Immunotherapeutic Strategy:
Immune Checkpoint Blockade

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Disclosures

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• **Other (Joint Scientific Committee):** Janssen Oncology, Polaris

• I will be discussing non-FDA approved indications during my presentation.
Immune Tumor Microenvironment

Immunotherapies

Not all the same!

• Vaccines
  – Directs immune system to focus on tumor antigen(s)

• Cellular therapies
  – CAR T cells target the tumor cells

• Immune checkpoint therapies
  – Increases T cell activation and function
New Understanding of T Cell Regulation: Positive/Negative Signals Govern Responses

TCR Signal Only
No Proliferation

Positive Costimulation
Proliferation

Negative Coinhibition
Attenuation

Epithelial Cells
Tumor Cells

Antigen Presenting Cell
(Dendritic Cells, Macrophages)

TCR
CD28
IL-2
APC
APC
CTLA-4

Courtesy of Jim Allison, PhD
Anti-CTLA-4 reduces tumor growth rate

Leach DR et al., Science, 1996.
Improving Survival with a New Drug
Anti-CTLA-4 (Ipilimumab) Improves Survival in Patients with Metastatic Melanoma

Anti-CTLA-4 Induces Durable Anti-Tumor Responses in Patients with Metastatic Melanoma

Improving Survival with Immune Checkpoint Therapy

- Control
- Standard or Other Therapy
- Immunotherapy (e.g. anti-CTLA-4)
2013: Breakthrough of the Year

December 20, 2013
FDA-Approved Immune Checkpoint Therapies

Melanoma
- Ipilimumab (2011)
- Nivolumab (2014)
- Ipilimumab + Nivolumab (2015)
- Pembrolizumab (2019)
- Atezolizumab (2020)

Lung Carcinoma
- Nivolumab (2015)
- Pembrolizumab (2015)
- Atezolizumab (2016)
- Durvalumab (2018)
- Ipilimumab + Nivolumab (2020)

Urothelial Carcinoma
- Atezolizumab (2016)
- Avelumab (2017)
- Durvalumab (2017)
- Nivolumab (2017)
- Pembrolizumab (2017)

Renal Cell Carcinoma
- Nivolumab (2015)
- Ipilimumab + Nivolumab (2018)
- Avelumab (2019)

Colorectal Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2017)
- Ipilimumab + Nivolumab (2018)

Head and Neck Squamous Cell Carcinoma
- Nivolumab (2016)
- Pembrolizumab (2016)

Hepatocellular Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2018)
- Ipilimumab + Nivolumab (2020)

Merkel Cell Carcinoma
- Avelumab (2017)
- Pembrolizumab (2018)

Cutaneous Squamous Cell Carcinoma
- Cemiplimab (2018)
- Pembrolizumab (2020)

2018: Nobel Prize in Physiology or Medicine

James P. Allison

Tasuku Honjo
## Differences Between Anti-CTLA-4 and Anti-PD-1

<table>
<thead>
<tr>
<th></th>
<th>Anti-CTLA-4</th>
<th>Anti-PD-1</th>
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</thead>
<tbody>
<tr>
<td>Targets</td>
<td>CD28 pathway</td>
<td>TCR pathway</td>
</tr>
<tr>
<td>Works on</td>
<td>T cell priming</td>
<td>exhausted T cells</td>
</tr>
<tr>
<td>Clonal Diversity</td>
<td>Expands</td>
<td>Does not expand</td>
</tr>
<tr>
<td>Primarily Affect</td>
<td>CD4 T cells</td>
<td>CD8 T cells</td>
</tr>
<tr>
<td>Tumor Location</td>
<td>Can move T cells into “cold” tumors</td>
<td>Cannot move T cells into “cold” tumors</td>
</tr>
<tr>
<td>Response Time</td>
<td>Responses often slow</td>
<td>Responses usually rapid</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>More adverse events</td>
<td>Less adverse events</td>
</tr>
<tr>
<td>Disease Recurrence</td>
<td>Disease recurrence after response rare</td>
<td>Disease recurrence after response significant</td>
</tr>
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Challenges/Limitations of Immune Checkpoint Therapies

• Measuring disease burden / treatment response
  – Immune-related response criteria (irRC)

• Subset of patients benefit

• Toxicities
  – Immune-related adverse events (irAEs)
Delayed Responses with Ipilimumab

Screening

Week 12
Initial increase in total tumour burden (mWHO PD)

Week 16
Responding

Week 72
Durable & ongoing response

Courtesy of K. Harmankaya
Moving Forward with Immune Checkpoint Therapies

• Improving patient selection

• Turning “cold” tumors “hot” / Resistance mechanisms

• Understanding toxicities
Moving Forward with Immune Checkpoint Therapies

- Improving patient selection
- Turning “cold” tumors “hot” / Resistance mechanisms
- Understanding toxicities
Ways to Improve Patient Selection

• Identify patients who will more likely respond

• Exclude patients who will most likely not respond
Tumor Neoantigens

- MICA/B
- ULBP
  - (Human)

- Rae-1
- H60
  - (Mouse)

- Danger*: uric acid,
  - ECM products

- e.g., ↓ p53
- ↓ Rb
- ↑ Ras

- Carcinogens
  - Radiation
  - Chronic inflammation
  - Inherited

- Viruses

The Immunobiology of Cancer
Immunosurveillance and Immunoediting
Gavin P. Dunn, Lloyd J. Old, Robert D. Schreiber
Genomic Defects that Increase Neoantigen Burden

Mismatch Repair (MMR) Defects

CDK12 Mutations


Wu YM et al., Cell, 2018.
Neoantigens and Mutational Load Linked to Efficacy of Immune Checkpoint Therapies
Defects in the IFN-γ Signaling Pathway Promote Resistance to Immune Checkpoint Therapies


Moving Forward with Immune Checkpoint Therapies

- Improving patient selection

- Turning “cold” tumors “hot” / Resistance mechanisms

- Understanding toxicities
More CD8 T Cells Makes Anti-PD-1/PD-L1 Work Better


Ipilimumab Increases Immune Infiltration Within the Primary Prostate Tumor Microenvironment

Increased Tumor-Infiltrating T Cells are Insufficient Due to Adaptive Resistance (PD-L1 Upregulation)

CTLA-4 and PD-1/PD-L1 Targeting in a Mouse Model of Prostate Cancer

Combination of “immune checkpoint targets” will improve efficacy
Patients with mCRPC
- Ongoing ADT confirmed by testosterone level ≤1.73 nmol/L (50 ng/dL)
- ECOG performance status ≤1

Cohort 1: Asymptomatic or minimally symptomatic patients who progressed after ≥1 second-generation hormone therapy and had not received chemotherapy in the mCRPC setting (N = 45)

Cohort 2: Patients who progressed after cytotoxic chemotherapy in the mCRPC setting (N = 45)

NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W for up to 4 doses

NIVO 480 mg IV Q4W

Co-primary endpoints:
- Investigator-assessed ORR (per RECIST 1.1)
- rPFS (per PCWG2 criteria)

Secondary endpoints:
- OS
- Safety

Exploratory endpoints:
- PSA response rate
- Correlation of biomarkers (PD-L1, HRD, DDR, TMB) with efficacy

Prolonged Responses

Responder at MD Anderson
Targeting a Conventional Prostate Cancer Antigen Induces T Cell Infiltration into the Tumor Microenvironment

Sipuleucel-T (DC Vaccine)


Personal Multi-Peptide Neoantigen Vaccine for Patients with High-Risk Melanoma

Making Immune Checkpoint Therapies More Effective

**Microenvironment**

1. Increase T cell infiltration
2. Increase T cell function
3. Inhibit immunosuppressive cells
4. Increase antigen presentation
5. Metabolism

**Tumor**

1. Increase tumor antigens
2. Change tumor phenotype
3. Exploit tumor genomic defects

**Targeting Strategies**

- Immune checkpoints
- Chemotherapy
- XRT
- Hormone therapy
- PARP inhibitors
- Vaccines
- Cytokines
- Epigenetic modulators
- Metabolites

Adapted from Jianjun Gao
Novel Immunotherapy Targets

Improving Survival with Combination Therapy

Moving Forward with Immune Checkpoint Therapies

• Improving patient selection

• Turning “cold” tumors “hot”

• Understanding toxicities
Organ-Specific Immune-Related Adverse Events (irAEs)

- Nervous system
  - Guillain–Barré syndrome
  - Myasthenia gravis
  - Encephalitis

- Pituitary
  - Hypophysitis

- Lungs
  - Pneumonitis

- Thyroid
  - Hypothyroid
  - Hyperthyroid

- Heart
  - Myocarditis

- Adrenal
  - Insufficiency

- Pancreas
  - T1D

- Gastrointestinal
  - Colitis
  - Autoimmune hepatitis

- Skin
  - Vitiligo
  - Psoriasis
  - Stevens–Johnson syndrome
  - DRESS syndrome

- Rheumatologic
  - Vasculitis
  - Arthritis

Immune-Related Colitis/Diarrhea

Immune-Related Pneumonitis

Nivo

Dyspnea

Antibiotic Therapy

Dyspnea

Pneumonia

Steroids

Infliximab
Monday Morning Quarterback

02/05/2015

02/18/2015

03/11/2015
Safety Considerations

• irAEs appear to be under-reported

• Early recognition/intervention with immunosuppressive/biological agents
  – Medical team
  – Patient/Family
  – Laboratory tests
  – Consult teams
Kinetics of Appearance of irAEs

Cases and Fatality Rates for Different Types of irAEs

Co-Occurring Fatal irAEs

Time to Symptom Onset for irAEs

Systemic CD8 Clonal Expansion Precedes Grade 2-3 irAEs

Subudhi SK et al., PNAS, 2016.
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Conclusions for Immune Checkpoint Therapies

- Each target has a different mechanism of action
- Induce durable responses in a subset of patients
- Responses are associated with TMB in some malignancies
- Can be used to turn “cold” tumors “hot”
- Toxicities can be fatal
- Better biomarkers are required to maximize efficacy and minimize toxicities