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Learning Objectives

1. Evaluate the principles of tumor immunology and the mechanisms of action of current and emerging cancer immunotherapies used in solid tumors.

2. Appraise the latest clinical trial data regarding emerging cancer immunotherapies in SCCHN, NSCLC, mesothelioma, gastric cancer, melanoma, and other solid tumors, including use of both monotherapy and combination regimens.

3. Explore the role of biomarkers in patient selection to improve targeted use of immune checkpoint inhibitors.

4. Identify practical strategies for using current and emerging cancer immunotherapies, including prevention, early detection, and management of immune-related adverse effects.
Cancer Immunotherapy in Solid Tumors

Current Concepts
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Disclosures

• I consult for and have received less than $10000 dollars per annum from BMS, Merck, Genentech, AstraZeneca, GSK, Novartis, Nektar Therapeutics, Medivation, Celldex Therapeutics, cCAM, CytomX, Lion Bioscience, Incyte and EMD Serono for membership on advisory boards

• I hold equity in Celldex, CytomX and cCAM

• I am not a member of any speakers’ bureau

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New Era in Cancer Therapy
Harnessing The Immune System

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Reproduced from Immunity, Vol. 39, Daniel S. Chen and Ira Mellman, Oncology Meets Immunology: The Cancer Immunity Cycle, Page 2, Copyright 2013, with permission from Elsevier via Copyright Clearance Center.
Activation of Antitumor T-Cells

*Two Signals Required*

Tumor or epithelial cells

- TCR signal only
  - Antigen + MHC
  - TCR

No T cell proliferation

APC’s (dendritic cells, macrophages)

- Positive costimulation
  - B7
  - CD28

T cell proliferation

Cytokines

Antitumor T-Cell Response

How It Happens

1. Tumor antigen presented by dendritic cell
2. Resting T cell enters lymph node
3. T-cell clonal expansion
   - Perforin
   - Granzyme
   - Cytokines (IL-2)
   - MHC
   - B7
   - TCR
   - CD28

Activated T cell

Tumor

Lymph node
Immune Checkpoints
Inhibitory and Stimulatory Effects
• Immune checkpoints modulate the duration and amplitude of the physiologic adaptive immune response.

• Immune checkpoint signals can be ‘hijacked’ by cancer cells to allow for tumor growth that is unchecked by the immune system.

• PD-L1, which binds PD-1, has been found to be expressed by almost all types of cancers.

• Antibodies that target immune checkpoints can be used to “disinhibit” T cell responses against cancer.
Tumor Rejection in Mice

Anti-CTLA-4 mAb and GM-CSF Vaccine

Mean Tumor Area (mm$^2$)

Day 4 Post-Challenge

- Hamster IgG
- BL6/GM + Hamster IgG
- Anti-CTLA4
- BL6/GM + Anti-CTLA4

Does Ipilimumab Cure Melanoma?

**Long-Term OS Data**

- **Median OS (95% CI):** 11.4 mos (10.7–12.1)
- **3-year OS Rate (95% CI):** 22% (20–24%)

Clinical Challenge

*When to Hold ‘em, When to Fold ‘em?*

• Unique patterns of response are seen with checkpoint inhibitory immunotherapies
  – Traditional RECIST response with regression at week 12
  – Slow response with prolonged SD followed by response
  – Progression followed by regression, with or without the development of new disease
  – Mixed response with regression in some disease and development of new disease followed by regression of the new disease
Clinical Challenge (cont.)

**When to Hold ‘em, When to Fold ‘em?**

- It is acceptable to continue therapy past week 12 with checkpoint inhibition if:
  - No decrease in performance status
  - No worsening of labs by more than one grade
  - No symptomatic worsening of disease
  - No major increase in disease burden (>50%)
- I suggest getting an interim scan 6 weeks after continuing
- If there is worsening of any of the above, or another 25% worsening in disease burden, time to fold ‘em!
- Otherwise, hold ‘em and continue to week 24
Immune Checkpoint Blockade

*irAEs and Outcomes*

- Preclinical melanoma tumor models using CTLA-4 knock-outs have demonstrated enhanced immune-mediated tumor rejection AND immune related depigmentation, but not irAEs as seen in patients\(^a\)

- Although still somewhat controversial, irAEs do not seem to correlate with response;\(^b,^c\) irAEs do seem to correlate with response with PD-1 and PD-1/CTLA-4 combinations\(^b-e\) but poorly with CTLA-4 blockade alone\(^b,^c\)

irAEs

General Issues

• Infections and other etiologies should be ruled out or deemed unlikely as contributing to the irAEs.

• Most irAEs occur during the first 3-4 months.
  – Late irAEs, however, also can occur (eg, one episode has been seen at month 47 during maintenance phase of therapy).
  – Each irAE has different kinetics of onset and some can wax and wane, particularly colitis.

• Steroids can be used to manage almost all irAEs.
  – Prolonged steroid tapers are required

irAEs

Colitis

Ulceration in Descending Colon

Alterations in Crypt Epithelium

Focal Active Colitis

T-Cell Tumor Immunity

Adaptive Resistance

Chen L, Han X. J Clin Invest. 2015.
PD-1 Pathway
Mechanisms of Immune Suppression

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Mechanisms of Immune Suppression

**MC38 Colon Cancer**
Antibody Rx Only

- **mlG**
  - 0/12 Tumor Free

- **anti-PD-1**
  - 1/12 Tumor Free

- **anti-CTLA-4**
  - 0/12 Tumor Free

- **anti-PD-1 + anti-CTLA-4**
  - 9/12 Tumor Free

**B16BL6 Melanoma**
Antibody Rx + Cellular Vaccine

- **Untreated**
  - 0/12 Tumor Free

- **GVAX αCTLA-4**
  - 0/12 Tumor Free

- **GVAX αCTLA-4/αPD-1**
  - 0/12 Tumor Free

- **FVAX αPD-1**
  - 0/12 Tumor Free

- **FVAX αCTLA-4/αPD-1**
  - 0/12 Tumor Free

A 100
75
50
25
0
0 25 50 75 100 125
Percent survival

B 100
75
50
25
0
0 25 50 75 100 125
Percent survival

30/47 (64%) of patients randomized to IPI crossed over to receive any systemic therapy at progression
Ipilimumab induces durable objective responses in a small fraction of patients leading to an OS plateau, but no shift of the early portion of the OS curve.

Boosting Antitumor Immunity

Targeting Four Nodes
**Node 1**

**Blocking Immune Suppression**

- PGE₂
- TGF-β
- MDSC
- Adenosine
- NKG2A
- KIR
- CTLA-4
- PD-1
- LAG-3
- TIM-3
- BTLA
- VISTA/PD-1H
- TIGIT
- CD96
- Inhibitory

- Immature dendritic cell
- TREG
- M2
- Paracrine effect

- Arginase-1
- HIF-1α
- VEGF
- CCL2
- IDO
- IL-10
- Tie2
- IL-13
- CSF1
- IL-23

- STAT3 activators

Node 2

*Inducing Immunogenic Cancer-Cell Death*

- TRAIL-R agonists
- Conventional therapy
  - Radiotherapy
  - Chemotherapy (e.g., anthracycline, oxaliplatin)
- Oncogene inhibitors
- HDAC inhibitors
- Chemokines to attract CTL and $T_{H1}$
- Vaccines to generate CTL and $T_{H1}$
- p53 rescue
- Proteasome inhibitors

**Node 3**

*Enhancing APC Function/Adjuvanticity*

- **STING activator**
- **TLR agonists**
- **SIRPα antagonists**
- **CD40 agonists**
  - α-GalCer or α-C-GalCer
- **Type I IFN**
- **GM-CSF**

Node 4
Enhancing T/Macrophage Effector Activity

CD28
ICOS
CD137
OX40
GITR
CD27
CD30
HVEM
DNAM-1
CD28H

Agonistic

IL-2
IL-15
IL-21

α-B7-H5
α-B7-H6
α-B7-H4
α-B7-H3
α-CD73
α-CD47
α-CD200

Tumour cells

ADCC/ADCP

FcγR

CD40

Checkpoint Blockade
*Current Concepts and Future Prospects*

- Checkpoint blockade is a major advance in cancer treatment that is supported by extensive murine pre-clinical data.
- Multiple checkpoints and agonists regulate antitumor immunity, and their modulation is clinically feasible.
- Unique kinetics of response is associated with checkpoint inhibitory therapy.
- irAEs typify checkpoint inhibition and may be associated with benefit.
- Strong scientific rationale for novel combinations raises the hope for cures in multiple different cancers.
Thank you!

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