The Rapidly Evolving Field of Immunotherapy in Cancer: Checkpoint Inhibitors to CAR-T

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Disclosures

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• Advisory Board
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  - TransEnterix, Mazor Robotics, Bellicum

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Objectives

• Understand the role of the immune system in cancer development (Cancer-immunity cycle)
• Discuss checkpoint inhibitor therapy in human cancer
• Introduce biomarker development in immuno-oncology
• Outline newer immune strategies in cancer

Achieve all above in 20 minutes
• **Immune system:** looking for things to fix

• Immune system tolerates “self” (tolerance, thymus)

• Immune system rejects “non-self”

• Immunity deals with “abnormal self” (cancer)
How are cancer cells different?

Does immunity matter?
CLINICAL EVIDENCE

- Tumors are often infiltrated with immune effectors
- Solid organ transplant patients on immunosuppressive drugs and HIV positive individuals have a higher rate of tumors
- Patients with and without cancer have developed immune responses to tumor antigens
- Tumors have a loss of immune recognition molecules (e.g. MHC)
CONTRIBUTION TO OUR KNOWLEDGE OF

By WILLIAM COLEY, M.D.,

1891: Coley's toxin
IT injection of step
Where did this originate?

Treatment by Proxy

• Give the patient a ‘new’ immune system
  – Allogeneic stem/marrow transplant
  – Adoptive auto-transfer
    • LAK, TIL, CAR-T

• Give a component of the immune system that would boost the immune response
  – IL-2, interferon

• Block checkpoints of immune function
  – Anti-CTLA4, anti-PD1

• De novo immunization
There had been no significant improvement in overall survival for metastatic melanoma in three decades.

Survival in Melanoma: 2018

And then there were five

The Economist. June 6, 2015
Overall Survival with HD IL-2

Atkins M B et al. JCO 1999;17:2105-2105
Caveats with IL-2 Therapy

- Highly toxic therapy
  - Capillary leak syndrome
  - Toxic to virtually every organ system
  - Needs to be administered in specialized centers in an ICU-like setting with continuous cardiac monitoring

- Pre-requisites
  - Nuclear stress test
  - PFT
  - Brain imaging
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation
- Antibodies to CTLA-4
- Antibodies binds to CTLA-4 on the cell surface

Unrestrained Proliferation
- CTLA-4 cannot bind B7

Slide courtesy: Michael Wong, MD, PhD
Clinical Case Study

May 2013

Dec 2013
Can Cure be a Reality in Metastatic Disease?

• N=4846
  – 1861 (on clinical trials)
  – 2985 (off protocol use)

• Median OS = 9.5 months (11.4m in 1861 pts)

• 3-year survival 22%

• No patient who survived beyond 7 years had died
  – (7-year survival = 17%)

• Longest OS survival is 9.9 years

YES

Schadendorf D. *J Clin Oncol* 2015, 33:1889
Pooled Analysis: OS

Schadendorf D. J Clin Oncol 2015, 33:1889
The PD-1 Pathway

Nivolumab and Pembrolizumab

A. Overall Survival

- Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73); P<0.001
- Dacarbazine
- Nivolumab

Patients who died 10.8 (9.3–12.1)

No. at Risk
Nivolumab 210 185 150 105 45 8 0
Dacarbazine 208 177 121 82 22 3 0

B. Progression-free Survival

- Patients without progression 2.2 (2.1–2.4)
- Patients who died or had disease progression 3.1 (3.5–10.8)

No. at Risk
Nivolumab 210 116 82 57 12 1 0
Dacarbazine 208 74 28 12 0 0 0

Combining nivolumumab and ipilimumab is much more toxic than nivolumumab alone

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=313)</th>
<th>Nivolumab plus Ipilimumab (N=313)</th>
<th>Ipilimumab (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Grade 3 or 4</td>
<td>Any</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>311 (99.4)</td>
<td>136 (43.5)</td>
<td>312 (99.7)</td>
</tr>
<tr>
<td>Treatment-related adverse event†</td>
<td>257 (82.1)</td>
<td>51 (16.3)</td>
<td>299 (95.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (19.2)</td>
<td>7 (2.2)</td>
<td>138 (44.1)</td>
</tr>
</tbody>
</table>

More Grade 3 or 4 AEs (69% vs 44%)
Six times as many Grade 3 or 4 AEs leading to treatment discontinuation (30% vs 5%)

### Approved PD-1, PD-L1 Antibodies

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Pembrolizumab (Pembro)</th>
<th>Atezolizumab (Atezo)</th>
<th>Durvalumab</th>
<th>Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC, SCLC, Melanoma, HCC, RCC, HNSCC, Urothelial, Hodgkin’s, MSI-H cancer</td>
<td>Melanoma, NSCLC, HNSCC, Hodgkin’s, PMBCL, Gastric, Cervical, Urothelial, MSI-H cancer</td>
<td>NSCLC, Bladder</td>
<td>NSCLC, Urothelial</td>
<td>MCC</td>
</tr>
</tbody>
</table>
T-Cell Targets: A Balancing Act

Future Combinations
But a sobering phase 3 result...

### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E + P</td>
<td>106 (29.9)</td>
<td>NR (NR, NR)</td>
</tr>
<tr>
<td>Placebo + P</td>
<td>98 (27.8)</td>
<td>NR (NR, NR)</td>
</tr>
</tbody>
</table>

HR (95% CI): 1.13 (0.86–1.49)  
P = 0.807

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>E + P</td>
<td>354</td>
<td>340</td>
<td>322</td>
<td>290</td>
<td>274</td>
<td>263</td>
<td>183</td>
<td>96</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Placebo + P</td>
<td>352</td>
<td>342</td>
<td>323</td>
<td>304</td>
<td>285</td>
<td>263</td>
<td>186</td>
<td>115</td>
<td>43</td>
<td>2</td>
</tr>
</tbody>
</table>

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.
Adoptive Cell Transfer (TIL)

S Rosenberg and Restifo. Science 2015;348:62-68
Chimeric Antigen Receptor Structures

ZUMA Trial in NHL

CRS Toxicity

Neurologic:
- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial nerve palsy
- Seizures

Hepatic:
- Transaminitis
- Hyperbilirubinemia

Hematologic:
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

Constitutional:
- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

Cardiovascular:
- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Troponinemia
- QT prolongation

Pulmonary:
- Tachypnea
- Hypoxia

Renal:
- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

Gastrointestinal:
- Nausea
- Emesis
- Diarrhea

Musculoskeletal:
- Myalgias
- Elevated creatine kinase
- Weakness

Jennifer N. Brudno, and James N. Kochenderfer.
Blood 2016;127:3321-3330
Improving CAR-T Therapy

“Not everything that matters can be measured, and not everything that is measured matters”

Albert Einstein
1207 Patients, 4 Regimens: Same Result

We now know better – EGFR, ALK, ROS-1, BRAF

The Need for Biomarkers

- Response to IO is not universal
  - Melanoma (40%), NSCLC (20%), RCC (22%)
- Adverse events to IO can range from mild to severe, yet do not necessarily correlate with response
- High drug costs

*Giving an *expensive* IO drug to a patient who develops severe *toxicity*, and *fails* to respond – *failure on all fronts*
IO Biomarkers

- Blood based (Static and Dynamic)
  - Cell count
  - LDH
  - Neutrophil to Lymphocyte Ratio
  - Immunoprofile (Flow Cytometry)
- Histology (eg, Desmoplastic melanoma)
- Tissue IHC
- Mutational Burden
- Gene Expression
- Gut Microbiome
- And ........ many yet undefined
Phenotype and Prognosis

• Model using LDH ($\leq 2.5$), Relative Eosinophil Count ($\geq 1.5\%$), Relative Lymphocyte Count ($\geq 17.5\%$), and Location of Metastases (Soft tissue/lung)

• $n=616$ (discovery, confirmation, validation)

• Results:
  - 4/4: 84% 1-yr survival, RR 58%
  - 0/4: 15% 1-yr survival, RR 3%

IO and Cutaneous irAEs

Sanlorenzo et al. JAMA Dermat. 2015;151:1206
PD-L1 Expression

- IHC on archival tissue
- Variable definitions of positive results
  - 1%, 5%, 50%, Any
  - Tumor, TIL, both
- PD-L1 negative tumors also respond
- Level of expression may vary on treatment
PD-L1 Expression in Different Cancers

PD-L1 Expression

Daud et al. J Clin Oncol. 2016;34:4102-09
PD-L1 Expression and Response

Sunshine J et al. Curr Opin Pharmacol. 2015;23:32
Key Takeaway

Tumoral PD-L1 status cannot be used as a stand-alone biomarker of response to anti-PD1 therapy
Mutational Load

• The number of mutations per coding area of the tumor genome
  – Low in pediatric tumors, low grade tumors
  – High in tumors associated with DNA damage
    • Smokers with NSCLC have a higher response to IO therapy compared to non-smokers with NSCLC
  – Encode for neoantigens that may drive enhanced T-cell response
Mutation Frequency in Tumors

TMB and Response to Anti-PD-1/PD-L1 Therapy

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

Cemiplimab in CSCC

PD-1, PD-L1 & MSI-H

First tumor agnostic biomarker driven drug approval on May 23, 2017

Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status

A. Progression-free Survival in Cohorts with Colorectal Cancer

B. Overall Survival in Cohorts with Colorectal Cancer

C. Progression-free Survival in Cohort with Mismatch Repair–Deficient Noncolorectal Cancer

D. Overall Survival in Cohort with Mismatch Repair–Deficient Noncolorectal Cancer

Unconventional, yet groundbreaking

- Biomarker-based approval
- High unmet need
- High response rate (40%)
- Established safety profile
- Extended to pediatric solid tumors
- No companion diagnostic to identify MSH-H or dMMR cancers
Mutational Burden and Survival in NSCLC

**A** Progression-free Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Nivolumab</th>
<th>chemotherapy</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>271</td>
<td>270</td>
<td>1.19 (0.97–1.46)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>123</td>
<td>137</td>
<td>1.21 (0.91–1.62)</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>148</td>
<td>133</td>
<td>1.17 (0.88–1.56)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>184</td>
<td>148</td>
<td>1.05 (0.81–1.37)</td>
</tr>
<tr>
<td>Female</td>
<td>87</td>
<td>122</td>
<td>1.36 (0.95–1.90)</td>
</tr>
<tr>
<td>ECOG performance status score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>85</td>
<td>93</td>
<td>1.69 (1.18–2.42)</td>
</tr>
<tr>
<td>≥1</td>
<td>185</td>
<td>177</td>
<td>1.01 (0.79–1.30)</td>
</tr>
<tr>
<td>Tumor histologic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>65</td>
<td>64</td>
<td>0.83 (0.54–1.26)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>206</td>
<td>206</td>
<td>1.29 (1.02–1.63)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>30</td>
<td>29</td>
<td>2.51 (1.31–4.83)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>186</td>
<td>182</td>
<td>1.14 (0.83–1.57)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>52</td>
<td>55</td>
<td>1.03 (0.66–1.62)</td>
</tr>
<tr>
<td>≥50% PD-L1 expression level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>88</td>
<td>126</td>
<td>1.07 (0.77–1.49)</td>
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**B** Overall Survival

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<td>0.97 (0.74–1.26)</td>
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<td>122</td>
<td>1.15 (0.79–1.66)</td>
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</tr>
</tbody>
</table>

**C** Progression-free Survival among Patients with High Tumor-Mutation Burden

[Graph showing progression-free survival rates]

**D** Progression-free Survival among Patients with Low or Medium Tumor-Mutation Burden

[Graph showing progression-free survival rates]
Key Takeaway

High mutational burden in a tumor may be predictive of response to anti-PD1 therapy
More than a ‘gut’ feeling…

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients


… He cautioned that the study findings are a "first step," but also a "very intriguing" one.

Khushalani said the findings raise the possibility of testing patients' stool samples to see who has a greater likelihood of responding to PD-1 therapy. "That could help us in truly tailoring treatment," he suggested.

Then there's the possibility of actually altering patients' microbiomes -- whether through probiotics or even fecal transplants, Khushalani added.
More than just one biomarker...

Cancer Immunogram

The Ideal IO Patient

Low disease burden with normal LDH, high eosinophils and lymphocytes, low NLR, with high mutational burden tumor with TIL present and an inflamed molecular signature and without an IPRES signature, with low Tregs and MDSCs, with good bacteria in the gut, who does not mind developing vitiligo, plus has good health care coverage
Summary

• 2010 - 2018
  – True renaissance with immunotherapy in oncology

• Immunotherapy is potentially curative, yet not all will benefit

• Biomarker discovery and validation is paramount to realize the goal of ‘precision medicine’