Abnormal LFT’s (AST, ALT, Bilirubin)

### Toxicities: Skin

- Pruritis
- Rash
Toxicities: Neurologic

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

Toxicities: Endocrine

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Hypotension
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests

Guarded optimism... Don't celebrate too soon!!
“...The more we talked to them (Beau’s Doctors), the more we understood that we are on the cusp of a real inflection point in the fight against cancer.”

Table 1 Examples of immune checkpoint inhibitors in development

### Table 1: Anticancer immunomodulatory agents in clinical development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Phase of study</th>
<th>Most frequent toxicities (grade 3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>I, II, III</td>
<td>Fatigue, pruritus, diarrhea, nausea</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>PD-1</td>
<td>II, III</td>
<td>Fatigue, pyrexia, nausea, pruritus</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>I, II, III</td>
<td>Fatigue, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>I, II</td>
<td>Fatigue, rash, pyrexia, diarrhea</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>I, II</td>
<td>Fatigue, rash, pruritus, diarrhea</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>I</td>
<td>Fatigue, rash, dyspnea, pyrexia</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>MET</td>
<td>I</td>
<td>Hypertension, proteinuria, fatigue</td>
</tr>
</tbody>
</table>


### Table 2: General management of ipilimumab immune-mediated adverse events

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Management</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Supportive care, including topical steroids</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Calcium replacement, thyroid hormone replacement</td>
<td></td>
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</table>